IRON TRICARBONYL PROMOTED CYCLIZATIONS: POTENTIAL APPLICATION
TOWARD TOTAL SYNTHESIS OF 18-DEOXYCYTOCHALASIN H

by

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Submitted in partial fulfillment of the requirements
For the degree of Doctor of Philosophy

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CASE WESTERN RESERVE UNIVERSITY
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Malcolm E. Kenney

(date) 09/13/2007

*We also certify that written approval has been obtained for any proprietary material contained therein.
Dedicated to my wife and my parents
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TMS  tetramethylsilane
Ts    \textit{p}-toluenesulfonyl
Iron Triarbonyl Promoted Cyclizations and Their Potential Application

in Total Synthesis of 18-Deoxycytochalasin H

Abstract

by

HUIKAI SUN

Dynamic diastereoselectivity during Fe(CO)$_3$ promoted [6 + 2] ene spirocyclization of amide complexes, having a chiral center on the pendant side chain, was investigated to show that the introduction of chirality can dictate the stereochemistry of the cyclization products by strong steric hindrance effect in reaction intermediates. One substrate underwent diastereoselective cyclization to afford two high optical purity products, which might be possible important intermediates for total synthesis of the natural product 18-deoxycytochalasin H. Furthermore, a stepwise second cyclization and a tandem double cyclization mediated by the Fe(CO)$_3$ moiety was investigated.

An intramolecular iron tricarbonyl 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.

An all-carbon double cyclization reaction was also investigated, but it could not proceed to give the anticipated cyclized products due to the difficulty in cyclohexadiene double bond migration before the cyclization step. An alternative strategy was designed and is still under investigation.
CHAPTER ONE

General Introduction
1.1 Preparation and Properties of Cyclohexadieneiron Tricarbonyl Complexes

The tricarbonyliron moiety [Fe(CO)₃] is coordinated to the 1,3-diene in a cyclohexadieneiron tricarbonyl complex and its derivatives as presented in Figure 1.1, and its presence makes these complexes useful intermediates in organic synthesis.

![Structure representation of cyclohexadieneiron tricarbonyl complex](image)

Figure 1.1 Structure representation of cyclohexadieneiron tricarbonyl complex

These cyclohexadieneiron tricarbonyl complexes are readily accessible by a direct reaction of conjugated or isolated diene compounds with commercially available iron pentacarbonyl at elevated temperature.⁴⁻⁶ An alternative method is to treat 1,3-dienes with nonacarboyndiiron (Fe₅(CO)₉) or dodecacarbonyltriiiron (Fe₃(CO)₁₂) under milder conditions, which has advantages for complexation of some sensitive dienes.⁴ Some efficient transfer reagents, like tricarbonyl[η⁴-1-oxa-1,3-diene]iron and tricarbonyl[η⁴-1-aza-1,3-diene]iron complexes, have also been developed to serve as a source of the tricarbonyliron moiety that can be used under mild conditions.⁵⁻⁷ The introduction of the tricarbonyliron group also introduces asymmetry to a planar diene with appropriate substitution, but the above methods, in most cases, afford only racemic products. Some enantioselective complexations have been reported based on some special diene substrates.⁸

The tricarbonyliron moiety can be used as a directing group to lead to stereoselectivity during transformations of functional groups,⁴⁻⁹ and can also be used as a
protecting group for some transformations, which makes the conjugated diene inert to many reaction conditions such as Dibal reduction, hydroboration, hydration, osmylation, hydrogenation, epoxidation and cyclopropanation.\textsuperscript{10-12}

The presence of the tricarbonyliron group also increases the electrophility of the conjugated diene, and complexed dienes react with a variety of carbanion nucleophiles at low temperature, followed by appropriate workup to afford several demetallated monoolefin regioisomers as products (eq 1.1).\textsuperscript{13-16}

\begin{equation}
\begin{array}{c}
\text{Fe(CO)}_3 \\
\text{Li}^+ \\
\text{CN} \\
\text{THF/HMPA} \\
\cdot 78 \degree \text{C} \\
\text{CF}_3\text{COOH} \\
\end{array}
\quad \begin{array}{c}
\text{CN} \\
\text{87\%} \\
\text{CN} \\
\text{9\%} \\
\text{CN} \\
\text{4\%} \\
\end{array}
\end{equation}

In addition, Friedel-Crafts acetylation has been reported to occur by treating cyclohexadiene-iron tricarbonyl complex with acetyl chloride in the presence of aluminum chloride (eq 1.2).\textsuperscript{17}

\begin{equation}
\begin{array}{c}
\text{Fe(CO)}_3 \\
\text{AlCl}_3, \text{CH}_2\text{Cl}_2 \\
\text{MeCOCl} \\
\text{35\%, endo:exo/1:4} \\
\end{array}
\quad \begin{array}{c}
\text{(OC)}_3\text{Fe} \\
\text{endo} \\
\text{(OC)}_3\text{Fe} \\
\text{COMe} \\
\text{endo} \\
\text{(OC)}_3\text{Fe} \\
\text{exo} \\
\text{COMe} \\
\text{exo} \\
\end{array}
\end{equation}
1.2 Construction of Quaternary Carbon Centers Using Cationic Cyclohexadienyliron Tricarbonyl Complexes.

Compared with the properties and the reactivity of cyclohexadieneiron tricarbonyl complexes mentioned above, cationic cyclohexadienyliron tricarbonyl complexes are more reactive electrophiles and have more extensive applications in organic synthesis.

Cyclohexadienyliron tricarbonyl complexes can be readily obtained by treating the corresponding cyclohexadieneiron tricarbonyl complexes with the hydride abstracting reagent, triphenylmethyl tetrafluoroborate,\(^2, 10, 18-21\) to provide a water-soluble cationic salt \(1.2a\), or with triphenylmethyl hexafluorophosphate to give the corresponding water-insoluble salt \(1.2b\) quantitatively as shown in Scheme 1.1.\(^{15}\) Excellent regioselectivity can be achieved for complexed dienes with substituents on the cyclohexadiene ring (complexes \(1.4a/b, 1.10\) and \(1.13\)), which depends on electronic properties and steric effect of the substituents.\(^{22}\) Treatment of methoxy substituted complexed dienes with strong acid followed by ion exchange with ammonium hexafluorophosphonate can also afford the corresponding cationic salts (conversion of \(1.3a/b\) to \(1.2a\)).\(^{23}\) Oxidation of complexed dienes (\(1.1\) and \(1.9\) in Scheme 1.1) with thallium (III) tris(trifluoroacetate) at rt or DDQ at -78 °C in the presence of tetrafluoroboric acid is another good alternative to hydride abstracting reagents, especially for some cyclohexadiene complex derivatives, from which much better yields can be obtained.\(^{24}\)
Scheme 1.1 Preparation of cyclohexadienyliniron tricarbonyl complexes

These cyclohexadienyliniron tricarbonyl salts can react with a wide variety of nucleophiles including amides (eq 1.3),\textsuperscript{19} amines,\textsuperscript{25-27} carbanion salts (eq 1.4, 1.5),\textsuperscript{28-31}
alkoxides, sodium cyanide, aqueous sodium carbonate,\(^3\) pyridine derivatives,\(^32\) fluoride\(^{33}\) and trialkylphosphines.\(^{34}\) All these reactions occur stereospecifically on the face opposite to the \(\text{Fe(CO)}_3\) group and regioselectively (controlled by substituents) as exemplified in eq 1.4. Reactions of cationic dienyl salts with carbon nucleophiles afford a useful method to form carbon-carbon bonds, especially to construct a quaternary carbon center (eq 1.5). The resulting complexed products can be readily demetallated by treatment with trimethylamine \(\text{N-oxide}^{35}\) or copper (II) chloride\(^{10}\) to give the corresponding cyclohexadiene derivatives.

\[
\begin{align*}
\text{Fe(CO)}_3 &+ \text{BF}_4^- \\
\text{1.2a} &\xrightarrow{\text{NaCO}_aq, \text{MeCN, rt}, 83\%} \text{Fe(CO)}_3(\text{OC})_3 \text{Fe} + \text{NH}_2\text{Boc} \\
\end{align*}
\]

\[
\begin{align*}
\text{Fe(CO)}_3 &+ \text{PF}_6^- \\
\text{1.13} &\xrightarrow{\text{Me}_2\text{CuLi, THF, 0 oC}} \text{60\%} \text{Fe(CO)}_3 + 5\% \text{Fe(CO)}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} &+ \text{PO}_3\text{Me}^- \\
\text{1.13} &\xrightarrow{\text{THF, 100\%}} \text{MeO} \text{PO}_3\text{Me} \\
\end{align*}
\]

The stereospecific construction of a quaternary carbon center by using these cationic dienyl complexes has been applied to the total synthesis of many natural products, including steroids,\(^{36,\, 37}\) aspidosperma alkaloids,\(^{38-40}\) aphidicolanes,\(^{36,\, 41}\) trichothecenes\(^{42-44}\) and their analogs.\(^{45,\, 46}\) Especially, the application of this methodology afforded the most efficient synthesis of trichodermol (1.15) with the shortest pathway and
the highest overall yield as illustrated in Scheme 1.2. The Fe(CO)₃ moiety functions as a stabilizing group for the cation, a stereodirecting group for the anti addition of the nucleophile and a protecting group for the diene.

Scheme 1.2 Synthesis of trichodermol using organoiron chemistry

However, attempts to synthesize more complex trichothecenes failed, such as verrucarol (1.17) and calonectrin (1.18). Retrosynthetic analysis shows cationic dienyl complexes 1.19 and 1.20 are potential intermediates for synthesis of 1.17 and 1.18 via this organoiron methodology as illustrated in Scheme 1.3. Unfortunately, attempted conversions of 1.21 to 1.19 and 1.22 to 1.20 by hydride abstraction were unsuccessful.
1.3 Iron Promoted [6+2] Ene Type of Spirocyclization

Considering the aforementioned negative observation, new methodologies to construct quaternary carbon centers using these organoiron intermediates were investigated and developed. The first strategy was to explore the reactivity of cyclohexadienyliron complex 1.23 with zinc dust as shown in Scheme 1.4.\textsuperscript{50} The formation of dimerized product 1.25, presumably via free radical intermediate 1.24, encouraged Pearson and Zettler to design a new cyclohexadienyliron complex substrate 1.27 with pendant double bonds, which they expected could undergo an intramolecular spirocyclization. The reaction of dienyliron complex 1.27 with zinc dust occurred to furnish spirocyclic product 1.28 (Scheme 1.5), but in low yield, which prompted further studies on new reaction conditions or even new methods.
Green and coworkers reported cyclohexadieneiron tricarbonyl reacted with polyhalogenated or polycyano-substituted alkenes like 1.29 under photochemical conditions to provide π-allyl complexes such as 1.30 (eq 1.6).\textsuperscript{51, 52} This intermolecular reaction is limited to highly electron deficient alkenes and so far its products have not been converted to useful organic molecules.
Table 1.1 Iron promoted [6+2] ene type of spirocyclization

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Based on the results mentioned above, an iron promoted intramolecular diene-ene coupling reaction was developed by using cyclohexadieneiron tricarbonyl complexes with a pendant olefin as substrates (1.31a-n), which can be amide, ester, thioester or ketone derivatives.53-56

This cyclization reaction furnished spirocyclic products 1.32a-n under either thermal conditions (CO atmosphere, n-Bu₂O, 140 °C) or photothermal conditions (CO atmosphere, 350 nm UV, benzene, reflux) as shown in Table 1.1. It turns out that amide derivatives are the best substrates for formation of a 5-membered ring (1.32a-c).53 Reactions with formation of a 6-membered ring generally gave the expected products in poorer yields (1.32d-g).56 The spirocyclization of ester, thioester and ketone derivatives were limited to substrates with a very low degree of substitution on the pendant olefin (1.31h-n),53-55 and thioester derivatives underwent spirocyclization in better yields under photothermal conditions than under thermal conditions.

The lack of reactivity for ester and thioester derivatives was attributed to steric effects.53, 54 A high degree of substitution on the pendant olefin increased the steric hindrance effect during coordination of a 16-electron iron intermediate to the substituted double bond, which finally leads to cyclization in low yields. The low reactivity was also rationalized in terms of stereoelectronic effects. Esters and thioesters exist in two isomeric forms Z (orbital interaction structure A) and E (orbital interaction structure B) as represented in Figure 1.2. Both conformations Z and E are stabilized by delocalization of the lone pair of the ester (or thioester) through the carbonyl group (primary electronic effect) and a n-σ* interaction between a lone pair of the carbonyl oxygen and the σ* orbital of the C-O (or C-S) bond (secondary electronic effect, A and B in Figure 1.2).57
Figure 1.2 Orbital interactions for ester, thioester and amide substrates

The Z conformation is further stabilized by another secondary electronic effect between the lone pair of the ester oxygen or sulfur oriented antiperiplanar to the CO bond and the σ* orbital of the CO carbonyl bond (A in Figure 1.2). As a result, esters and
thioesters adopt preferentially the $Z$ conformation, which is unfavorable for the spirocyclization and there is a high energy barrier for its conversion to the $E$ conformation, the favorable one for the spirocyclization.

In the case of amide substrates, only the primary and secondary electronic effects exist in both conformers (C and D in Figure 1.2), so amide derivatives adopt preferentially the less sterically hindered conformation 1.33a, which is the favorable one for spirocyclization. This conformational preference for amides is predominantly controlled by the steric assistance effect from a bulky phenyl group instead of the stereoelectronic effect. The low reactivity of ketone substrates can also be explained by the lack of this steric assistance effect, so their more stable conformations are unfavorable for the spirocyclization.

Studies on X-ray structures of some spirocompounds obtained from this intramolecular spirocyclization$^{53, 54}$ and the work of Kerber at al. using a $^{13}$CO atmosphere$^{58}$ indicated that the first step of this reaction is the disengagement of one CO ligand from the iron complex substrate and the formation of the new carbon-carbon bond is syn to the Fe(CO)$_3$ group. A mechanism was proposed as shown in Scheme 1.6. Under either thermal or photothermal conditions, one carbonyl ligand is dissociated from the iron atom in substrate 1.34 to lead to a 16e iron complex 1.35 with a vacant coordination site, which can be occupied by $\eta^2$ coordination of the iron atom with the carbon-carbon double bond to form intermediate 1.36. Subsequent cyclization gives $\pi$ allyl complex 1.37 followed by hydride migration to afford 1.38. Then reductive elimination followed by recapture of one carbonyl group affords the final product 1.40, which can be converted to regioisomer 1.41 via a postcyclization rearrangement.
Scheme 1.6 Proposed mechanism of the spirocyclization

The stereochemistry at the C4 position is determined by the conformation of the metallabicyclooctane-like intermediate 1.37, which is formed exclusively as the cis $\eta^3$-metallacycle as illustrated in Figure 1.3.

Figure 1.3 Comparison of cis vs trans $\eta^3$-metallacycle intermediate
Actually, both spirocyclization products 1.40 and 1.41 (Scheme 1.6) are racemic as a result of iron mediated diene rearrangement in substrates 1.34 prior to cyclization (precyclization rearrangement) as shown in Scheme 1.7. Under cyclization conditions, 1.34a and 1.34b, a pair of enantiomers, are interconvertible via a hydrogen migration mechanism, a well-precedented phenomenon,\(^{59, 60}\) and give products 1.40a and 1.40b, respectively, a pair of enantiomers. Considering this precyclization racemization, generally, readily obtained racemic substrates were used during these spirocyclization reactions instead of their optically pure counterparts. The formation of regioisomer 1.41 (Scheme 1.6) can be explained by a postcyclization rearrangement as shown in Scheme 1.8.

![Scheme 1.7 Racemization due to a precyclization rearrangement](image-url)
In all, this iron promoted spirocyclization of simple substrates can afford two pairs of enantiomers 1.40a/b and 1.41a/b as products due to both precyclization and postcyclization rearrangements as outlined in Scheme 1.9.

In order to apply this methodology to organic synthesis, methods to circumvent the precyclization and the postcyclization rearrangements have been developed. It has been found that rearrangements can be controlled during this intramolecular spirocyclization.
by using some substrates that incorporate a substituent at the C5 position of the
cyclohexadiene ring, such as enantiomerically pure substrates 1.43 and 1.46 shown in
Scheme 1.10.53 The electronic property of each substituent determines the regiochemistry
of the diene and the stereoselectivity for the formation of the new carbon-carbon bond in
cyclization products 1.44 and 1.47, which have opposite stereochemistry at the C4
position.

Scheme 1.10 Control of the rearrangements using C5-substitution

Attaching a methoxy substituent to the C3 position of the cyclohexadiene ring can
also efficiently avoid the precyclization rearrangement, which has been proved by
subjecting substrate 1.48 to thermal cyclization conditions to give no diene migration
products (eq 1.7).61 Although the spirocyclization of substrate 1.49 still afforded two
regioisomers 1.50a/b as products, these two isomers could be converted to a single
cyclohexenone molecule 1.52 through subsequent demetallation followed by hydrolysis
under acidic conditions (Scheme 1.11). Thus the regioisomerization problem caused by postcyclization rearrangement is also solved.

Scheme 1.11 Control of the rearrangements using C3-methoxy group

A more convenient and useful reaction was developed, which was based on readily obtained substrate 1.53 having a pendant conjugated diene as shown in Scheme 1.12. Subjection of 1.53 to thermal cyclization conditions afforded a single tricyclic molecule 1.55 as the sole product with excellent stereocontrol. This iron promoted tandem double cyclization was expected to proceed via simple cyclization products 1.54a/b as intermediates followed by an in situ second cyclization. Intermediate 1.54b is
unfavorable for the second cyclization, but is converted to favorable intermediate 1.54a via equilibrium under the reaction conditions.

Scheme 1.12 Iron promoted tandem double cyclization

Cyclization of substrate 1.56 can also occur under thermal spirocyclization conditions in the presence of 1-1.5 equivalents of iron pentacarbonyl as illustrated in Scheme 1.13. Firstly, substrate 1.56 is converted to intermediate 1.57 via an iron pentacarbonyl mediated double bond migration, and then an in situ cyclization reaction furnished a single racemic product 1.58. A one-pot procedure was also developed to convert uncomplexed substrate 1.59 to a single complexed bicyclic product 1.60 under the catalysis of iron pentacarbonyl. The postcyclization rearrangement was also avoided during this cyclization reaction.
The objective of this thesis is to further explore the stereochemistry of [6+2] ene-type cyclization reactions to obtain optically pure products, to expand the scope of this cyclization reaction, and to seek applications in the total synthesis of natural products.
1.4 Literature References


CHAPTER TWO

Dynamic Diastereoselectivity During Iron Carbonyl Mediated Spirocyclization Reactions and Its Potential Application to the Total Synthesis of 18-Deoxycytochalasin H
2.1 Dynamic Diastereoselectivity During Iron Carbonyl Mediated Spirocyclization Reactions and Their Potential Application to the Total Synthesis of 18-Deoxycytochalasin H

As mentioned earlier, an Fe(CO)\(_3\) promoted [6+2] ene type of cyclization was developed in our laboratory to provide spirocyclic lactams as final products.\(^1\) While several approaches have been developed to control the loss of regio and/or stereochemistry caused by postcyclization diene rearrangement, none of them adequately addresses the racemization caused by precyclization interconversion of two substrate enantiomers.\(^2\)-\(^4\) To a great extent, the application of this methodology to organic synthesis is limited by all the above disadvantages. Some previous work also showed precyclization racemization could be avoided by introduction of substituents on the cyclohexadienyl ring, but this requires an often difficult optical resolution of the starting material.\(^5\),\(^6\) This inspired us to further explore the stereochemistry of this cyclization reaction to obtain optically pure products.

Generally, racemic starting materials, including two enantiomers which behave identically, are used in this [6+2] ene type of spirocyclization reaction, so all products are also racemic. Even if only one enantiomer is used, this reaction will still give racemic products due to an iron promoted precyclization diene migration which can lead to formation of the corresponding enantiomer. If a chiral center is introduced on the pendant olefinic side chain, the starting materials become two diastereomers and should undergo cyclization at different rates. Most likely, these different rates are determined by different steric hindrance effects from the introduction of the chiral element in two reaction
intermediates. Under certain conditions, if we can induce one diastereomer to cyclize, but not the other, which instead can be converted to the former via an iron-promoted diene migration, we would obtain only one single enantiomerically pure product in the absence of postcyclization isomerization. In order to test this idea, some preliminary work has been done by a previous graduate student to give some positive results as expected, but all reaction conditions were not optimized and most compounds had not been fully characterized.

My research work continued this study on diastereoselectivity during this iron-promoted [6+2] ene type of spirocyclization. Considering the ready accessibility of starting materials, substrates 2.6a and 2.6b were designed and prepared starting with the known aldehyde 2.2 (Scheme 2.1), which was derived in 59% yield over four steps from L-phenylalanine (2.1). Unsaturated ester E-2.3 was obtained in 53% yield from aldehyde 2.2 through a Horner-Wadsworth-Emmons reaction, accompanied by formation of the Z isomer (E:Z/1.4:1), which was separated chromatographically. Amine deprotection occurred by treatment with TFA to afford 2.4 quantitatively, which was coupled with racemic complexed acid 2.5 to afford the expected substrates, two diastereomers 2.6a and 2.6b, in 82% combined yield.
Scheme 2.1 Synthesis of substrates 2.6a and 2.6b

Heating substrates 2.6a and 2.6b in n-Bu₂O under a CO atmosphere at 142 °C generated several inseparable products which could not be fully characterized by ¹H NMR spectroscopy. Without further purification, the mixture of these products was demetallated with CuCl₂¹⁰ followed by hydrogenation over 10% Pd/C to deliver two major products, 2.9a and 2.9b in a ratio of 1.5 to 1, in 50% isolated yield over three steps. Compounds 2.9a and 2.9b were easily characterized and the stereochemistry of 2.9a was determined from the NOE difference NMR spectra as shown in Figure 2.1. A strong NOE (5.14%) between one H₄ and H₄ and very weak NOEs (< 0.5%) between H₃ and H₄ indicate that H₃ and H₄ are trans on the lactam ring.
Scheme 2.2 Spirocyclization of substrates 2.6a and 2.6b

(a) n-Bu$_2$O, CO, 142 °C. (b) Sat. CuCl$_2$ in EtOH. (c) 10% Pd/C, H$_2$, MeOH, 50% yield over three steps.
Based on our understanding of the likely mechanism, the spirocyclization of substrates 2.6a and 2.6b is outlined in Scheme 2.2, and involves reaction intermediates 2.7a and 2.7b. Since both demetallation and hydrogenation were complete, the ratio of direct cyclization products 2.8a/a’ over 2.8b/b’ can also be deduced as 1.5 to 1 from the ratio of 2.9a over 2.9b. Considering the difference in configurations of intermediates 2.7a and 2.7b, we speculate that the stereoselectivity of this reaction is due to different steric hindrance effects in these structures. In intermediate 2.7b, eclipsed Ha and Bn experience a repulsive interaction, which is relieved in 2.7a because H_a and H_b are now eclipsed. Therefore, the spirocyclization reaction favors the pathway through intermediate 2.7a, and equilibration between 2.6a and 2.6b (via metal-mediated H-shifts) gives rise to 2.8a as the major product. Even though the stereoselectivity was not as good as we hoped, these results encouraged us to investigate this reaction further.

Replacement of H_a with a sterically more demanding substituent should introduce greater steric hindrance in intermediate 2.7b, which may lead to much better stereocontrol if our rationale for the selectivity is correct. Based on this proposition,
substrates 2.15a and 2.15b were prepared (Scheme 2.3) starting with aldehyde 2.2 via a Horner-Wadsworth-Emmons reaction. Several reaction conditions were examined for conversion of aldehyde 2.2 to compounds 2.10 and 2.11. Method A (ethyl 2-(diethoxyphosphoryl)propionate, n-BuLi, THF, -78 °C) \textsuperscript{7} furnished 67% of 2.10 and 14% of 2.11, and further Boc deprotection of compound 2.10 gave rise to free secondary amine 2.13 with 94% ee, which was determined by converting amine 2.13 to Mosher amides 2.14a and 2.14b. Method B (ethyl 2-(diethoxyphosphoryl)propionate, LiCl, DBU, MeCN, 0 °C) \textsuperscript{11} afforded 65% and 13% of 2.10 and 2.11, respectively, however, the deprotection product 2.13 showed only 74% ee. The milder method C ((carbethoxyethylidene)triphenylphosphorane, CH\textsubscript{2}Cl\textsubscript{2}) \textsuperscript{12, 13} gave even poorer ee, 71%, for compound 2.13. So, finally, secondary amine 2.13 prepared using method A was taken on to the coupling reaction with racemic complexed acid 2.5 to provide the desired substrates 2.15a and 2.15b. It is noteworthy that deprotection of compound 2.11 spontaneously afforded lactam 2.12 instead of the corresponding free secondary amine (as expected), which is also the reason why only substrates 2.15a and 2.15b with pendant E olefin were prepared via this route. The analogous Z olefins were obtained by a different route, described later.
Scheme 2.3 Preparation of substrates 2.15a and 2.15b

As mentioned above, the optical purity of free amine 2.13 was determined by conversion to Mosher amides 2.14a and 2.14b. The \(^1\)H NMR spectrum of 2.14a/b showed 4 isomers in different proportions, which made optical purity measurement difficult because of the uncertainty concerning the presence of amide resonance rotamers of 2.14a and 2.14b. To confirm this, racemic amine 2.13 was prepared (Scheme 2.4).
Firstly, aldehyde 2.2 was racemized by treatment with DBU in the presence of LiCl in acetonitrile, confirmed by the change of specific rotation from -131 to 0. Subsequent subjection of racemic 2.2 to method B conditions described in Scheme 2.3, followed by Boc-removal with TFA and amidation with Mosher’s chloride, provided two chromatographically separable products 2.14a and 2.14b in 1:1 ratio. Variable temperature $^1$H NMR spectra confirmed the presence of rotamers for both of them. Comparison with these $^1$H NMR spectra allowed determination of the optical purity of amines 2.13 prepared earlier.
Scheme 2.5 Spirocyclization of substrates 2.15a and 2.15b
With substrates 2.15a and 2.15b in hand, their spirocyclization was investigated under thermal conditions (in n-Bu₂O, reflux and under CO atmosphere). Gratifyingly, only spirocyclic lactams 2.17a and 2.17a′ were isolated and no compounds 2.17b or 2.17b′ could be detected in the \(^1\)H NMR spectrum of the crude mixture of products (Scheme 2.5). These results indicate that the increased steric hindrance between methyl and benzyl groups in 2.16b suppresses formation of this intermediate, and spirocyclization proceeds only via intermediate 2.16a. Equilibration between 2.15a and 2.15b under these reaction conditions channels the conversion through 2.16a to afford only 2.17a which subsequently rearranges to afford the mixture of 2.17a and 2.17a′. These results further support our rationale for the diastereoselectivity of this type of spirocyclization. However, only 35% of expected products 2.17a and 2.17a′ were obtained reproducibly under thermal conditions. Major side products were characterized to be 2.19a and 2.19b in 9:1 ratio and in 36% combined yield, which might be derived from demetallated intermediate 2.18 followed by an immediate intramolecular Diels-Alder reaction. Compounds 2.19a and 2.19b were confirmed to be products of endo/exo cycloaddition by converting them to a single hydrogenation product, 2.20. After a series of optimization experiments, photothermal reaction conditions (benzene, CO, 85 °C, 350 nm) afforded the best yield, 67%, for compounds 2.17a and 2.17a′ with formation of their demetallation products 2.21a/b in 4% yield, and Diels-Alder products 2.19a and 2.19b in 12% yield. Experimental results showed that rigorous deoxygenation (Freeze-Pump-Thaw) and fully wrapping all joints of the reaction apparatus is very important to the reaction yield. Then demetallation with copper (II) chloride in ethanol followed by hydrogenation converted products 2.17a and 2.17a′ to the same compound 2.22, whose
optical purity was determined (ee > 94%) through reduction with LiBH₄, followed by esterification with Mosher’s chloride to furnish compound 2.23. Thus, no stereochemical leakage occurs throughout the reaction sequence, and the cyclization event itself is stereospecific.

Scheme 2.6 Investigation of Diels-Alder reaction based on substrate 2.15a/b

As previously mentioned, major side products during the reaction in Scheme 2.5 were two [4+2] cycloaddition products in 9:1 ratio. Treatment of 2.15a and 2.15b with copper(II) chloride at room temperature also gave compounds 2.19a and 2.19b in 9:1 ratio and in 86% yield (Scheme 2.6). However, we did not have any proof whether this cyclization might be promoted by the Fe(CO)₃ moiety or an iron catalyst formed during demetallation, or derived directly from demetallated compound 2.18, via a simple intramolecular Diels-Alder reaction. Attempted synthesis of compound 2.18 via the acyl
mesylate from acid 2.26\textsuperscript{14} and amine 2.13 afforded only 2.19\textsubscript{a} and 2.19\textsubscript{b} in 9:1 ratio and in 84\% yield. This result confirms that uncomplexed compound 2.18 undergoes spontaneous intramolecular Diels-Alder reaction as soon as it is formed. More importantly, it further confirms the need to use diene-Fe(CO)\textsubscript{3} complexes stoichiometrically, because coordination of the diene with Fe(CO)\textsubscript{3} prevents Diels-Alder cycloaddition and allows the substrate to follow a [6+2] ene pathway, thereby increasing molecular diversity that is accessible from such materials.

Scheme 2.7 A possible approach to 18-deoxycytochalasin H

18-Deoxycytochalasin H (2.27 in Scheme 2.7) is a potent HIV-1 protease inhibitor and related compounds can regulate plant growth.\textsuperscript{15} The presence of a densely substituted spirolactam skeleton in its structure attracted our interest because this type of subunit is produced from our ene type cyclization. One can envision 18-deoxycytochalasin H to be accessible from an intermediate such as 2.28 by further
manipulation of the cyclohexadiene, and 2.28 might in turn be available from 2.29a/b. Alternatively, 2.28 might also be available from 2.30a, which can be obtained from demetallation of 2.29a, via a series of transformations. As intermediates for total synthesis, compounds 2.30a and 2.29a/b require S, S, S chirality at C3, C4 and C11, respectively. However, compounds 2.17a and 2.17a', prepared from the spirocyclization reaction in Scheme 2.5, show one different chiral center, R, at C11. Based upon our understanding of the mechanism of this [6+2] ene spirocyclization reaction, intermediate 2.30a with the same chirality as 18-deoxycytochalasin H, or its complexed precursors, 2.29a and 2.29b, should be accessible from precursors 2.31 having a pendant trisubstituted Z olefin.

Since deprotection of compound 2.11 resulted in spontaneous cyclization to give lactam 2.12 instead of a free secondary amine (Scheme 2.3), substrates 2.31a and 2.31b were prepared by a different route starting with methyl L-phenylalanine hydrochloride (2.32). Known secondary amine 2.33 was prepared according to a published procedure by treating 2.32 with sodium hydroxide, followed by anisaldehyde and a catalytic amount of acetic acid, and then reduction with sodium borohydride (Scheme 2.8). The optical purity of secondary amine 2.33 (ee = 100%) was also determined by conversion to the Mosher amide 2.34a. As far as we are aware, the optical purity of 2.33 obtained by this route has not previously been measured.

![Scheme 2.8 Preparation of secondary amine 2.33](image-url)
In order to determine the optical purity of amine 2.33, its racemic counterpart needed to be prepared. Considering the small specific rotation value of 2.33, its hydrochloride salt 2.35 was prepared and used as a reference for the degree of racemization (Scheme 2.9). Treatment of 2.35 with sodium methoxide in methanol led to racemic aminoacid 2.36 in only 45% yield due to the difficulty in extracting the product from the aqueous work-up solution. Considering that the aim of this synthesis was to obtain a reference for optical purity measurement, the reaction conditions were not further optimized. Subsequent esterification gave 2.35 with a specific rotation value of -1.3, and the comparison with the specific rotation value of 2.35 (+26) indicated the racemization was complete (the small negative rotation is likely due to instrument error). Finally, a 1:1 mixture of 2.34a and 2.34b, as references, was obtained by treating racemic 2.35 with Mosher’s chloride.

![Chemical diagram]

**Scheme 2.9** Determination of optical purity of amine 2.33

Coupling of amine 2.33 with complexed acid 2.5 led to amide 2.37, as two diastereomers, which could be converted in 56% yield over two steps to substrates 2.31a
and 2.31b through DIBAl-H reduction and a Still-Gennari phosphonate olefination reaction (Scheme 2.10).\textsuperscript{18, 19}

\[ \text{BnCO}_2\text{Me} \xrightarrow{2.5, CH}_2\text{Cl}_2, \text{DIEA, MsCl, 0 °C then 2.33, 40 °C} \quad 75\% \]

\[ \text{DIBAl-H, Et}_2\text{O} \xrightarrow{-78 °C, 80\%} \]

\[ \text{BnFe(CO)}_3(\text{OC})_3\text{FeCO}_2\text{Et} \xrightarrow{2.39, \text{KH, THF}} -78 °C, 70\% \]

\[ \xrightarrow{\text{Benzene, CO}_2, \text{CO, 350 nm, 85 °C}} 72\% \]

\[ \xrightarrow{\text{Sat. CuCl}_2 \text{in EtOH}} 80\% \]

\[ \xrightarrow{10\% \text{Pd/C}, \text{H}_2, \text{MeOH}, 84\%} \]

\[ \xrightarrow{\text{LiBH}_4, \text{Et}_2\text{O}} \]

\[ \text{BnOMTPA} \xrightarrow{\text{Mosher's chloride}} \text{DIEA, benzene, 80 °C} \quad 70\% \text{ over two steps} \]

\[ \text{de} > 86\% \]

\textbf{Scheme 2.10} Preparation and spirocyclization reaction of substrates 2.31a/b
As expected, subjection of substrates 2.31a and 2.31b to photothermal conditions furnished spirocyclic lactams 2.29a and 2.29b, two diastereomers, as the only [6+2] ene spirocyclization products in 72% yield (Scheme 2.10). In this reaction, rigorous deoxygenation (Freeze-Pump-Thaw) and fully wrapping all joints of the reaction apparatus is also very important to the reaction yield. As before, excellent dynamic diastereoselectivity resulted from different steric hindrance in the two diastereomeric reaction intermediates. Compounds 2.17a and 2.17a’ were also isolated (4%, combined yield), which were attributed to formation of substrates 2.15a and 2.15b through Z double bond isomerization of 2.31a and 2.31b under the reaction conditions.

Compounds 2.29a and 2.29b were demetallated with copper chloride in ethanol to afford decomplexed dienes 2.30a and 2.30b in 80% yield, which were hydrogenated to give a single compound 2.40 in 84% yield. We attempted to determine the optical purity of compound 2.40 by conversion to the Mosher ester 2.41, $^1$H NMR of which indicated its diastereomeric purity to be greater than 86%, but this could not be determined accurately. Based on analysis of the reactions in Scheme 2.10, the most likely point for partial racemization to occur is during conversion of aldehyde 2.38 to substrates 2.31a and 2.31b in the presence of a strong base, KH, and not during the spirocyclization reaction. Consequently, any future work directed at applying this transformation in synthesis should address this problem.

Diels-Alder reaction products were also formed during the photothermal spirocyclization reaction through decomplexed intermediate 2.42 to give rise to compound 2.43, in this case in 14% yield (structures are in Scheme 2.11). When substrates 2.31a and 2.31b were subjected to demetallation (sat. CuCl$_2$ in EtOH), the
product 2.42 underwent spontaneous Diels-Alder reaction to provide 2.43 as a single stereoisomer in 81% yield. This also confirmed that the [6+2] ene spirocyclization reaction, described in Scheme 2.10, is only feasible if the diene is masked by complexation with Fe(CO)₃, and is not directly accessible from 2.42 by any catalytic method.

(a) Benzene, CO, 350 nm, 85 °C, 14%, side product from spirocyclization. (b) Sat. CuCl₂ in EtOH, 81%.

**Scheme 2.11** Diels-Alder reaction from substrates 2.31a and 2.31b

The stereochemistry at C3 and C4 in compounds 2.30a and 2.30b was confirmed by NOESY as shown in Figure 2.2. Observation of NOEs between H₃ and Me₆, and between H₄ and H₆, and no NOE between H₃ and H₄ indicate that H₃ and H₄ are *trans* on the lactam ring of 2.30a. A NOE between H₃ and H₆ determines the position of the diene
double bonds on the cyclohexadiene ring. The stereochemistry of $2.30b$ is supported by a NOE between $H_3$ and $Me_b$. The chirality of $C_b$ on the side chain of this spirocyclic structure was assigned to be $S$ in both compounds, based on the reaction mechanism, but could not be determined directly by NMR spectroscopy. However, this was confirmed by subsequent experiments.

![Figure 2.2 Determination of the stereochemistry for compounds $2.30a$ and $2.30b$](image)

We also wanted to explore the possibility of a second cyclization reaction through introduction of a second double bond on the side chain. Substrates for this model study, $2.45a$ and $2.45b$ were prepared from spirocyclization products $2.29a$ and $2.29b$ through reduction of these esters to aldehydes $2.44a$ and $2.44b$ and subsequent Wittig olefination reaction (Scheme 2.12). Investigation of the $[6+2]$ ene-type cyclization of $2.45a/b$ showed that the best isolated yield, 52% with 25% of recovered starting materials, was obtained using more forcing photothermal conditions in mesitylene at 160 °C for 9 h, affording $2.46$ as the only characterizable product. Prolonged reaction time gave poorer yield, possibly due to decomposition of product $2.46$ at high temperature. Based on the
reaction mechanism, only substrate 2.45a can directly undergo cyclization to afford compound 2.46; however, substrate 2.45b is isomerized to 2.45a under thermal equilibration, and then undergoes cyclization to afford 2.46. Treatment of 2.46 with copper chloride in ethanol furnished demetallated compound 2.47 in 72% yield.

Scheme 2.12 Exploration of a second Fe(CO)\textsubscript{3} promoted cyclization

The stereochemistry of compound 2.47 was confirmed by 2D COSY and NOESY spectra (Figure 2.3). A strong NOE was observed between Me\textsubscript{5a} protons and H\textsubscript{3}, H\textsubscript{4} and both of H\textsubscript{3a} and H\textsubscript{3b}, but no NOE was observed between H\textsubscript{3} and H\textsubscript{5}, which indicated the stereochemical relationship is trans for H\textsubscript{3} with H\textsubscript{4}, and cis for H\textsubscript{4} with H\textsubscript{5}. Since the chirality of C7 is fixed by the reaction mechanism via alkene coordination to Fe during
the reaction, the stereochemistry at C6 was confirmed by the cis relationship between H6 and H7, which results in a strong NOE between them, and no NOE between H7 and Me6a, while the latter showed strong NOE with H8. This assignment also confirms the S stereochemistry assigned for the side chain propionate moiety of 2.30a/b discussed earlier. While 2.47 is clearly not convertible to 2.28, and therefore is not a viable intermediate en route to 18-deoxycytochalasin H, the success of this tandem sequence provides the impetus for development of a more appropriate homologous reaction.

![Diagram of compound 2.47 with NOEs](image)

**Figure 2.3** Determination of the stereochemistry for compound 2.47

The success of the above stepwise second Fe(CO)3 promoted cyclization encouraged us to explore a tandem double cyclization based on a substrate with a conjugated diene in the pendant side chain. The involvement of the iron complex in multiple steps described in Schemes 2.10 and 2.12 might be avoided through this tandem approach. For this preliminary study, substrate 2.52 was prepared starting with intermediate 2.11, which was the side product during preparation of 2.10. Reduction of
2.11 with DIBAl-H at rt led to alcohol 2.48 in 92% yield. Subsequent attempts to oxidize allylic alcohol 2.48 to Z - α, β unsaturated aldehyde 2.49 with MnO2, PCC, Dess Martin reagent or Swern oxidation were compromised because double bond isomerization occurred to give rise to E - α, β unsaturated aldehyde which was inseparable from 2.49. Recently, a new method for oxidation of allylic alcohols to aldehydes was developed in our laboratory by using Fe(CO)4PPh3 as catalyst and Me3NO as oxidant in benzene solution.20 Subjection of 2.48 to this reaction afforded aldehyde 2.49 in 71% yield without any formation of E isomer. Diene 2.50 was obtained through Wittig methylenation, and subsequent Boc removal with Me3SiI gave rise to free secondary amine 2.51 in 53% yield,21 which was used in the next step without further purification. Finally, coupling of amine 2.51 with racemic complexed acid 2.5 furnished the desired substrate 2.52 as two diastereomers. Unfortunately, subjection of 2.52 to photothermal conditions in benzene provided only 10% of expected product 2.46, accompanied by many uncharacterized side products. Other attempts under different reaction conditions led to even poorer yield. Consequently, the better approach to these multicyclic structures is via the interrupted tandem sequence of Schemes 2.10 and 2.12.
Scheme 2.13 Investigation of a tandem double cyclization mediated by the Fe(CO)$_3$ moiety
2.2 Conclusions

The work described here has shown that spirocyclization using our iron-promoted [6+2] ene-type reaction can be used to produce densely substituted spirolactams in high optical purity, using a single stereogenic center as a control element. This procedure is akin to a dynamic kinetic resolution and allows a racemic mixture of planar chiral diene iron complexes such as 2.5 to be converted to a single enantiomer of a product such as 2.22 or 2.41.

A second ene-type cyclization allows the construction of a tricyclic structure, again with complete stereocontrol. Provided this second cyclization can be engineered to produce a six-membered ring as in structure 2.28 (rather than the five-membered ring from the present work), we envisioned that this technology can be used to produce the main structural features present in the 18-deoxycytochalasin H molecule. Studies to achieve that synthetic goal will be described in the next chapter.
2.3 Experimental Section

General Methods

All glassware used was oven dried (overnight at 140 °C) or flame dried prior to use. Organic solvents/reagents were purified prior to use as follows: THF, diethyl ether, benzene and toluene were freshly distilled from Na/benzophenone; CH₃CN and CH₂Cl₂ were distilled from CaH₂; n-Bu₂O was distilled from Na; All other solvents were used as purchased. Column chromatography was performed with silica gel (0.04-0.063 mm). Eluting solvents are reported as V/V percent mixture. All yields given refer to as isolated yields. Optical rotations were measured on a precision automated polarimeter. NMR spectra were recorded on a 200 MHz or 400 MHz spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane. HRMS experiments were performed on a high resolution magnetic sector mass spectrometer. Melting points are uncorrected.

**General procedure for the thermally induced cyclization.** The appropriate amide was dissolved in freshly distilled n-Bu₂O ether (0.02 mmol/mL) under argon in a dried glass round bottomed flask. The air in the solution was removed by 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 8-20 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, xylene 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 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 3-24 h under a balloon of CO. 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 demetallation. Method A: To the solution of complexed intermediate in benzene, was added trimethylamine oxide (30 equivalents). 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. CuCl₂ solution in EtOH (2.5 mL). The solution was stirred at rt for 18-24 h, then concentrated in vacuo. After water (4 mL) was added to the residue, the mixture was extracted with ether (3 mL x 3). The organic layer was washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The crude products were purified by preparative TLC or flash chromatography.
(4S, 2E)-Ethyl 4-[tert-butoxycarbonyl-(4-methoxybenzyl)amino]-5-phenylpent-2-enoate (2.3). To a solution of ethyl 2-(diethoxyphosphoryl)propanoate (0.51 g, 2.26 mmol) in THF (23 mL) under Ar at -78 °C, was slowly added n-BuLi (0.83 mL, 2.5 M in hexanes, 2.07 mmol) via a syringe. The reaction mixture was stirred at this temperature for 1 h. A solution of aldehyde 2.2 (0.70 g, 1.89 mmol) in THF (5.5 mL) was added, then the mixture was stirred at -78 °C for 3 h. After the temperature was allowed to rise to rt over 30 min, the reaction mixture was quenched with sat. aq. NH$_4$Cl (10 mL) and extracted with Et$_2$O (12 mL x 3). The combined organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Hex:EA/8:1) to provide 2.3 (0.44 g, 53%). $R_f = 0.70$ (Hex:EA/4:1). $[\alpha]_D^{25} = -53$ (c = 1.26, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.22-6.90 (7H), 6.74 (d, $J = 8.4$ Hz, 2H), 6.50-6.30 (br, 1H), 5.66 (d, $J = 11.2$ Hz, 1H), 5.50-5.20 (br, 1H), 4.40-4.15 (br, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 3.40-3.00 (br, 1H), 2.96-2.82 (m, 1H), 1.47 (s, 9H), 1.25 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.0, 158.8, 147.8, 138.2, 130.9, 129.6, 129.1, 128.5, 126.4, 119.4, 113.8, 60.3, 59.4, 57.5, 55.4, 52.5, 38.2, 28.8, 14.4. HRMS (FAB) calcd for MH$^+$ (C$_{26}$H$_{34}$NO$_5$) 440.2437, found, 440.2435. This reaction also afforded (4S, 2Z)-ethyl 4-[tert-butoxycarbonyl-(4-methoxybenzyl)amino]-5-phenylpent-2-enoate in 39% yield. $R_f = 0.75$ (Hex:EA/4:1). $[\alpha]_D^{25} = +97$ (c = 2.74, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24-7.06 (7H), 6.78 (d, $J = 8.8$ Hz, 2H), 5.80-5.60 (br, 1H), 4.65-4.20 (m, 2H), 4.15 (q, $J = 6.8$ Hz, 2H), 4.00-3.80 (br, 1H), 3.78 (s, 3H), 3.20-3.00 (br, 1H), 2.91 (dd, $J = 13.6$, 6.8 Hz, 1H), 1.44 (s, 9H), 1.25 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.4, 138.0,
129.4, 128.7, 126.8, 114.0, 60.6, 59.5, 55.5, 49.9, 28.6, 14.4. Some peaks were not recorded due to the presence of amide resonance rotamers. HRMS (FAB) calcd for MH$^+$ (C$_{26}$H$_{34}$NO$_5$) 440.2437, found, 440.2430.

(4S, 2E)-Ethyl 4-(4-methoxy-benzylamino)-5-phenylpent-2-enoate (2.4). Ester 2.3 (322 mg, 0.73 mmol) was dissolved in dry CH$_2$Cl$_2$ (3.8 mL) and cooled to 0 °C. TFA (1.9 mL) was added slowly to the reaction solution, which was then stirred at the same temperature for 1 h, quenched by aq sat NaHCO$_3$ solution at 0 °C (pH = 8-9), and extracted with CH$_2$Cl$_2$ (5 mL x 3). The combined organic layer was dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product 2.4 (236 mg, 96%) was used in the next reaction without further purification. $[\alpha]_D^{25} = -27$ (c = 1.18, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.30-7.04 (7H), 6.85 (dd, $J$ = 15.6, 7.6 Hz, 1H), 6.80 (dt, $J$ = 8.4, 1.6 Hz, 2H), 5.92 (dd, $J$ = 15.6, 0.8 Hz, 1H), 4.20 (q, $J$ = 7.2 Hz, 2H), 3.78 (s, 3H), 3.73, 3.51 (ABq, $J$ = 13.2 Hz, 2H), 3.48-3.44 (m, 1H), 2.85 (dd, $J$ = 14.4, 6.0 Hz, 1H), 2.76 (dd, $J$ = 13.6, 8.4 Hz, 1H), 1.43 (br, 1H), 1.30 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.6, 158.8, 150.4, 137.8, 132.2, 129.5, 129.3, 128.8, 126.9, 122.3, 114.0, 60.6, 59.9, 55.5, 51.0, 41.9, 14.5. HRMS (FAB) calcd for MH$^+$ (C$_{21}$H$_{26}$NO$_3$) 340.1913, found, 340.1918.

[4S, 2E]-ethyl 4-(N-(4-methoxy benzyl)cyclohexa-1,3-dienecarboxamido)-5-phenylpent-2-enoate|tricarbonyliron (2.6a
and 2.6b). To a solution of complexed carboxylic acid 2.5 (123 mg, 0.47 mmol) and
diisopropylethylamine (92 μL, 0.56 mmol) in freshly distilled CH₂Cl₂ (6.0 mL) under
argon at 0 °C, was quickly added methanesulfonyl chloride (47 μL, 0.60 mmol). Stirring
was continued at this temperature for 1 h. Diisopropylethylamine (169 μL, 1.02 mmol)
was added, followed by a solution of amine 2.4 (236 mg, 0.70 mmol) in freshly distilled
CH₂Cl₂ (2.0 mL). The temperature was allowed to reach rt and then the reaction mixture
was stirred for 24 h. After CH₂Cl₂ (15 mL) was added, the organic layer was washed with
1 N HCl (5 mL x 2) and brine (5 mL x 2), dried (Na₂SO₄), filtered and concentrated in
vacuo. Flash chromatography (Hex:EA/4:1) allowed partial separation of 2.6a and 2.6b
(223 mg, 82% combined yield). One diastereomer: Rf = 0.50 (Hex:EA/4:1). [α]D²⁵ = -29
(c = 0.84, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.25-7.05 (7H), 6.92 (br, 1H), 6.81 (dt,
J = 8.8, 2.0Hz, 2H), 6.16 (br, 1H), 5.56 (br, 1H), 5.28 (br, 1H), 4.42 (br, 1H), 4.13 (q, J =
7.2 Hz, 2H), 3.80 (s, 3H), 3.83-3.70 (m, 1H), 3.52-3.40 (2H), 3.05 (br, 1H), 1.92-1.62
(3H), 1.42-1.36 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 174.2,
166.2, 159.3, 146.0, 129.7, 128.9, 128.7, 126.9, 122.7, 114.4, 85.7, 70.8, 64.6, 62.1, 60.6,
55.5, 53.6, 38.0, 27.0, 23.9, 14.4. HRMS (FAB) calcd for MH⁺ (C₃₁H₃₂FeNO₇) 586.1528,
found, 586.1529. The other diastereomer: Rf = 0.51 (Hex:EA/4:1). [α]D²⁵ = -53 (c = 0.90,
CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.27-7.05 (8H), 6.88 (d, J = 8.4 Hz, 2H), 5.97 (d,
J = 4.0 Hz, 1H), 5.56 (d, J = 16.4 Hz, 1H), 5.23 (dd, J = 6.0, 4.8 Hz, 1H), 4.84 (d, J =
15.6 Hz, 1H), 4.13 (q, J = 68 Hz, 2H), 4.22-4.05 (2H), 3.80 (s, 3H), 3.38-3.36 (m, 1H),
3.20-3.10 (br, 2H), 1.96-1.80 (2H), 1.78-1.64 (m, 1H), 1.44-1.33 (m, 1H), 1.24 (t, J = 6.8
Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 166.3, 159.4, 146.3, 138.2, 129.5, 128.9,
128.8, 128.7, 126.9, 122.4, 114.5, 85.1, 84.7, 77.4, 64.1, 61.2, 60.6, 55.5, 38.0, 27.0, 26.5, 24.7, 14.4. HRMS (FAB) calcd for MH\(^+\) (C\(_{31}\)H\(_{32}\)FeNO\(_7\)) 586.1528, found, 586.1556.

Ethyl 2-[(3\(S\), 4\(S\)]-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]decan-4-yl]acetate (2.9a) and ethyl 2-[(3\(S\), 4\(R\)]-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]decan-4-yl]acetate (2.9b). The mixture of 2.6a and 2.6b (71 mg, 0.121 mmol) in n-Bu\(_2\)O (8 mL) was subjected to thermal cyclization conditions under reflux for 12 h. Rapid purification by flash chromatography (Hex:EA/2:1) afforded 2.8a and 2.8b together with three other isomers, which were inseparable and used without further purification. According to general procedure method A for demetallation, to the above mixture was added sat. CuCl\(_2\) in ethanol (2.0 mL). Stirring was continued for 18 h. Evaporation in vacuo gave the crude products as a pale yellow oil. To a solution of this oil in MeOH (4.0 mL), was added 10% Pd/C (39 mg), and the mixture was stirred under H\(_2\) for 15 h. After filtration to remove the catalyst, the solvent was evaporated in vacuo. Purification by flash chromatography (Hexanes:EA/2:1) afforded compounds 2.9a and 2.9b in 1.5:1 ratio and in 50% combined yield over 3 steps. 2.9a: \(R_f = 0.50\) (Hex:EA/2:1). \([\alpha]_{D}^{25} = -5\) (c = 1.12, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.30-7.20\) (3H), 7.05 (d, \(J = 6.4\) Hz, 2H), 6.90 (d, \(J = 8.4\) Hz, 2H), 6.79 (d, \(J = 8.8\) Hz, 2H), 4.98 (ABq, \(J = 14.8\) Hz, 1H), 3.99-3.76 (2H), 3.72 (ABq, \(J = 14.8\) Hz, 1H), 3.22-3.18 (m, 1H), 2.98 (dd, \(J = 14.0, 6.4\) Hz, 1H), 2.83 (dd, \(J = 14.0, 7.2\) Hz, 1H), 2.41-2.37 (m, 1H), 2.32 (dd, \(J = 14.8, 4.4\) Hz, 1H), 1.94-1.87 (m, 1H), 1.83 (dd, \(J = 14.8, 10.4\) Hz, 1H), 1.85-1.76 (1H), 1.74-1.64 (2H), 1.59-1.24 (6H), 1.09 (t,
$J = 6.8 \text{ Hz}, 3\text{H}$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.6, 172.5, 159.2, 138.2, 129.6, 129.5, 128.9, 128.8, 126.9, 114.1, 61.8, 60.7, 55.4, 46.3, 44.3, 41.9, 40.9, 35.6, 35.4, 29.1, 25.6, 22.5, 22.4, 14.3. HRMS (FAB) calcd for MH$^+$ (C$_{28}$H$_{36}$NO$_4$) 450.2644, found, 450.2649.

$2.9b$: $R_f = 0.60$ (Hex:EA/2:1). $[^{[\alpha]}D]_{25} = -72$ ($c = 0.85$, CHCl$_3$). $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.03-6.94 (5H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 5.20 (ABq, $J = 14.8$ Hz, 1H), 4.0-3.95 (m, 1H), 3.80-3.65 (2H), 3.22 (ABq, $J = 14.8$ Hz, 1H), 3.18 (s, 3H), 2.80-2.70 (2H), 2.47 (dd, $J = 14.0$, 8.8 Hz, 1H), 2.43-2.37 (m, 1H), 2.22-2.08 (3H), 1.76-1.68 (2H), 1.66-1.58 (m, 1H), 1.50-1.42 (2H), 1.17-1.05 (3H), 0.84 (t, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.8, 172.5, 159.0, 139.1, 129.3, 129.2, 129.1, 128.9, 126.8, 114.1, 60.9, 57.9, 55.4, 44.7, 44.4, 44.3, 37.7, 34.4, 31.3, 30.9, 25.9, 22.3, 22.2, 14.3. HRMS (FAB) calcd for MH$^+$ (C$_{28}$H$_{36}$NO$_4$) 450.2644, found, 450.2646.

(4$S$, 2$E$)-Ethyl 4-[tert-butoxycarbonyl-(4-methoxybenzyl)amino]-2-methyl-5-phenyl-pent-2-enoate (2.10) and (4$S$, 2$Z$)-ethyl 4-[tert-butoxycarbonyl-(4-methoxybenzyl)amino]-2-methyl-5-phenyl-pent-2-enoate (2.11). Method A: To a solution of ethyl 2-(diethoxyphosphoryl)propanoate (3.50 g, 14.6 mmol) in THF (82 mL) under Ar at -78 °C, was slowly added n-BuLi (5.2 mL, 2.5 M in hexanes, 13.0 mmol) via a syringe. The reaction mixture was stirred at this temperature for 30 min and then warmed to 0 °C for 10 minutes. The temperature was again cooled to -78 °C, aldehyde 2.2 (2.99 g, 8.1 mmol) dissolved in THF (20 mL) was added, and the mixture was stirred at -78 °C for 3 h. After the temperature was allowed to rise to rt for 15 min, the reaction mixture was quenched with
sat. aq NH₄Cl (30 mL) and extracted with Et₂O (40 mL x 3). The combined organic layer was washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The product was purified by flash chromatography (Hex:EA/6:1) to provide 2.10 (2.40 g, 67%, ee = 94%, [α]D²⁵ = -2.9 (c = 5.07, CHCl₃)) and 2.11 (0.50 g, 14%, [α]D²⁵ = +73 (c = 0.80, CHCl₃)) as colorless viscous oils. **Method B:** To a solution of ethyl 2-(diethoxyphosphoryl)propanoate (199 mg, 0.83 mmol) in CH₃CN (5.5 mL), was added LiCl (36.0 mg, 0.83 mmol, dried in a vacuum oven), followed by DBU (0.13 mL, 0.83 mmol). The reaction mixture was stirred at rt for 20 min until the LiCl dissolved completely, then cooled to 0 °C. Aldehyde 2.2 (190 mg, 0.51 mmol) in CH₃CN (0.5 mL) was added dropwise via syringe and the reaction mixture was stirred at 0 °C for 3 h (monitored by TLC). The same workup and purification procedure as method A afforded 2.10 (150 mg, 65%, ee = 74%) and 2.11 (30 mg, 13%) as colorless viscous oils. **Method C:** To a solution of aldehyde 2.2 (115 mg, 0.31 mmol) in CH₂Cl₂ (0.5 mL), was added a solution of (carbethoxyethylidene)triphenylphosphorane (141 mg, 0.39 mmol) in CH₂Cl₂ (0.5 mL) at 0 °C. Then the temperature was allowed to rise to rt and the mixture was stirred for 22 h. The same workup and purification procedure as method A afforded 2.10 (103 mg, 73%, ee = 71%) and 2.11 (18 mg, 13%). 2.10: Rf = 0.50 (Hex:EA/4:1). ¹H NMR (200 MHz, DMSO-d): δ 7.35-7.05 (7H), 6.86-6.82 (d, J = 8.2 Hz, 2H), 6.76-6.72 (d, J = 8.0 Hz, 1H), 4.90-4.62 (s, br, 1H), 4.30 (s, 3H), 4.05 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.09-2.78 (2H), 1.49 (s, 3H), 1.35 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 167.8, 158.7, 155.6, 139.0, 137.9, 131.1, 129.3, 128.8, 128.4, 126.5, 113.8, 80.2, 60.7, 56.2, 55.3, 48.7, 39.8, 39.7, 28.5, 14.3, 12.5. HRMS (FAB) calec for MH⁺ (C₂₇H₃₆NO₅) 454.2593, found, 454.2593. 2.11: Rf = 0.65 (Hex:EA/4:1). ¹H NMR
(200 MHz, CDCl₃): δ 7.21-6.70 (9H), 6.50-6.00 (br, 1H), 5.20-5.00 (br, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.30-4.00 (br, 1H), 3.78 (s, 3H), 3.40-3.00 (br, 1H), 2.80-2.75 (m, 1H), 1.83 (s, 3H), 1.46 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 167.2, 158.5, 140.3, 138.8, 130.9, 129.4, 128.8, 128.2, 127.9, 127.8, 126.2, 113.6, 60.4, 55.3, 29.6, 20.6, 14.3. HRMS (FAB) calcd for MH⁺ (C₂₇H₃₆NO₅) 454.2593, found, 454.2586.

(5S)-5-Benzyl-1-(4-methoxybenzyl)-3-methyl-1,5-dihydro pyrrolo-2-one (2.12). Compound 2.11 (90 mg) was dissolved in dry CH₂Cl₂ (1 mL) and cooled to 0 °C. TFA (0.5 mL) was then added slowly to the reaction mixture, which was stirred at the same temperature for 15 min, quenched by slow addition of sat NaHCO₃ solution (10 mL) at 0 °C, extracted with CH₂Cl₂, dried over MgSO₄, and concentrated to give 2.12 (61 mg, 100%) as a light yellow oil. Rf = 0.47 (Hex:EA/19:1). ¹H NMR (200 MHz, CDCl₃): 7.40-6.80 (9H), 6.48 (t, J = 1.6 Hz, 1H), 5.14 (d, J = 15.0 Hz, 1H), 4.11 (d, J = 15.0 Hz, 1H), 4.00-3.85 (m, 1H), 3.78 (s, 3H), 3.15 (dd, J = 13.2, 5.6 Hz, 1H), 3.48 (dd, J = 13.2, 9.3 Hz, 1H), 1.88 (t, J = 1.7 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): 171.9, 159.0, 140.2, 136.7, 134.9, 129.8, 129.3, 129.2, 128.6, 126.9, 114.1, 60.5, 55.3, 43.7, 38.0, 11.3. HRMS (FAB) calcd for MH⁺ (C₂₀H₂₂NO₂) 308.1650, found, 308.1646.

(4S, 2Z)-Ethyl 4-(4-methoxybenzylamino)-2-methyl-5-phenylpent-2-enoate (2.13). Following the procedure for preparation of compound 2.4, compound 2.10 (600 mg, 1.32 mmol) was dissolved in dry CH₂Cl₂ (6 mL) and cooled to 0 °C, followed by addition of TFA
(3 mL). Stirring was continued for 1h. Crude product 2.13 was used in the following reaction without further purification. \( R_f = 0.50 \) (Hex:EA/1:1). \( [\alpha]_D^{25} = +3.4 \) (c = 1.02, CHCl₃). \(^1\text{H} \) NMR (400 MHz, CDCl₃): \( \delta \) 7.26-7.16 (2H), 7.11 (dt, \( J = 6.8, 1.6 \) Hz, 2H), 7.04 (dt, \( J = 8.4, 2.0 \) Hz, 2H), 6.78 (dt, \( J = 8.8, 2.0 \) Hz, 1H), 6.62-6.59 (m, 1H), 4.17 (dq, \( J = 14.4, 0.4 \) Hz, 2H), 3.76 (s, 3H), 3.66-3.62 (m, 1H), 3.73 and 3.49 (ABq, \( J = 13.2 \) Hz, 2H), 2.81-2.68 (2H), 1.60 (d, \( J = 1.2 \) Hz, 3H), 1.46 (s, br, 1H), 1.28 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\text{C} \) NMR (50 MHz, CDCl₃): \( \delta \) 168.1, 158.8, 144.2, 138.0, 132.4, 129.6, 129.3, 128.6, 126.7, 113.9, 60.8, 56.8, 55.4, 51.2, 41.7, 14.4, 12.9. HRMS (FAB) calcd for MH\(^+\) (C₂₂H₂₈NO₃) 354.2069, found, 354.2075.

**Preparation of racemic N-(tert-butoxycarbonyl)-N-(methoxy benzyl)-L-phenylalaninal (rac 2.2).** To a solution of aldehyde 2.2 (88 mg, 0.24 mmol) in freshly distilled acetonitrile (25 mL) at 0°C, was added lithium chloride (17 mg, 0.4 mmol, dried in a vacuum oven) and DBU (0.06 mL). The reaction mixture was stirred at this temperature for 2 h, quenched by 1 N HCl (5 mL), and extracted with ether (15 mL x 3). The combined organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by flash chromatography (Hex:EA/ 2:1) afforded racemic aldehyde 2.2 (75 mg, 85%) as a colorless oil.

\[
\begin{align*}
\text{Preparation of racemic N-(tert-butoxycarbonyl)-N-(methoxy benzyl)-L-phenylalaninal (rac 2.2).} \\
\end{align*}
\]
3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)-2-methyl-5-phenylpent-2-noate (2.14b). To a solution of racemic amine 2.13 (4.0 mg, 11.4 μmol) and diisopropylethylamine (9.3 μL, 56.8 μmol) in freshly distilled CH₂Cl₂ (0.30 mL), was added Mosher’s chloride (8.6 μL, 56.8 μmol) under argon. The reaction solution was stirred at rt for 12 h, quenched with 1 N HCl (0.5 mL), and extracted with CH₂Cl₂ (1 mL x 3). The combined organic layer was washed with brine (1 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by preparative TLC (Hex:EA/6:1) afforded 2.14a (2.5 mg, 41%) as a colorless oil. R₇ = 0.35 (Hex:EA/4:1). Two rotamers. ¹H NMR (400 MHz, CDCl₃) Major rotamer: δ 7.61-6.42 (15H), 4.44-4.38 (m, 1H), 4.37 and 4.00 (ABq, J = 14.8 Hz, 2H), 4.26-4.15 (2H), 3.74 (s, 3H), 3.53 (q, J = 2.0 Hz, 3H), 3.35 (dd, J = 7.6, 13.6 Hz, 1H), 2.79 (dd, J = 8.8, 13.6 Hz, 1H), 1.33 (t, J = 5.4 Hz, 3H), 1.29 (d, J = 1.2 Hz, 3H). Minor rotamer: δ 7.61-6.35 (15H), 5.00, 4.59 (ABq, J = 14.8 Hz, 2H), 4.06-4.01 (2H), 3.82 (s, 3H), 3.66 (q, J = 2.0 Hz, 3H), 3.06 (dd, J = 13.6, 7.6 Hz, 1H), 2.72 (dd, J = 13.6, 8.8 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H), 0.21 (d, J = 1.6 Hz, 3H). HRMS (FAB) calcd for MH⁺ (C₃₂H₃₅F₃NO₅) 570.2467, found, 570.2475. 2.14b (2.7 mg, 42%, colorless oil). R₇ = 0.30 (Hex:EA/4:1). Two rotamers. ¹H NMR (400 MHz, CDCl₃) Major rotamer: δ 7.70-6.00 (15H), 4.93-4.80 (m, 1H), 4.85 and 4.66 (ABq, J = 15.2 Hz, 2H), 4.18-4.09 (2H), 3.81 (s, 3H), 3.40 (q, J = 1.6 Hz, 3H), 2.56 (dd, J = 12, 12 Hz, 1H), 2.26 (dd, J = 3.2, 13.4 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H), 0.90 (d, J = 1.6 Hz, 3H). Minor rotamer: δ 7.65-6.40 (15H), 4.60, 4.02 (ABq, J = 15.2 Hz, 2H), 4.44-4.38 (m, 1H), 3.76 (s, 3H), 3.60 (q, J = 1.6 Hz, 3H), 3.25 (dd, J = 13.6, 9.2 Hz, 1H), 3.00 (dd, J = 13.6, 6.8 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.42 (d, J = 1.6 Hz, 3H). HRMS (FAB) calcd for MH⁺ (C₃₂H₃₅F₃NO₅) 570.2467, found, 570.2460.
iron (2.15a) and (2.15b). To a solution of methanesulfonyl chloride (76.6 μL, 0.99 mmol) in freshly distilled CH₂Cl₂ (2.5 mL) under argon in a dried round bottom flask at 0 °C, was slowly added a solution of carboxylic acid 2.5 (175 mg, 0.66 mmol) and diisopropylethylamine (0.14 mL, 0.86 mmol) in freshly distilled CH₂Cl₂ (2.0 mL). Stirring was continued at this temperature for 1 h. Then diisopropylethylamine (0.24 mL, 1.45 mmol) was added, followed by a solution of amine 2.13 (465 mg, 1.32 mmol) in freshly distilled CH₂Cl₂ (2.0 mL). The temperature was allowed to rise to rt and the reaction mixture was stirred for 20 h, quenched with 1 N HCl (3 mL) and CH₂Cl₂ (20 mL) was added. The organic layer was washed with 1 N HCl (3 mL) and brine (5 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude products were partially purified by flash chromatography (Hex:EA/8:1) to provide 2.15a and 2.15b in 81% combined yield. One diastereom (163 mg, 41%): Rᵣ = 0.35 (Hex:EA/3:2). [α]Dₑ = +11.9 (c = 1.20, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.22-7.04 (5H), 6.93 (d, J = 9.6 Hz, 2H), 6.82-6.79 (2H), 6.20 (s, br, 1H), 5.30 (t, J = 4.8 Hz, 1H), 4.69 (ABq, J = 16 Hz, 1H), 4.36 (d, J = 16.4 Hz, 1H), 4.20-4.04 (3H), 3.80 (s, 3H), 3.45-340 (2H), 2.93 (dd, J = 13.6, 8.0 Hz, 1H), 1.87-1.68 (3H), 1.41-1.34 (m, 1H), 1.37 (d, J = 1.60 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ¹³C NMR (50 MHz, CDCl₃): δ 174.2, 167.8, 159.1, 138.5, 138.1, 129.9, 129.5, 128.5, 128.4, 128.3, 126.5, 114.2, 85.6, 85.5, 85.5, 85.4, 64.5, 60.6, 59.5, 55.3, 38.5, 26.8,
23.6, 14.2, 12.2, 12.1. HRMS (FAB) calcd for MH$^+$ (C$_{32}$H$_{34}$FeNO$_7$) 600.1685, found, 600.1685. Further purification by flash chromatography (1.5% CH$_3$OH in CH$_2$Cl$_2$) afforded the other diastereomer (160 mg, 40%). R$_f$ = 0.30 (1.5% MeOH in CH$_2$Cl$_2$). 
$[\alpha]_D^{25} = -16.1$ (c = 4.12, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.21-7.06 (7H), 6.87 (d, $J$ = 8.8 Hz, 2H), 5.94 (d, $J$ = 1.2 Hz, 1H), 5.20 (dd, $J$ = 5.2, 1.2 Hz, 1H), 5.00-4.80 (s, br, 1H), 4.45-4.20 (s, br, 1H), 4.14 (q, $J$ = 7.2 Hz, 2H), 3.80 (s, 3H), 3.35 (d, $J$ = 6.0 Hz, 1H), 3.17 (dd, $J$ = 13.2, 8.0 Hz, 1H), 2.98 (dd, $J$ = 12.8, 8.8 Hz, 1H), 1.95-1.35 (4H), 1.28 (s, 9H), 1.26 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 173.7, 167.9, 159.1, 137.7, 129.9, 129.6, 129.5, 128.4, 128.3, 126.5, 114.3, 114.2, 84.6, 84.2, 73.5, 63.7, 60.7, 59.5, 55.4, 26.3, 24.7, 14.2, 12.4. HRMS (FAB) calcd for MH$^+$ (C$_{32}$H$_{34}$FeNO$_7$) 600.1685, found, 600.1684.

[(2R)-Ethyl 2-[(3S, 4S, 5S)-6, 9, $\eta$-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate]tricarbonyliron (2.17a) and [(2R)-ethyl 2-[(3S, 4S, 5R)-6, 9, $\eta$-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate]tricarbonyliron (2.17a'). According to the general procedure for photothermally induced cyclization, a mixture of 2.15a and 2.15b (22.5 mg, 37.6 $\mu$mol) was refluxed in benzene (5.5 mL) in a dried quartz tube for 5.5 h to afford inseparable 2.17a and 2.17a' (15.1 mg, 67%), and dienes 2.21a and 2.21b from demetallation of 2.17a and 2.17a' (0.7 mg, 4%), and Diels-Alder reaction products 2.19a and 2.19b (2.0
mg 12%). **2.17a and 2.17a**: $R_f = 0.36$ (Hex:EA/2:1). $^1$H NMR (400 MHz, CDCl$_3$), mixture of two isomers: $\delta$ 7.34-6.76 (18H, two isomers), 5.77-5.74 (m, 1H, one isomer), 5.54-5.49 (2H, two isomers), 5.24-5.21 (m, 1H, another isomer), 4.87 (ABq, $J = 14.8$ Hz, 1H, another isomer), 4.67 (ABq, $J = 14.4$ Hz, 1H, one isomer), 3.78 (s, 3H, one isomer), 3.77 (s, 3H, another isomer), 4.00-2.3 (20H, two isomers), 2.20-1.80 (4H, two isomers), 1.13 (t, $J = 6.8$ Hz, 3H, another isomer), 0.99 (t, $J = 7.2$ Hz, 3H, one isomer), 0.59 (d, $J = 7.2$ Hz, 3H, one isomer), 0.42 (d, $J = 6.8$ Hz, 3H, another isomer). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 211.6, 177.6, 176.7, 174.8, 174.7, 159.5, 159.4, 137.8, 137.6, 130.6, 130.5, 130.0, 129.7, 129.0, 128.9, 128.6, 128.3, 127.2, 126.9, 114.2, 114.1, 8.5, 86.9, 86.0, 82.5, 68.2, 63.0, 60.8, 60.7, 59.8, 59.2, 58.4, 57.8, 55.4, 51.1, 50.6, 50.0, 47.6, 45.7, 45.5, 45.1, 41.0, 40.3, 39.4, 38.8, 34.0, 14.2, 13.9, 10.7, 10.5. HRMS (FAB) calcd for MH$^+$ (C$_{32}$H$_{34}$FeNO$_7$) 600.1685, found, 600.1670. **2.19a and 2.19b**: $R_f = 0.40$ (Hex:EA/2:1). $^1$H NMR (400 MHz, CDCl$_3$) Major isomer **2.19a**: $\delta$ 7.21-6.68 (9H), 6.32 (dd, $J = 6.8$, 8.0 Hz, 1H), 6.13 (d, $J = 8.0$ Hz, 1H), 5.00 and 3.86 (ABq, $J = 15.2$ Hz, 2H), 4.15 (dq, $J = 7.2$, 1.2 Hz, 2H), 3.78 (s, 3H), 3.63-3.31 (m, 1H), 3.04-3.00 (m, 1H), 2.89-2.80 (3H), 1.69-1.50 (3H), 1.24 (t, $J = 6.8$ Hz, 3H), 0.85 (s, 3H). Minor isomer **2.19b**: $\delta$ 7.21-6.68 (9H), 6.60 (d, $J = 8.0$, 1H), 6.22 (dd, $J = 6.0$, 8.0 Hz, 1H), 5.07 and 3.86 (ABq, $J = 14.4$ Hz, 2H), 4.06 (dq, $J = 7.2$, 1.2 Hz, 2H), 3.79 (s, 3H), 2.98-2.92 (m, 1H), 2.72-2.76 (m, 1H), 2.45-2.43 (m, 1H), 1.19 (t, $J = 7.2$ Hz, 3H), 0.93 (s, 3H), other peaks overlap with peaks of major isomer. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.1, 177.0, 158.8, 138.5, 134.3, 132.4, 129.2, 129.1, 129.0, 128.6, 126.7, 113.9, 61.3, 59.1, 55.4, 50.6, 49.2, 48.4, 43.6, 41.7, 40.3, 27.6, 20.9, 20.3, 14.4. HRMS (FAB) calcd for MH$^+$ (C$_{29}$H$_{34}$NO$_4$) 460.2488, found, 460.2496.
Preparation of tricyclic lactam 2.19a and 2.19b via a Diels-Alder reaction.

**Method A:** To a small vial was added the mixture of 2.15a and 2.15b (10.0 mg, 16.7 μmol) and sat. CuCl₂ solution in EtOH (0.3 mL). The reaction solution was stirred at rt for 24 h and then concentrated in vacuo. Water (1.5 mL) was added to the residue, which was extracted with ether (2 mL x 3). The combined ether layers were washed with brine (1.5 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by preparative TLC (Hex:EA/3:1) afforded inseparable 2.19a and 2.19b (6.5 mg, 86%) in 9:1 ratio as a colorless oil.

**Method B:** To a solution of methanesulfonyl chloride (42 μL, 0.54 mmol) in freshly distilled CH₂Cl₂ (2.0 mL) under argon at 0 °C, was slowly added a solution of carboxylic acid 2.26 (45 mg, 0.36 mmol) and diisopropylethylamine (78 μL, 0.47 mmol) in freshly distilled CH₂Cl₂ (1.3 mL). Stirring was continued at this temperature for 1 h, then diisopropylethylamine (0.13 mL, 0.80 mmol) was added, followed by a solution of amine 2.13 (204 mg, 0.58 mmol) in freshly distilled CH₂Cl₂ (1.6 mL). The temperature was allowed to reach rt and the reaction mixture was stirred for 20 h, and quenched with 1 N HCl (3 mL). After addition of CH₂Cl₂ (10 mL), the organic layer was washed with 1 N HCl (3 mL x 2) and brine (5 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Hex:EA/8:1) to provide 2.19a and 2.19b (140 mg, 84%) in 9:1 ratio.

Preparation of Compound 2.20 from reduction of tricyclic lactam 2.19a and 2.19b. Following the procedure to prepare 2.9a and 2.9b, the mixture of 2.19a and 2.19b (11.0 mg, 24.0 μmol) was hydrogenated in MeOH (1 mL) in
the presence of 10% Pd/C (5 mg). Removal of solvent in vacuo provided $2.20$ (10.8 mg, 98%) as a colorless solid without further purification. $R_f = 0.30$ (4% MeOH in CH$_2$Cl$_2$). MP 110-114 $^\circ$C. $[\alpha]_D^{25} = -28$ ($c = 0.95$, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.21-6.68 (9H), 4.99 and 3.82 (ABq, $J = 15.2$ Hz, 2H), 4.14-4.05 (2H), 3.78 (s, 3H), 3.65-3.60 (m, 1H), 3.06-2.93 (2H), 2.80 (dd, $J = 9.6$, 1.6 Hz, 1H), 1.86-1.74 (3H), 1.64-1.40 (5H), 1.20 (t, $J = 6.8$ Hz, 3H), 0.94 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.5, 177.5, 158.9, 138.9, 129.4, 129.3, 129.2, 128.6, 126.6, 113.9, 61.2, 57.3, 55.5, 46.3, 45.8, 43.4, 41.8, 40.0, 35.1, 26.3, 23.7, 23.1, 20.8, 19.1, 14.3. HRMS (FAB) calcd for MH$^+$ (C$_{29}$H$_{36}$NO$_4$) 462.2644, found, 462.2644.

(2$R$)-Ethyl 2-[(3$S$, 4$S$, 5$S$)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate (2.21a) and (2$R$)-ethyl 2-[(3$S$, 4$S$, 5$R$)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate (2.21b). Method A: According to the general procedure method A for demetallation, $E$ products 2.17a and 2.17a’ (13.8 mg, 23.0 $\mu$mol) were demetallated at rt for 24 h. Purification by flash chromatography (Hex:EA/3:1) provided two isomers (8.5 mg, 81%) as colorless oils. Method B: According to the general procedure method B for demetallation, $E$ products 2.17a and 2.17a’ (13.0 mg, 21.7 $\mu$mol) were demetallated for 24 h at rt. Purification by preparative TLC (Hex:EA/3:1) afforded two isomers 2.21a and 2.21b (8.3 mg, 83%) as colorless oils. One isomer: $R_f = 0.56$ (Hex:EA/2:1). $[\alpha]_D^{25} = +35.0$ ($c = 0.26$, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.33-6.79 (9H), 6.11 (dd, $J = 4.2$, 9.6 Hz, 1H), 5.97-5.92 (m, 1H), 5.77-5.73 (m, 1H),
5.57 (d, J = 9.6 Hz, 1H), 5.07 (ABq, J = 14.8 Hz, 1H), 3.90-3.67 (2H), 3.83 (ABq, J = 14.4 Hz, 1H), 3.80 (s, 3H), 3.57-3.55 (m, 1H), 2.93 (d, J = 5.6 Hz, 2H, 2.79-2.75 (m, 1H), 2.64 (dd, J = 3.2, 4.0 Hz, 1H), 2.47-2.41 (m, 1H), 1.88 (dd, J = 6.8, 17.2 Hz, 1H), 1.11 (t, J = 7.2 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H). 13C NMR (100 MHz, CDCl3): δ 178.6, 175.4, 159.3, 137.7, 130.3, 130.0, 128.9, 128.4, 127.4, 127.1, 125.1, 125.0, 124.3, 114.1, 60.6, 57.9, 55.5, 47.8, 44.6, 44.4, 40.6, 40.1, 34.6, 14.2, 12.8. HRMS (FAB) calcd for MH+ (C29H34NO4) 460.2488, found, 460.2449. The other isomer: Rf = 0.64 (Hex:EA/2:1). [α]D^25 = -86.0 (c = 0.45, CHCl3). 1H NMR (400 MHz, CDCl3): δ 7.31-6.80 (9H), 6.04-5.98 (2H), 5.89-5.85 (m, 1H), 5.69 (d, J = 8.0 Hz, 1H), 4.89 (ABq, J = 14.4 Hz, 1H), 3.98 (ABq, J = 14.4 Hz, 1H), 3.79 (s, 3H), 3.75-3.67 (m, 1H), 3.49-3.38 (2H), 3.04-2.96 (2H), 2.74 (dd, J = 13.6, 8.0 Hz, 1H), 2.49-2.48 (m, 1H), 2.45-2.40 (m, 1H), 2.21 (dd, J = 19.6, 6.4 Hz, 1H), 1.02 (t, J = 7.6 Hz, 3H), 0.61 (d, J = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl3): δ 177.5, 174.7, 159.4, 137.9, 130.7, 130.5, 129.8, 128.8, 128.7, 126.8, 126.0, 124.4, 124.3, 114.2, 60.7, 58.0, 55.5, 48.3, 47.2, 45.1, 43.1, 41.0, 26.2, 14.1, 11.9. HRMS (FAB) calcd for MH+ (C29H34NO4) 460.2488, found, 460.2496.

(2R)-Ethyl 2-[(3S, 4S)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]decadien-4-yl]propanoate (2.22). Following the procedure used to prepare 2.9a and 2.9b, the mixture of 2.21a and 2.21b (8.5 mg, 18.5 μmol) was hydrogenated to afford 2.22 (9.3 mg, 88%) as a colorless oil, which was purified by preparative TLC (2% MeOH in CH2Cl2). Rf = 0.30 (2% MeOH in CH2Cl2). [α]D^25 = -14.9 (c = 0.68, CHCl3). 1H NMR (400 MHz, CDCl3): δ 7.3-6.79 (9H), 4.81 (ABq, J = 14.8 Hz, 1H), 3.95 (ABq, J = 14.4 Hz, 1H), 3.79
(s, 3H), 3.75-3.67 (m, 1H), 3.54-3.50 (m, 1H), 3.42-3.34 (m, 1H), 3.05 (dd, \( J = 5.6, 13.2 \) Hz, 1H), 2.71 (dd, \( J = 8.4, 13.6 \) Hz, 1H), 2.58-2.52 (m, 1H), 2.46-2.45 (m, 1H), 1.90-1.60 (6H), 1.55-1.23 (4H), 1.03 (t, \( J = 6.8 \) Hz, 3H), 0.62 (d, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 179.0, 175.1, 159.3, 138.2, 130.5, 129.7, 128.9, 128.8, 126.8, 114.0, 60.6, 58.0, 55.4, 46.5, 44.6, 43.7, 41.1, 38.7, 37.2, 28.7, 25.7, 23.1, 22.6, 14.2, 11.3. HRMS (FAB) calcd for MH\(^+\) (C\(_{29}\)H\(_{38}\)NO\(_4\)) 464.2800, found, 464.2820.

\((2R)-2\-[(3S, 4S)-3-Benzyl-2-(4-methoxybenzyl)-1-oxo-2-aza\nspiro[4.5]decadien-4-yl]propyl \( \text{(2S)-3,3,3-trifluoro-2-methoxy-2-}
\text{phenylpropanoate (2.23). To a solution of 2.22 (5.3 mg, 11.4 \( \mu \)mol)}
in freshly distilled ether (0.2 mL), was carefully added LiBH\(_4\) (1.51 mg, 68.6 \( \mu \)mol) at rt. After stirring was continued for 2 h, the reaction mixture was quenched with water (1 mL) and extracted with ether (3 mL x 3). The ether layer was washed with brine (1 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by preparative TLC (2% MeOH in CH\(_2\)Cl\(_2\)) to afford \((2R)-2\-[(3S, 4S)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]decadien-4-yl]propanol (4.3 mg, 90%) as a colorless oil. \( R_f = 0.25 \) (2% MeOH in CH\(_2\)Cl\(_2\)). \([\alpha]_D^{25} = -3.4 \) (c = 0.36, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.38-6.86 (9H), 4.95 and 4.07 (ABq, \( J = 14.4 \) Hz, 2H), 3.81 (s, 3H), 3.26 (dd, \( J = 4.0, 12.8 \) Hz, 1H), 3.12 (dd, \( J = 4.4, 7.6 \) Hz, 1H), 2.79 (dd, \( J = 4.2, 11.2 \) Hz, 1H), 2.54 (dd, \( J = 11.6, 12.8 \) Hz, 1H), 2.33-2.28 (2H), 1.85-1.26 (12H), 0.24 (d, \( J = 6.8 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 179.7, 159.4, 138.4, 130.7, 129.8, 129.1, 128.8, 127.4, 114.2, 65.6, 57.1, 55.5, 46.6, 44.4, 39.8, 39.1, 37.8, 34.0, 28.5, 25.7, 23.2, 22.6, 11.2. HRMS (FAB) calcd for MH\(^+\) (C\(_{27}\)H\(_{36}\)NO\(_3\)) 422.2695, found, 422.2698.
To a solution of this alcohol (2.9 mg, 6.9 μmol) in freshly distilled toluene (0.15 mL), was added diisopropylethylamine (11.5 μL, 69 μmol) and Mosher’s chloride (10.4 μL, 55.0 μmol). Then the reaction mixture was heated to 100 °C and stirred for 16 h at this temperature. The cooled reaction mixture was quenched with 1 N HCl (0.5 mL) and extracted with ether (1 mL x 3). The combined organic layer was washed with brine (1 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Residual solvent was removed under vacuum oil pump for 12 h to afford 2.23 (3.1 mg, 72%, de > 94%) as a colorless oil. 

Rᵣ = 0.30 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.40-6.82 (14H), 4.96 and 3.93 (ABq, J = 14.8 Hz, 2H), 3.81 (s, 3H), 3.44 (q, J = 0.8 Hz, 3H), 3.39 (dd, J = 6.8, 10.8 Hz, 1H), 3.18-3.14 (2H), 3.08 (dd, J = 8.0, 10.8 Hz, 1H), 2.57 (dd, J = 10.4, 14.0 Hz, 1H), 2.14 (s, 1H), 2.00-1.69 (6H), 1.60-1.14 (5H), 0.31 (d, J = 6.8 Hz, 3H). ¹⁹F NMR (400 MHz, CDCl₃): δ 67.49 (s, 3F, major isomer), 67.53 (s, 3F, minor isomer). ¹³C NMR (100 MHz, CDCl₃):  δ 179.1, 166.3, 159.4, 138.0, 132.3, 130.7, 129.8, 129.2, 128.6, 127.5, 127.2, 114.1, 108.2, 77.4, 76.7, 69.4, 57.8, 55.5, 46.7, 44.4, 41.9, 40.4, 37.5, 31.5, 28.5, 25.6, 23.0, 22.3, 11.6. HRMS (FAB) calcd for MH⁺ (C₃₇H₄₃F₃NO₅) 638.3093, found, 638.3060.

(2S)-Methyl 2-(4-methoxybenzylamino)-3-phenylpropanoate (2.33). To a solution of (S)-methyl 2-amino-3-phenylpropanoate hydrochloride (2.32) (1.0 g, 4.6 mmol) in MeOH (26 mL) which was neutralized with NaOH (0.19 g, 4.8 mmol), anisaldehyde (0.94 g, 6.8 mL) and acetic acid (0.26 mL, 4.6 mmol) were added at room temperature. After stirring for 10 min at this temperature, the solution was cooled with an ice bath and NaBH₄ pellets (0.17 g, 4.6
mmol) were added. The reaction mixture was stirred for 1 h at 0 °C, then the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and the solution was filtered, then washed with saturated sodium carbonate solution (15 mL x 2) and dried (Na₂SO₄). Further purification by flash chromatography (Hex:EA/3:1) afforded 2.33 (1.13 g, 82%, ee = 100%) as a colorless oil. Rᵣ = 0.45 (Hex:EA/2:1). [α]D²⁵ = –5 (c = 0.63, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.30-6.78 (9H), 3.78 (s, 3H), 3.74 and 3.57 (ABq, J = 12.8 Hz, 2H), 3.53 (dd, J = 7.2, 7.2 Hz, 1H), 2.96-2.94 (2H), 1.78 (s, br, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 175.3, 158.9, 137.6, 131.9, 129.6, 129.4, 128.6, 126.9, 114.0, 62.2, 55.5, 51.9, 51.6, 40.0. HRMS (FAB) calcd for MH⁺ (C₁₈H₂₂NO₃) 300.1600, found, 300.1602.

(2S)-Methyl 2-(4-methoxybenzylamino)-3-phenylpropanoate hydrochloride (2.35). To a solution of amine 2.33 (1.13 g, 3.78 mmol) in diethyl ether (30 mL), was added a solution of HCl in dioxane (4.0 M, 2.0 mL). After the reaction was stirred for 15 min at rt, filtration and washing with dry ether afforded white solid 2.35 (1.27 g, 82%). M.P. 155-157 °C. [α]D²⁵ = +26.0 (c = 0.80, H₂O). ¹H NMR (400 MHz, D₂O): δ 7.30-6.90 (m, 9H), 4.21 (dd, J = 8.0, 6.4 Hz, 1H), 4.22, 4.20 ( ABq, J = 13.2 Hz, 2H), 3.71 (s, 3H), 3.56 (s, 3H), 3.24 (dd, J = 14.0, 6.0 Hz, 1H), 3.13 (dd, J = 14.4, 8.0 Hz, 1H). ¹³C NMR (100 MHz, D₂O): δ 169.5, 160.2, 133.5, 132.1, 129.4, 129.3, 128.3, 122.1, 114.8, 60.1, 55.6, 53.6, 50.0, 35.4.
Racemic 2-(4-methoxybenzylamino)-3-phenylpropanoic acid (2.36). To a stirred MeOH (5 mL) cooled by ice water, sodium (15.3 mg, 0.66 mmol) was added carefully. When all sodium disappeared, salt 2.35 (108 mg, 0.32 mmol) was added and the temperature was allowed to rise to 60 °C for 5 h. Then the reaction mixture was cooled to 0 °C, quenched with cold water (5 mL) carefully and acidified by 2 N HCl to pH = 5. The solid was collected by filtration and added to a solution of HCl in dioxane (4.0 M, 0.5 mL). After 10 min, filtration afforded pure product 2.36 as a white solid (46 mg, 45%). \([\alpha]D^{25} = 0 \ (c = 0.37, \text{CH}_3\text{OH})\). \(^1\)H NMR (400 MHz, CD$_3$OD): δ 7.38-6.90 (9H), 4.10-3.98 (m, 3H), 3.69 (s, 3H), 2.98 (dd, \(J = 14.4, 8.0 \text{ Hz}, 1\)H), one peak overlaps with water peak.

Racemic methyl 2-(4-methoxybenzylamino)-3-phenylpropanoate hydrochloride (rac. 2.35). To a stirred MeOH (0.2 mL) cooled to -10 °C was added thionyl chloride (25 μL, 0.35 mmol) carefully. The temperature was allowed to rise to r.t. and the stirring was continued for 3h. Then racemic 2.36 (35 mg, 0.11 mmol) was added and the reaction mixture was heated under reflux for 12 h. When the reaction mixture was cooled to r. t., the solvent was evaporated under vacuo. Then the residue was dissolved in MeOH (0.2 mL), followed by addition of diethyl ether (4.0 mL). After being shaken for 5 min, white solid precipitated, and was collected by filtration and washed with diethyl ether. Pure 2.35 (29.5 mg, 81%) was obtained. M.P. 154-157 °C. \([\alpha]D^{25} = -1.3 \ (c = 0.80, \text{H}_2\text{O})\). \(^1\)H NMR (400 MHz, D$_2$O): δ 7.30-6.90 (9H), 4.21 (dd, \(J = 8.0, 6.4 \text{ Hz}, 1\)H), 4.22, 4.20 ( ABq, \(J = 13.2 \text{ Hz}, 2\)H), 3.71 (s, 3H), 3.56 (s, 3H), 3.24 (dd, \(J = 14.0, 6.0 \text{ Hz}, 1\)H), 3.13 (dd, \(J = 14.4, 8.0 \text{ Hz}, 1\)H).
(2S)-Methyl 2-[N-(4-methoxybenzyl)-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoamido)]-3-phenylpropanoate (2.34a).

Following the procedure to prepare 2.14a and 2.14b, compound 2.33 (9.5 mg, 0.032 mmol) was dissolved in CH₂Cl₂ (0.4 mL), and diisopropylethylamine (32 μL, 0.191 mmol) was added. To this mixture, was added (2S)-3,3,3-trifluoro-2-methoxy-2-phenyl propionyl chloride (Mosher’s chloride, 24 μL, 0.128 mmol), and stirring was continued for 14 h at rt. The solvent was evaporated, and the residue was held under vacuum oil pump for 12 h to afford 2.34a (15.0 mg, 91%). This material was not further purified to avoid fractionation of the diastereomers and erroneous determination of de. Rᵣ = 0.50 (Hex:EA/2:1). Two rotamers. ¹H NMR (400 MHz, CDCl₃) Major rotamer: δ 7.64-6.42 (15H), 4.30 and 4.24 (ABq, J = 16.0 Hz, 2H), 3.97 (dd, J = 6.8, 6.40 Hz, 1H), 3.83 (q, J = 2.0 Hz, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.65 (dd, J = 13.6, 6.8 Hz, 1H), 2.91 (dd, J = 14.0, 6.4 Hz, 1H). ¹⁹F NMR (400 MHz, CDCl₃) Major rotamer: δ 66.51. ¹³C NMR (100 MHz, CDCl₃): δ 170.9, 167.1, 159.7, 138.5, 134.2, 130.7, 129.7, 129.6, 128.7, 128.4, 127.1, 126.7, 126.6, 114.2, 76.9, 60.9, 56.3, 55.5, 52.4, 51.8, 35.7. HRMS (FAB) calcd for MH⁺ (C₂₈H₂₉F₃NO₅) 516.1998, found, 516.1960.

(2R/2S)-Methyl 2-[N-(4-methoxybenzyl)-((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoamido)]-3-phenylpropanoate (mixture of 2.34a and 2.34b). The procedure was the same as preparation of 2.34a. Racemic 2.35 (7.8 mg, 0.023 mmol), diisopropylethylamine (23 μL, 0.138 mmol) and (2S)-3,3,3-trifluoro-2-
methoxy-2-phenyl propionyl chloride (mosher’s chloride, 17µL, 0.092 mmol) in CH₂Cl₂ (0.6 mL) were applied. The reaction mixture was heated under reflux for 24 h. The mixture of 2.34a and 2.34b (10.5 mg, 89%) was obtained as a colorless oil without any further purification. Rf = 0.50 (Hex:EA/2:1). Two equivalent diastereomers. ¹H NMR (400 MHz, CDCl₃) One diastereomer: δ 7.64-6.42 (15H), 4.30, 4.24 (ABq, J = 16.0 Hz, 2H), 3.97 (dd, J = 6.8, 6.4 Hz, 1H), 3.83 (q, J = 2.0 Hz, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.65 (dd, J = 13.6, 6.8 Hz, 1H), 2.91 (dd, J = 14.0, 6.4 Hz, 1H). Another diastereomer: δ 7.64-6.42 (15H), 4.52, 3.81 (ABq, J = 14.4 Hz, 2H), 3.93 (dd, J = 9.2, 5.6 Hz, 1H), 3.74(s, 3H), 3.72 (s, 3H), 3.60 (q, J = 2.0 Hz, 3H), 3.53 (dd, J = 14.4, 5.6 Hz, 1H), 3.28 (dd, J = 14.4, 9.2 Hz, 1H). ¹⁹F NMR (400 MHz, CDCl₃) One isomer: δ 66.52 (s, 3F). Another isomer: δ 66.17 (s, 3F).

![Structure 2.37](image)

[(2S)-Methyl 2-(N-(4-methoxybenzyl)cyclohexa-1,3-dienecarboxamido)-3-phenylpropanoate|tricarbonyliron (2.37). To a solution of methanesulfonyl chloride (0.17 mL, 2.16 mmol) in freshly distilled CH₂Cl₂ (8 mL) at 0 ºC under argon in a dried round bottom flask, was slowly added a solution of carboxylic acid 2.5 (382 mg, 1.44 mmol) and diisopropylethylamine (0.31 mL, 1.87 mmol) in freshly distilled CH₂Cl₂ (5 mL). Stirring was continued at this temperature for 1 h, then diisopropylethylamine (0.52 mL, 3.17 mmol) was added, followed by a solution of amine 2.33 (777 mg, 2.60 mmol) in freshly distilled CH₂Cl₂ (4 mL). The temperature was raised to 40 ºC and the reaction mixture was stirred for 24 h. After the reaction mixture was cooled to rt, CH₂Cl₂ (30 mL) was added and the solution was washed with 1 N HCl (20
mL x 3) and brine (20 mL x 2), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude products were purified by flash chromatography (Hex:EA/4:1) to provide 2.37 as a yellow viscous liquid. One isomer was obtained in 38% yield after a further purification by gravity chromatography (1% MeOH in CH₂Cl₂). Rₜ = 0.55 (Hex:EA/2:1). [α]₀²⁵ = -84 (c = 1.21, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.27-6.76 (9H), 6.21 (s, br, 1H), 5.30 (s, br, 1H), 4.76 (ABq, J = 14.8 Hz, 1H), 3.84-3.78 (br, 1H), 3.80 (s, 3H), 3.64-3.58 (br, 1H), 3.58 (s, 3H), 3.44- 3.22 (3H), 1.95-1.41 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 173.6, 171.2, 159.5, 130.2, 129.9, 128.6, 126.8, 114.1, 113.9, 110.0, 86.3, 85.7, 69.1, 64.7, 60.4, 55.5, 54.5, 52.1, 35.0, 27.2, 23.6. HRMS (FAB) calcd for MH⁺ (C₂₈H₂₈FeNO₇) 546.1216, found, 546.1208. The other isomer was obtained in 37% yield. Rₜ = 0.45 (Hex:EA/2:1). [α]₀²⁵ = -135 (c = 0.68, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.09 (7H), 6.88 (d, J = 8.8 Hz, 2H), 6.03 (d, J = 4.4 Hz, 1H), 5.23 (dd, J = 6.0, 4.4 Hz, 1H), 4.92 (ABq, J = 16.0 Hz, 1H), 3.88-3.73 (2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.55 (dd, J = 14.4, 6.0 Hz, 1H), 3.77 (d, J = 5.6 Hz, 1H), 3.09 (dd, J = 14.0, 7.6 Hz, 1H), 1.96-1.44 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 195.8, 173.5, 170.8, 159.5, 139.1, 129.6, 129.0, 128.7, 127.7, 126.7, 114.4, 85.2, 84.6, 64.0, 61.3, 55.5, 53.1, 52.4, 35.6, 26.3, 24.7. HRMS (FAB) calcd for MH⁺ (C₂₈H₂₈FeNO₇) 546.1216, found, 546.1202.

[N-(4-Methoxybenzyl)-N-((2S)-1-formyl-2-phenylethyl)cyclohexa-1,3-diene carboxamide]tricarbonyl iron (2.38). To a solution of ester 2.37 (503 mg, 0.92 mmol) in Et₂O (4.4 mL) at -78 °C, was added dropwise DIBAl-H (1.5 M in toluene, 2.45 mL, 3.68 mmol) After stirring at this temperature for 15 min, MeOH (4.4 mL) was added
slowly, followed by saturated NaK tartrate (8 mL) at -78 °C. Then the reaction mixture was allowed to warm to rt and extracted with diethyl ether (15 mL x 3). The combined extract was dried (Na₂SO₄) and concentrated. Flash chromatography (Hex:EA/3:1) provided pure products 2.38. One diastereomer (208 mg, 44%). Rₛ = 0.60 (Hex:EA/2:1). [α]D²⁵ = −79 (c = 1.71, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 9.35 (s, 1H), 7.36- 6.85 (9H), 6.25 (d, 1H, J = 4.0 Hz), 5.35 (dd, 1H, J = 6.0, 4.8 Hz), 4.96 (ABq, 1H, J = 14.0 Hz), 3.80 (s, 3H), 3.53-3.51 (m, 1H), 3.37-3.30 (2H), 3.16-3.05 (2H), 2.02-1.41 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 197.2, 173.7, 159.8, 138.8, 129.9, 129.7, 128.8, 127.4, 127.0, 114.9, 86.3, 85.9, 67.3, 65.8, 65.6, 55.5, 53.8, 32.7, 27.7, 23.1. HRMS (FAB) calcd for MH⁺ (C₂₇H₂₆FeNO₆) 516.1112, found, 516.1100. The other diastereomer (171 mg, 36%). Rₛ = 0.50 (Hex:EA/2:1). [α]D²⁵ = −115 (c = 1.36, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 9.50 (s, 1H), 7.31- 6.88 (9H), 6.06 (d, 1H, J = 4.0 Hz), 5.27 (dd, 1H, J = 5.6, 5.2 Hz), 5.00 and 3.77 (ABq, 1H, J = 16.8 Hz), 3.80 (s, 3H), 3.56 (dd, 1H, J = 14.0, 5.2 Hz), 3.47-3.40 (2H), 3.02 (dd, 1H, J = 14.0, 8.0 Hz), 1.98-1.47 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 196.4, 173.8, 159.7, 138.8, 129.4, 129.0, 128.4, 127.4, 126.9, 114.9, 85.3, 85.2, 69.5, 66.6, 64.6, 55.6, 52.4, 33.5, 26.7, 24.5. HRMS (FAB) calcd for MH⁺ (C₂₇H₂₆FeNO₆) 516.1112, found, 516.1098.

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\text{[(4S, 2Z)-Ethyl 4-(N-(4-methoxybenzyl)cyclohexa-1,3-dienecarboxamido)-2-methyl-5-phenylpent-2-enoate|tricarbonyliron (2.31a) and (2.31b). To a solution of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propanoate (2.39) (347 mg, 1.00 mmol) in}
\]
THF (6 mL) at 0 °C, was carefully added potassium hydride (35% in oil, 68.7 mg, 0.60 mmol). The reaction was maintained at 0 °C for 30 min, then cooled to -78 °C, and aldehyde 2.38 (344 mg, 0.67 mmol) in THF (5 mL) was added. The reaction mixture was stirred at -78 °C for 3 h, then allowed to warm to 0 °C, quenched with 1 N HCl (25 mL) and extracted with diethyl ether (20 mL x 3). The combined organic layer was washed with brine (10 mL x 2) and dried (Na₂SO₄). The solvent was evaporated in vacuo and the residue was further purified by flash chromatography (Hex:EA/6:1) to provide inseparable products 2.31a and 2.31b (251 mg, 70%). Rᵣ = 0.70 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃) two diastereomers: δ 7.20- 6.56 (10H), 6.22, 5.70 (br, 1H), 5.31, 5.05 (br, 1H), 6.27-4.30 (3H), 3.93 (q, J = 7.2 Hz, 2H), 3.79, 3.78 (s, 3H), 3.60-3.22 (2H), 2.98 (dd, J = 12.8, 5.6 Hz, 1H), 1.84, 1.80 (d, J = 1.2 Hz, 3H), 2.0-1.0 (7H). ¹³C NMR (100 MHz, CDCl₃): δ 174.3, 173.8, 167.3, 167.2, 159.0, 139.5, 139.2, 129.9, 129.8, 128.9, 128.7, 128.5, 128.4, 126.4, 114.5, 114.3, 114.0, 85.9, 83.8, 71.2, 64.9, 60.8, 60.6, 60.4, 55.5, 55.4, 54.3, 37.8, 27.0, 26.2, 25.5, 23.4, 20.7, 20.5, 14.2. HRMS (FAB) calcd for MH⁺ (C₃₂H₃₄FeNO₇) 600.1685, found, 600.1682.

![Diagram](attachment://2.29.png)

[(2S)-Ethyl 2-][(3S, 4S, 5S)-6, 9, η-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate]tricarbonyliron (2.29a) and [(2S)-ethyl 2-][(3S, 4S, 5R)-6, 9, η-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate]tricarbonyliron (2.29b). According to the general procedure for
photothermally induced cyclization, a mixture of 2.31a and 2.31b (24.3 mg, 0.04 mmol) was refluxed in 5.5 mL of benzene under CO atmosphere for 5.5 h. Preparative TLC (1% THF in CH₂Cl₂) provided two isomers 2.29a and 2.29b in 72% combined yield. One isomer (12.6 mg, 52%, yellow sticky oil): Rᵣ = 0.55 (Hex:EA/2:1 two developments). [α]D²⁵ = +64 (c = 0.84, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.35-6.84 (9H), 5.53 (dd, J = 4.2, 4.2 Hz, 1H), 5.28-5.25 (m, 1H), 4.48 and 4.43 (ABq, J = 14.8 Hz, 2H), 3.87-3.54 (2H), 3.79 (s, 3H), 3.54-3.50 (m, 1H), 3.36-3.32 (m, 1H), 2.95 (dd, J = 13.2, 4.4 Hz, 1H), 2.74-2.65 (2H), 2.50 (dd, J = 6.8, 1.2 Hz, 1H), 2.07 (dd, J = 2.0, 2.4 Hz, 1H), 2.02-1.92 (2H), 1.05 (t, J = 7.2 Hz, 3H), 0.56 (d, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 211.9, 177.9, 173.8, 159.3, 137.1, 130.5, 130.2, 129.3, 128.9, 127.3, 114.1, 88.5, 82.7, 69.1, 64.0, 60.6, 60.5, 55.5, 51.0, 49.6, 46.3, 41.4, 38.3, 34.3, 15.4, 14.2. HRMS (FAB) calcd for MH⁺ (C₃₂H₃₄FeNO₇) 600.1685, found, 600.1673. The other isomer (4.9 mg, 20%, yellow sticky oil): Rᵣ = 0.65 (Hex:EA/2:1 two developments). [α]D²⁵ = –10 (c = 0.38, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.30-6.82 (9H), 5.76-7.72 (m, 1H), 5.53-5.50 (m, 1H), 4.66 and 4.11 (ABq, J = 14.8 Hz, 2H), 3.93-3.84 (2H), 3.78 (s, 3H), 3.62 (dd, J = 10.8, 4.0 Hz, 1H), 3.14-3.10 (2H), 2.91 (dq, J = 6.8, 2.0 Hz, 1H), 2.80 (dd, J = 13.2, 4.4 Hz, 1H), 2.2-2.11 (2H), 2.00 (dd, J = 15.2, 3.6 Hz, 1H), 1.93 (d, J = 1.6 Hz, 1H), 1.15 (t, J = 6.8 Hz, 3H), 0.46 (d, J = 8.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 174.3, 173.8, 167.3, 167.2, 159.0, 139.5, 139.2, 129.9, 129.8, 128.9, 128.7, 128.5, 128.4, 126.4, 114.3, 114.0, 85.9, 83.8, 71.2, 64.9, 60.8, 60.6, 60.4, 55.5, 55.4, 64.3, 37.8, 27.0, 25.5, 23.4, 20.7, 20.5, 14.2. HRMS (FAB) calcd for MH⁺ (C₃₂H₃₄FeNO₇) 600.1685, found, 600.1673. Products 2.17a and 2.17a’ from E-substrates were also obtained in 3% yield and Diels-Alder products 2.43 in 14% yield.
Preparation of tricyclic lactam 2.43 through a Diels-Alder reaction. Following the procedure for the preparation of compounds 2.19a and 2.19b, the mixture of Z-substrates 2.31a and 2.31b (11.5 mg, 19.2 μmol) was treated with saturated ethanolic CuCl₂ (0.35 mL) for 24 h to give compound 2.43 (7.0 mg, 81%) as a colorless oil which was purified by preparative TLC (Hex:EA/3:1). Rᵢ = 0.35 (Hex:EA/2:1). [α]D²⁵ = +25 (c = 0.65, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.27- 6.65 (9H), 4.99 and 3.86 (ABq, J = 14.8 Hz, 2H), 4.16-3.99 (2H), 3.94-3.89 (m, 1H), 3.76 (s, 3H), 3.48 (d, J = 15.2 Hz, 1H), 2.82-2.75 (2H), 1.8-1.2 (5H), 1.37 (s, 3H), 1.18 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 177.0, 175.5, 158.8, 138.5, 137.9, 130.4, 129.6, 129.1, 129.0, 128.7, 126.6, 113.8, 60.8, 59.3, 55.5, 55.4, 51.2, 48.3, 43.7, 40.4, 39.3, 28.9, 27.7, 18.4, 14.3. HRMS (FAB) calcd for MH⁺ (C₂₉H₃₄NO₄) 460.2488, found, 460.2489.

(2S)-Ethyl 2-[(3S, 4S, 5S)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]propanoate (2.30a) and (2S)-ethyl 2-[(3S,4S,5R)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6, 8-dien-4-yl]propanoate (2.30b). According to the general procedure for demetallation method B, Z-products 2.29a and 2.29b (15.6 mg, 26.0 μmol) and sat. CuCl₂ solution in EtOH (0.7 mL) were mixed. Stirring was continued at rt for 24 h. The crude products were purified by preparative TLC (Hex:EA/3:1) to afford 2.30a and 2.30b in 80% combined yield. 2.30a (3.7 mg, 31%, colorless oil): Rᵢ = 0.40 (Hex:EA/2:1). [α]D²⁵ = +37 (c = 0.31, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.31- 6.82
(9H), 6.06 (dd, J = 10.0, 5.2 Hz, 1H), 5.94-5.90 (m, 1H), 5.75-5.71 (m, 1H), 5.55 (d, J = 9.6 Hz, 1H), 4.87 and 4.24 (ABq, J = 15.2 Hz, 2H), 3.99-3.89 (2H), 3.80 (s, 3H), 3.67-3.63 (m, 1H), 2.87-2.74 (3H), 2.45-2.38 (m, 1H), 2.22 (dd, J = 4.4, 4.8 Hz, 1H), 1.85 (dd, J = 17.6, 5.6 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H), 0.74 (d, J = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl 3): δ 178.7, 175.0, 159.3, 137.3, 130.2, 130.0, 128.8, 127.1, 126.7, 125.7, 124.8, 124.1, 114.1, 60.5, 59.8, 55.5, 47.9, 46.9, 45.3, 40.5, 40.3, 35.2, 16.2, 14.3. HRMS (FAB) calcd for MH + (C 29H34NO4) 460.2488, found, 460.2475.

2.30b (5.8 mg, 49%, colorless oil): R f = 0.60 (Hex:EA/2:1). [α] D 25 = -20 (c = 0.48, CHCl 3). 1H NMR (400 MHz, CDCl 3): δ 7.28- 6.83 (9H), 6.03-5.95 (2H), 5.89-5.84 (m, 1H), 5.68 (dd, J = 8.4, 1.2 Hz, 1H), 4.56 and 4.43 (ABq, J = 14.8 Hz, 2H), 4.01-3.86 (2H), 3.79 (s, 3H), 3.55-3.51 (m, 1H), 2.93-2.83 (2H), 2.58-2.40 (3H), 2.13 (dd, J = 3.6, 2.4 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H), 0.56 (d, J = 6.8 Hz, 3H). 13C NMR (100 MHz, CDCl 3): δ 177.6, 174.6, 159.2, 137.8, 131.2, 130.1, 129.8, 129.6, 128.8, 126.9, 126.3, 124.2, 124.0, 114.2, 60.8, 60.7, 55.5, 51.3, 47.5, 46.1, 42.0, 41.0, 26.5, 16.1, 14.2. HRMS (FAB) calcd for MH + (C 29H34NO4) 460.2488, found, 460.2489.

(2S)-Ethyl 2-[(3S, 4S)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]decadien-4-yl]propanoate (2.40). The procedure was the same as for the preparation of compound 2.9a and 2.9b. The mixture of decomplexed products 2.30a and 2.30b (6.2 mg, 13.5 µmol) in methanol (0.7 mL) was hydrogenated over 10% Pd/C (6 mg) for 24 h. The crude product was purified by preparative TLC (Hex:EA/2:1) to afford 2.40 (5.2 mg, 84%) as a colorless oil. R f = 0.50 (Hex:EA/2:1). [α] D 25 = +21 (c = 0.49, CHCl 3).
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.30-6.83\) (9H), 4.67 and 4.27 (ABq, \(J = 14.8\) Hz, 2H), 3.98-3.86 (2H), 3.79 (s, 3H), 3.61 (dd, \(J = 12.0, 4.4, 2.0\) Hz, 1H), 2.89 (dd, \(J = 13.2, 4.0\) Hz, 1H), 2.58 (dq, \(J = 7.2, 2.7\) Hz, 1H), 2.46 (dd, \(J = 13.4, 10.4\) Hz, 1H), 2.02 (dd, \(J = 2.4, 2.0\) Hz, 1H), 1.87-1.21 (10H), 1.15 (t, \(J = 7.2\) Hz, 3H), 0.46 (d, \(J = 7.2\) Hz, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 179.3, 174.8, 159.1, 138.1, 130.3, 129.9, 129.8, 128.8, 126.9, 114.1, 61.1, 60.7, 55.5, 46.9, 46.6, 46.0, 41.4, 38.0, 37.6, 28.8, 25.7, 23.0, 22.6, 16.3, 14.2.

HRMS (FAB) calcd for MH\(^+\) (C\(_{29}\)H\(_{38}\)NO\(_4\)) 464.2800, found, 464.2807.

\((2S)-2-[(3S,4S)-3-Benzyl-2-(4-methoxybenzyl)-1-oxo-2-aza\nspirow4.5decdien-4-yl]proply (2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.41).\right) Following the procedure for the preparation of 2.23, a solution of ester 2.40 (3.0 mg, 6.4 \(\mu\)mol) in freshly distilled ether (0.2 mL) was treated with LiBH\(_4\) (1.28 mg, 58.3 \(\mu\)mol) at rt for 2 h. The crude product, (2S)-2-[(3S, 4S)-3-benzyl-2-(4-methoxybenzyl)-1-oxo-2-aza\nspirow4.5decdien-4-yl]propanol, was used in the following reaction without any further purification. \(R_f = 0.20\) (Hex:EA/1:1). \([\alpha]_D^{25} = -12\) (\(c = 0.20, \text{CHCl}_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.31-6.87\) (9H), 4.96 and 3.94 (ABq, \(J = 14.4\) Hz, 2H), 3.81 (s, 3H), 3.23-3.18 (3H), 2.56 (dd, \(J = 12.8, 10.0\) Hz, 2H), 1.98 (s, br, 1H), 1.84-0.74 (12 H), 0.23 (d, \(J = 6.8\) Hz, 3H). To a solution of the crude product (2.0 mg, 4.7 \(\mu\)mol) in freshly distilled benzene (0.15 mL), was added diisopropylethylamine (11.2 \(\mu\)L, 66.4 \(\mu\)mol) and Mosher’s chloride (10.8 \(\mu\)L, 57.0 \(\mu\)mol). The reaction mixture was heated to 80 °C and stirred for 24 h at this temperature. The cooled reaction mixture was quenched with 1 N HCl (0.6 mL) and extracted with ether (1 mL x 3). The combined organic layer was washed with
brine (1 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product **2.41** (2.8 mg, de > 86%, 70% yield over two steps) was subjected to $^1$H NMR without any further purification for determination of de. $R_t = 0.70$ (Hex:EA/3:2). $[\alpha]_D^{25} = -3$ (c = 0.23, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) Major isomer: $\delta$ 7.37-6.83 (9H), 4.99 and 3.97 (ABq, $J = 14.4$ Hz, 2H), 3.92 (d, $J = 2.8$ Hz, 1H), 3.78 (s, 3H), 3.44 (q, $J = 0.8$ Hz, 3H), 3.23-3.13 (3H), 2.54 (dd, $J = 12.0$, 2.0 Hz, 1H), 2.00 (s, br, 1H), 1.90-1.20 (11H), 0.10 (d, $J = 6.8$ Hz, 3H). $^{19}$F NMR (400 MHz, CDCl$_3$) Major isomer: $\delta$ –72.0, 93%; Minor isomer: $\delta$ –72.1, 7%. $^{13}$C NMR (100 MHz, CDCl$_3$) Major isomer: $\delta$ 178.7, 166.2, 159.5, 137.8, 132.4, 130.5, 129.8, 128.9, 128.6, 128.4, 127.5, 127.1, 114.5, 77.4, 68.4, 57.9, 55.4, 46.8, 44.4, 40.2, 37.4, 31.8, 28.6, 25.6, 23.2, 22.6, 15.9. HRMS (FAB) calcd for MH$^+$ (C$_{37}$H$_{43}$F$_3$NO$_5$) 638.3093, found, 638.3056.

![Chemical structures](image)

To a solution of **2.29a** and **2.29b** (21.7 mg, 36.2 μL) in Et$_2$O (0.3 mL) at -78 °C, was added dropwise DIBAl-H solution (1.5 M in toluene, 0.12 mL 181.1μL). Stirring was continued for 1h and the reaction was quenched slowly with MeOH (0.6 mL), immediately followed by addition of sat. KNa tartrate solution (1 mL). the product was extracted with Et$_2$O (1.5 mL x 3), and the organic layer was dried (Na$_2$SO$_4$), concentrated, and the residue was purified by flash chromatography.
(Hex:EA/3:1) to afford two diastereomers 2.44a and 2.44b (15.6 mg, 77% combined yield). One isomer (11.1 mg, 55%, pale yellow oil): Rf = 0.50 (Hex:EA/1:1). [α]D²⁵ = +54 (c = 0.98, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 9.12 (s, 1H), 7.35-6.84 (9H), 5.55 (dd, J = 5.2, 5.2 Hz, 1H), 5.30-5.27 (m, 1H), 4.89 and 4.06 (ABq, J = 14.8 Hz, 2H), 3.80 (s, 3H), 3.36-3.33 (m, 1H), 3.16-3.12 (m, 1H), 3.06 (dd, J = 13.2, 4.4 Hz, 1H), 2.72 (dd, J = 13.6, 9.2 Hz, 1H), 2.67-2.60 (m, 1H), 2.49 (dd, J = 6.4, 1.2 Hz, 1H), 2.16 (dd, J = 2.0, 2.8 Hz, 1H), 2.01-1.88 (2H), 0.49 (d, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 211.8, 202.6, 177.4, 159.5, 136.8, 130.5, 130.1, 129.1, 127.9, 127.5, 114.2, 88.6, 82.7, 68.7, 63.6, 59.4, 55.5, 50.7, 48.4, 46.4, 45.4, 40.7, 34.3, 11.8. HRMS (FAB) calcd for MH⁺ (C₃₀H₃₀FeNO₆) 556.1423, found, 556.1413. Further purification by a preparative TLC (1.5% THF in CH₂Cl₂) provided the other isomer (4.5 mg, 22%, pale yellow oil). Rf = 0.60 (Hex:EA/1:1) or 0.70 (1.5% THF in CH₂Cl₂, three developments). [α]D²⁵ = -48 (c = 0.39, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 9.20 (d, J = 1.6 Hz, 1H), 7.33-6.86 (9H), 5.78-5.75 (m, 1H), 5.53 (dd, J = 6.4, 4.4 Hz, 1H), 4.67 and 4.15 (ABq, J = 14.4 Hz, 2H), 3.81 (s, 3H), 3.20 (dd, J = 9.6, 4.0 Hz, 1H), 3.16-3.13 (m, 1H), 3.04 (dd, J = 13.2, 4.0 Hz, 1H), 2.84-2.80 (m, 1H), 2.76 (d, J = 6.0 Hz, 1H), 2.27 (dd, J = 13.2, 10.8 Hz, 1H), 2.15 (dd, J = 15.2, 2.0 Hz, 1H), 2.06-1.99 (2H), 0.39 (d, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 203.4, 176.3, 159.6, 137.1, 130.5, 129.6, 129.1, 128.1, 127.3, 114.3, 87.1, 85.9, 60.8, 59.9, 59.8, 55.5, 53.3, 52.0, 45.7, 45.5, 40.1, 12.4. HRMS (FAB) calcd for MH⁺ (C₃₀H₃₀FeNO₆) 556.1423, found, 556.1392.

\[(3S, 4S, 5S)-6, 9, \eta-3-Benzyl-4-((3R)-but-1-en-3-yl)-2-(4-methoxybenzyl)-1-oxo-2-\]
azaspiro[4.5]deca-6,8-diene|tricarbonyliron (2.45a) and [(3S, 4S, 5R)-6, 9, η-3-benzyl-4-((3R)-but-1-en-3-yl)-2-(4-methoxybenzyl)-1-oxo-2-azaspiro[4.5]deca-6,8-diene|tricarbonyliron (2.45b). To a suspension of methyltriphenylphosphonium bromide (98 mg, 0.275 mmol) in THF (2.5 mL) at 0 °C, was slowly added n-BuLi (2.5 M solution in hexanes, 0.11 mL, 0.275 mmol). After 1 h at this temperature, a solution of aldehydes 2.44a and 2.44b (61 mg, 0.11 mmol) in THF (2.5 mL) was added quickly. Stirring was continued at 0 °C for 10 min, then the reaction was allowed to reach rt and maintained at this temperature for 1.5 h. Finally, the reaction was quenched with 1 N HCl (2 mL) and extracted with Et₂O (4 mL × 3). The organic layer was dried (Na₂SO₄), concentrated in vacuo, and the residue was purified by flash chromatography (Hex:EA/4:1) to afford 2.45a and 2.45b (55 mg, 92% combined yield). One isomer (43 mg, 72%, pale yellow oil): 

\[ R_f = 0.65 \] (Hex:EA/2:1). \[ \alpha_D^{25} = +42 \] (\( c = 0.23 \), CHCl₃). 

\( ^1H \) NMR (400 MHz, CDCl₃): δ 7.36-6.80 (9H), 5.54 (dd, \( J = 6.4, 4.4 \) Hz, 1H), 5.29-5.26 (m, 1H), 4.97-4.88 (m, 1H), 4.85 and 3.94 (ABq, \( J = 14.4 \) Hz, 2H), 4.69-4.56 (2H), 3.80 (s, 3H), 3.36-3.25 (m, 1H), 3.19-3.16 (m, 1H), 3.09 (dd, \( J = 13.2, 4.8 \) Hz, 1H), 2.75 (dd, \( J = 13.6, 9.2 \) Hz, 1H), 2.63 (dd, \( J = 6.4, 1.2 \) Hz, 1H), 2.50-2.43 (m, 1H), 2.09 (dd, \( J = 16.0, 3.6 \) Hz, 1H), 2.05-1.93 (2H), 0.35 (d, \( J = 6.8 \) Hz, 3H). 

\( ^13C \) NMR (100 MHz, CDCl₃): δ 211.9, 177.9, 159.4, 137.7, 137.6, 130.7, 130.0, 129.0, 128.5, 127.2, 116.3, 114.0, 88.6, 82.6, 69.0, 63.9, 58.1, 55.5, 50.7, 50.6, 45.1, 41.0, 35.9, 33.4, 16.9. HRMS (FAB) calcd for MH⁺ (C₃₁H₃₂FeNO₅) 554.1630, found, 554.1627. The other isomer (12 mg, 20%, pale yellow oil): \( R_f = 0.63 \) (Hex:EA/2:1). \[ \alpha_D^{25} = -63 \] (\( c = 0.19 \), CHCl₃). 

\( ^1H \) NMR (400 MHz, CDCl₃): δ 7.31-6.84 (9H), 5.74-5.70 (m, 1H), 5.50 (dd, \( J = 6.4, 4.4 \) Hz, 1H), 5.15-5.07 (m, 1H), 4.78-4.65 (m, 2H), 4.70 and 4.03 (ABq, \( J = 14.4 \) Hz, 2H), 3.81 (s, 3H), 3.18-3.10
(2H), 3.03 (dd, \( J = 13.2, 4.4 \) Hz, 1H), 2.89 (d, \( J = 6.0 \) Hz, 1H), 2.69-2.65 (m, 1H), 2.32 (d, \( J = 13.2, 10.4 \) Hz, 1H), 2.12-1.99 (2H), 1.86 (d, \( J = 1.2 \) Hz, 1H), 0.28 (d, \( J = 6.8 \) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 177.0, 159.5, 138.5, 137.7, 130.7, 129.7, 128.9, 128.6, 127.1, 116.3, 114.1, 87.0, 85.8, 60.9, 60.0, 58.8, 55.5, 54.0, 52.1, 45.5, 45.3, 40.2, 36.0, 18.0. HRMS (FAB) calcd for MH\(^+\) (C\(_{31}\)H\(_{32}\)FeNO\(_5\)) 554.1630, found, 554.1620.

\([3S, 3aR, 4R, 5R, 5aS]-6, 9, \eta-3\)-Benzyl-2-(4-methoxybenzyl)-2, 3, 3a, 4, 5, 5a-hexahydro-4, 5-dimethylindeno [1-c]pyrrol-1-one|tricarbonyliron (2.46). According to the general photothermally induced cyclization procedure, a mixture of 2.45a and 2.45b (8.3 mg, 15 \( \mu \)mol) was heated at 160 \(^\circ\)C in mesitylene (2.3 mL) under CO atmosphere for 9 h. Preparative TLC (Hex:EA/3:1) provided compound 2.46 (4.3 mg, 52%). Starting material (25%) was also recovered. \( R_f = 0.60 \) (Hex:EA/2:1).

\([\alpha]_D^{25} = +23 \) (c = 0.80, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.33-6.83 \) (9H), 5.37 (dd, \( J = 6.4, 4.4 \) Hz, 1H), 5.31-5.28 (m, 1H), 5.12 and 3.89 (ABq, \( J = 14.8 \) Hz, 2H), 3.81 (s, 3H), 3.42-3.87 (m, 1H), 2.94 (d, \( J = 6.4 \) Hz, 1H), 2.83-2.74 (2H), 2.39 (dd, \( J = 9.2, 3.6 \) Hz, 1H), 2.35-2.28 (m, 1H), 2.17 (dd, \( J = 6.4, 1.2 \) Hz, 1H), 2.11 (d, \( J = 8.4 \) Hz, 1H), 1.24-1.19 (m, 1H), 0.88 (d, \( J = 7.2 \) Hz, 3H), 0.47 (d, \( J = 6.4 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 212.3, 176.5, 159.3, 136.6, 130.4, 129.6, 128.6, 128.6, 127.1, 114.3, 86.6, 83.6, 67.8, 65.8, 61.4, 55.5, 54.9, 52.1, 51.4, 44.8, 43.3, 41.3, 40.1, 13.8. HRMS (FAB) calcd for MH\(^+\) (C\(_{31}\)H\(_{32}\)FeNO\(_5\)) 554.1630, found, 554.1654.
(3S, 3aR, 4R, 5R, 5aS)-2-(4-Methoxybenzyl)-3-benzyl-2, 3, 3a, 4, 5, 5a-hexahydro-4, 5-dimethylindeno[1-c]pyrrol-1-one (2.47). According to the general procedure method B for demetallation, compound 2.46 (10.0 mg, 18.0 μmol) was treated with sat. CuCl₂ solution in EtOH (0.5 mL) at rt for 24 h. The purification by preparative TLC (Hex:EA/3:1) afforded 2.47 (5.3 mg, 72%) as a colorless oil. R₇ = 0.40 (Hex:EA/2:1). [α]D²⁵ = -20 (c = 0.45, CHCl₃). ¹H NMR (400 MHz, CDCl₃/C₆D₆=1/3): δ 7.11-6.73 (9H), 5.84-5.70 (2H), 5.55-5.45 (2H), 5.22 and 3.70 (ABq, J = 14.4 Hz, 2H), 3.44-3.40 (m, 1H), 3.34-3.32 (m, 1H), 3.35 (s, 3H), 2.87 (dd, J = 13.2, 4.0 Hz, 1H), 2.32 (dd, J = 13.6, 9.2 Hz, 1H), 2.26 (dd, J = 9.2, 1.6 Hz, 1H), 1.45-1.40 (m, 1H), 1.35-1.28 (m, 1H), 0.77 (d, J = 6.4 Hz, 3H), 0.22 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 178.4, 159.4, 137.4, 130.2, 129.8, 128.8, 127.2, 126.9, 125.3, 123.3, 123.30, 114.3, 100.4, 56.7, 56.2, 55.5, 55.3, 47.0, 44.7, 44.4, 44.3, 40.9, 14.2, 13.2. HRMS (FAB) calcld for MH⁺ (C₂₈H₃₂NO₂) 414.2433, found, 414.2426.

(2S, 3Z)-tert-Butyl 5-hydroxy-2-(N-4-methoxybenzyl)-4-methyl-1-phenylpent-3-en-2-ylcarbamate (2.48). To a solution of 2.11 (133 mg, 0.294 mmol) in CH₂Cl₂ (4.0 mL) at -78 °C, was added dropwise DIBAl-H solution (1.5 M in toluene, 0.78 mL, 1.174 mmol). Stirring was continued at -78 °C for 1 h, and then the reaction was quenched slowly with MeOH (1.5 mL) at this temperature, followed by addition of water (2.0 mL). After the reaction mixture was allowed to reach rt, it was extracted with CH₂Cl₂ (4 mL x 3) and the organic
layer was dried (Na$_2$SO$_4$). The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (Hex:EA/2:1) to provide 2.48 (110 mg, 92%) as a colorless oil. R$_f$ = 0.15 (Hex:EA/4:1). [$\alpha$]$_D^{25}$ = -3 (c = 0.87, CHCl$_3$). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 7.27-6.82 (9H), 5.34 (d, $J = 10.1$ Hz, 1H), 5.10-4.88 (br, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.90-3.70 (m, 1H), 3.70-3.50 (m, 1H), 2.92 (dd, $J = 13.2$, 5.9 Hz, 1H), 2.73 (dd, $J = 13.0$, 8.8 Hz, 1H), 1.66 (d, $J = 1.2$ Hz, 3H), 1.41 (s, 9H). 13C NMR (50 MHz, CDCl$_3$): $\delta$ 158.6, 155.8, 138.5, 131.8, 129.4, 128.5, 128.3, 126.4, 125.6, 113.7, 113.6, 80.3, 61.5, 55.3, 47.5, 40.6, 40.5, 29.5, 21.8. HRMS (FAB) calcd for MH$^+$ (C$_{25}$H$_{34}$NO$_4$) 412.2488, found, 412.2483.

(2S, 3Z)-tert-Butyl 4-formyl-2-(N-4-methoxybenzyl)-1-phenyl pent-3-en-2-ylcarbamate (2.49). To a solution of alcohol 2.48 (95 mg, 0.231 mmol) in benzene (1.7 mL), was added Fe(CO)$_4$PPh$_3$ (30 mg, 0.069 mmol) and trimethylamine oxide (52 mg, 0.693 mmol). After stirring for 12 h, the reaction mixture was filtered through Celite, then Fe(CO)$_4$PPh$_3$ (30 mg, 0.069 mmol) and trimethylamine oxide (52 mg, 0.693 mmol) was added to the filtrate. The mixture was maintained at rt for a further 12 h. After a second filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography (Hex:EA/8:1) to afford aldehyde 2.49 (67 mg, 71%) as a colorless oil. R$_f$ = 0.70 (Hex:EA/4:1). [$\alpha$]$_D^{25}$ = +47 (c = 0.62, CHCl$_3$). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 9.61 (s, 1H), 7.26-6.80 (9H), 6.55 (br, 1H), 5.35-5.20 (m, 1H), 4.30 (br, 2H), 3.80 (s, 3H), 3.20-2.80 (2H), 1.63 (d, $J = 1.2$ Hz, 3H), 1.46 (s, 9H). 13C NMR (50 MHz, CDCl$_3$): $\delta$ 190.6, 158.9, 144.5, 137.4, 136.8, 130.7,
To a suspension of methyltriphenylphosphonium bromide (91 mg, 0.254 mmol) in THF (2.0 mL) at 0 °C, was slowly added n-BuLi (2.5 M solution in hexanes, 86 μL, 0.215 mmol). After 45 min at this temperature, the mixture was cooled to -78 °C and then a solution of aldehyde 2.49 (80 mg, 0.196 mmol) in THF (1.0 mL) was added quickly. Stirring was continued at -78 °C for 30 min, then the reaction was allowed to warm to rt and maintained at this temperature for 2 h. Finally, the reaction was quenched with 1 N HCl (3 mL) and extracted with Et₂O (5 mL x 3). The organic layer was dried (Na₂SO₄), concentrated in vacuo, and the residue was purified by flash chromatography (Hex:EA/8:1) to provide 2.50 (68 mg, 85%) as a colorless oil. R_f = 0.70 (Hex:EA/6:1). 

**[1]_D_25 = +7 (c = 0.62, CHCl₃).** ¹H NMR (200 MHz, CDCl₃): δ 7.26-6.76 (9H), 6.6 (br, 1H), 5.47 (br, 1H), 5.20-5.00 (3H), 4.25 (2 H), 3.79 (s, 3H), 3.05-2.65 (2H), 1.73 (d, J = 2.0 Hz, 3H), 1.38 (s, 9H). ¹³C NMR (50 MHz, CDCl₃): δ 158.4, 138.5, 135.5, 133.4, 131.8, 129.3, 128.8, 128.7, 128.5, 128.3, 126.2, 115.4., 113.6, 79.7, 55.3, 54.8, 43.8, 40.7, 28.5, 19.7. HRMS (FAB) calcd for MH⁺ (C₂₆H₃₄NO₃) 408.2538, found, 408.2528.

To a solution of 2.50 (40 mg, 0.098 mmol) in chloroform (0.4 mL), was added dropwise iodosotrimethylsilane (16.8
μL, 0.118 mmol) and then the mixture was heated at 50 °C for 40 min. After cooling to rt, MeOH (75 μL) was added and the solvent was evaporated in vacuo. Then Et₂O (0.5 mL) and acetic acid (30%, 0.5 mL) were added and stirring was continued for 10 min. The solution was basified by sat. Na₂CO₃ to pH = 9 and then extracted with Et₂O (5 mL x 3). The organic layer was washed with brine (3 mL) and dried (Na₂SO₄). After evaporation of the solvent, the crude product 2.51 (16 mg, 53%) was used in the following reaction without further purification. [α]D²⁵ = +6 (c = 1.40, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.28-6.78 (9H), 6.57 (dd, J = 17.2, 10.4 Hz, 1H), 5.29 (d, J = 9.2 Hz, 1H), 5.20 (dq, J = 17.2, 0.8 Hz, 1H), 5.04 (dq, J = 11.2, 1.6 Hz, 1H), 3.83-3.77 (m, 1H), 3.78 (s, 3H), 3.71 and 3.51 (ABq, J = 13.6 Hz, 2H), 2.79-2.68 (2H), 1.86 (d, J = 1.2 Hz, 3H), 1.7 (br, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 158.7, 138.8, 134.6, 133.9, 133.7, 132.7, 129.6, 129.4, 128.6, 126.5, 114.7, 113.9, 55.5, 55.1, 50.9, 42.7, 20.1. HRMS (FAB) calcd for MH⁺ (C₂₁H₂₆NO) 308.2014, found, 308.2021.

[N-(4-Methoxybenzyl)-N-((2S, 3Z)-4-methyl-1-phenyl hexa-3, 5-dien-2-yl)cyclohexa-1, 3-dienecarboxamide]tricarbonyliron (2.52). Following the procedure for preparation of 2.15a and 2.15b, to a solution of methanesulfonyl chloride (7.4 μL, 0.096 mmol) in freshly distilled CH₂Cl₂ (0.3 mL) was slowly added a solution of carboxylic acid 2.5 (17 mg, 0.065 mmol) and diisopropylethylamine (13.8 μL, 0.083 mmol) in freshly distilled CH₂Cl₂ (0.3 mL). Stirring was continued for 1 h, then diisopropylethylamine (23.3 μL, 0.141 mmol) was added, followed by a the solution of amine 2.51 (32 mg, 0.104 mmol) in freshly distilled
CH$_2$Cl$_2$ (0.3 mL). The reaction was maintained at rt for 24 h, then the temperature was allowed to rise to 40 °C and the reaction mixture was stirred for 10 h. The crude products were purified by flash chromatography (Hex:EA/4:1) to provide two inseparable diastereomers 2.52 (29 mg, 83%). R$_f$ = 0.75 (Hex:EA/2:1). $^1$H NMR (400 MHz, CDCl$_3$) two diastereomers: δ 7.20-6.77 (9H), 6.26-5.60 (3H), 5.40-4.20 (6H), 3.81 (s, 3H), 3.50-3.14 (2H), 2.88-2.81 (m, 1H), 2.10-1.40 (4H), 1.73, 1.72 (d, $J$ = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 174.4, 173.7, 168.5, 168.2, 159.0, 139.4, 135.5, 133.3, 133.0, 129.8, 129.7, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 126.4, 115.3, 114.3, 114.2, 88.9, 88.8, 86.3, 86.2, 85.7, 84.9, 84.2, 74.2, 71.6, 64.6, 64.0, 63.8, 63.5, 58.1, 55.5, 55.4, 52.5, 40.7, 39.8, 26.8, 26.5, 25.7, 25.6, 24.9, 24.0, 22.8, 19.9, 19.8. HRMS (FAB) calcd for MH$^+$ (C$_{31}$H$_{32}$FeNO$_5$) 554.1630, found, 554.1613.

Prepartion of 2.46 from substrates 2.52. According to the general photothermally induced cyclization procedure, a mixture of 2.52 (7.0 mg, 13 μmol) was heated under reflux in 2.5 mL of benzene under CO atmosphere for 10 h to give tricyclic product 2.46 in 10% yield (calculated from $^1$H NMR).
2.4 Literature References


CHAPTER THREE

Iron-Promoted Aldehyde-Diene Cyclocoupling

Reaction
3.1 Introduction

Prins reported a coupling reaction between olefins \(3.1\) and formaldehyde \(3.2\) under the catalysis of an acid in an aqueous solution as shown in Scheme 3.1.\(^1\)\(^2\) Carbon cation \(3.3\) is the key intermediate, and further proceeds to give three different products \(3.4, 3.5,\) and \(3.6\) in different proportions depending on reaction conditions.

\[
\begin{align*}
3.1 + 3.2 &\xrightarrow{H^+ \text{ or } E1} 3.4 + 3.5 + 3.6 \\
\rightarrow &\xrightarrow{H^+ \text{ or } E1} 3.3
\end{align*}
\]

Scheme 3.1 Prins reaction and its mechanism

This carbonyl-ene reaction attracted considerable attention due to its convenience for the construction of a carbon-carbon bond. Recently, many Lewis acid catalysts,\(^3\)\(^-\)\(^8\) such as magnesium, copper, zinc, scandium, ytterbium, titanium and palladium complexes, have been developed for this carbonyl ene reaction, which can give directly coupling products \((3.8 \text{ and } 3.11)\) with retention of the double bond as shown in equations 3.1 and 3.2. The presence of a hydride source can cause loss of the double bond in the products (eq 3.3).\(^9\) Generally, intramolecular reactions lead to results with better chemoselectivity than intermolecular reactions. Significant progress has also been made
in enantioselective intramolecular and intermolecular carbonyl-ene reactions catalyzed by chiral Lewis acids.

In spite of the significance of constructing carbon-carbon bonds, in most cases, these carbonyl-ene reactions are limited to carbonyl groups with an adjacent electron withdrawing group, especially for intermolecular reactions. The other disadvantage is the isomerization of products caused by double bond migration.

Carbonyl-diene reactions catalyzed by nickel complexes in the presence of a hydride source (Et$_3$B or Et$_2$Zn) were also reported to afford product 3.13 with loss of one double bond as shown in equation 3.3.$^9,^{10}$

\[
\begin{align*}
3.7 \xrightarrow{Yb(OTf)_3, \text{CH}_2\text{Cl}_2, \text{rt}} & 3.8a : 3.8b \\
\text{(3.1)} & 20 : 1
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \text{Me} + \text{HCOOMe} \xrightarrow{(R)\text{-catalyst, Sieves, } -30^\circ\text{C}} \text{Me} \text{Me} \xrightarrow{\text{OH}} \text{Me} \text{Me} \\
3.9 & \text{3.10} \hspace{1cm} 3.11a \hspace{1cm} 3.11b \\
\text{(3.2)} & \text{36% (91% ee)} \hspace{1cm} \text{53% (98% ee)}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \text{CHO} \xrightarrow{\text{Nickel complex, Et}_3\text{B or Et}_2\text{Zn, THF, rt}} \text{MeO}_2\text{C} \\
3.12 & \text{3.13} \\
\text{(3.3)} & \text{n = 1 or 2}
\end{align*}
\]

As mentioned in Chapter 2, compounds 2.29a/b might be important intermediates for the total synthesis of 18-deoxycytochalasin H and need to be converted to the corresponding aldehydes 3.14a/b as shown in Scheme 3.2. Subsequently accomplishing
conversion of both aldehydes 3.14a/b to the key intermediate 2.28 would require a carbonyl-ene type of coupling reaction. Consequently, considering the limited studies on carbonyl-diene coupling reactions, we initiated a study on an intramolecular carbonyl-diene cyclocoupling reaction promoted by an iron tricarbonyl moiety.

Scheme 3.2 Retrosynthetic analysis for 18-deoxyctochalasin H

3.2 An intramolecular carbonyl-diene cyclocoupling reaction promoted by iron tricarbonyl moiety
With aldehydes 2.44a/b (intermediates in Chapter 2) in hand, we investigated the possibility of this iron-promoted carbonyl-diene cyclocoupling reaction to form a 5-membered ring as shown in equation 3.4. Subjection of 2.44a/b to photothermal cyclization conditions (mesitylene, CO, 350 nm, 165 °C) afforded a demetallated cyclization product 3.15 with retention of the conjugated diene in 19% yield. Two decarbonylation products 3.16 and 3.17 were also isolated in 36% combined yield. Attempted optimization of this reaction at lower temperature or under thermal cyclization conditions gave even worse results. In order to more easily examine this type of reaction further, a simple model system was studied before converting 2.44a/b to aldehydes 3.14a/b (Scheme 3.2).

![Scheme 3.3 Preparation of substrates](image)

We examined the reactivity of substrates 3.20a-c and 3.21, each having a pendant carbonyl group, in anticipation that a carbonyl-diene spirocyclization could also be promoted by iron to afford products with a functionalizable hydroxyl group at C4 (for numbering, see Table 3.1 graphic). Racemic complexes 3.20a-c were readily prepared in
good yields starting with racemic iron complexed dienylcarboxylic acids 3.18a-c\textsuperscript{11-14} through amidation followed by ester to aldehyde reduction with DIBAl-H at low temperature (Scheme 3.3). Treatment of 3.20a with MeMgBr at -78 °C followed by in situ Mukaiyama oxidation of the alkoxide afforded racemic substrate 3.21 with a pendant ketone in 62% yield over two steps.\textsuperscript{15}

Table 3.1. Cyclization of substrates 3.20a-c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions\textsuperscript{a}</th>
<th>Time (h)</th>
<th>Products (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.22</td>
</tr>
<tr>
<td>1</td>
<td>3.20a</td>
<td>A</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3.20a</td>
<td>B</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>3.20a</td>
<td>C</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>3.20a</td>
<td>D</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>3.20a</td>
<td>E</td>
<td>12</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>3.20a</td>
<td>E</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>3.20b</td>
<td>C</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>3.20c</td>
<td>E</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Conditions: A: n-Bu\textsubscript{2}O, 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. \textsuperscript{a}Temperature of oil bath. \textsuperscript{b}Isolated percent yields.
With these substrates in hand, we investigated their reactivity under various conditions previously found to effect diene/alkene cyclocoupling. Substrate 3.20a was subjected to thermal cyclization conditions (n-Bu₂O, CO, 145 °C) and the anticipated spirolactam complex 3.22a was isolated in only 4% yield with loss of most starting material (Table 3.1, entry 1). Photothermal cyclization (benzene, 350 nm, CO, 80 °C) afforded 3.22a in better yield (17%) with 42% recovered starting material (Table 3.1, 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 3.25a, obtained in 5% yield. The hydrogen source for formation of this monoolefin compound was not determined. When the cyclization of 3.20a was attempted under various conditions by changing solvent, reaction temperature and reaction time (Table 3.1, 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 3.22a (47%), 3.24a (7%), demetallated product 3.23a (6%), and side product 3.25a (8%). The combined yield for both diene regioisomers was 60% in 8:1 ratio ((3.22a+3.23a)/3.24a).

Complexes 3.22a and 3.24a were easily distinguished by their NOESY spectra, in which NOE effects can be observed between H₁₀ and H₄ in 3.22a and between H₆ and H₄ in 3.24a (see structures for numbering). The stereochemistry at C₄ and C₅ is presumed to be the same as for our previously reported [6+2] ene type of spirocyclization.¹⁶ Complex 3.22a was readily demetallated by CuCl₂ in EtOH to provide 3.23a in 79% yield.¹⁷
Cyclization of methyl-substituted complex 3.20b under photothermal conditions afforded a 4:1 mixture of regioisomeric spirolactam complexes 3.22b and 3.24b in 25% combined yield (Table 3.1, entry 7). Methoxy-substituted substrate 3.20c underwent cyclization to give a single product 3.22c but in only 7% yield (Table 3.1, entry 8). Substantial amounts of polar, uncharacterizable material were also formed during this reaction.

Subjection of ketone substrate 3.21 to photothermal cyclization conditions (CO, benzene, 350 nm and under reflux) gave uncyclized regioisomers 3.26a and 3.26b from diene rearrangement and no cyclization products were observed as shown in equation 3.5.

\[
\begin{align*}
\text{Fe(CO)}_3\text{N} & \text{O} \quad \text{O} \\
\text{3.21} & \quad \text{CO, Mesitylene} \quad \text{350 nm, 160 °C} \\
\rightarrow & \\
\text{Fe(CO)}_3\text{N} & \text{O} \\
\text{3.26a} & \quad \text{24%} \\
\quad & \\
\text{O} & \text{Ph} \\
\text{3.26b} & \quad \text{31%}
\end{align*}
\]

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.\textsuperscript{16} Under either thermal or photothermal conditions, one carbonyl ligand is dissociated from the iron atom in substrate 3.20a to lead to a 16e iron complex 3.27 with a vacant coordination site, which can be occupied by coordination of the iron atom with the aldehyde carbonyl double bond to form intermediate 3.28 (Scheme 3.4, \(\eta^2\) coordination is assumed by analogy with the reactions of alkenes, but we cannot rule out initial \(\eta^1\) coordination at the present time). Subsequent cyclization gives \(\pi\) allyl complex 3.29 followed by hydride migration to afford 3.30. Then reductive elimination followed
by recapture of one carbonyl ligand affords product 3.22a, which can undergo diene migration through intermediates 3.31 and 3.32 under the reaction conditions to give regioisomer 3.24a as a minor product.

Scheme 3.4 Proposed mechanism for aldehyde-diene cyclocoupling reaction

Generally, iron promoted [6+2] ene spirocyclization affords these two regioisomers in equivalent amounts, but this carbonyl-ene reaction gives the directly formed lactam 3.22a as major product. This stereoselectivity is likely due to coordination of the iron atom with the newly formed hydroxyl group in a 16e complexed intermediate 3.31, also formed through dissociation of one carbonyl from 3.22a under the reaction conditions, which stabilizes 3.31. This coordination effect geometrically favors the position for the diene in the 16e intermediate 3.31 and disfavors postcyclization diene migration to form
intermediate 3.32, which can lead to minor product 3.24a by analogy with the related alkene coupling reaction. Since racemic starting materials are used in this model study, both products 3.22a and 3.24a are also racemic. Even if optically pure starting materials are used, this carbonyl-diene coupling reaction will still give racemic products due to an iron-promoted precyclization diene migration from reaction intermediate 3.27 as observed for [6+2] ene type of spirocyclization reactions.16

In order to investigate the capability of this iron-promoted carbonyl ene reaction for the formation of a 6-membered lactam, substrate 3.33 was prepared in good yield through homologation of aldehyde 3.20a as shown in Scheme 3.5.18 Subjection of 3.33 to photothermal conditions gave complexed secondary amide 3.34 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 demetallated products. Considering the length of the side chain of 3.33, a retro Michael reaction to generate 3.34 is not unexpected under these reaction conditions.

Scheme 3.5 Preparation and cyclization of 3.33

Complexes 3.41a/b and 3.42a/b were also prepared starting with commercially available aminoalcohol 3.35, which was protected and then oxidized (Swern oxidation) to give aldehyde 3.36 in 88% yield over two steps (Scheme 3.6).19 Treatment of 3.36 with triethyl phosphonoacetate under Masamune-Roush conditions,20 followed by deprotection of the amino group afforded 3.37 in 73% yield over two steps. Coupling of acid 3.18a via
its acyl mesylate with secondary amine 3.37 afforded amide complex 3.38 (76% yield) with a pendant olefin, which underwent [6+2] ene type of spirocyclization under photothermal conditions to give a 1.7:1 mixture of lactam complexes 3.39a and 3.39b in 78% yield.

Scheme 3.6 Preparation of substrates 3.41a/b and 3.42a/b
Attempted direct reduction of ester 3.39 to aldehyde 3.41 using DIBAI-H was problematic. Aldehydes 3.41a/b (as a 3.5:1 mixture) were therefore obtained by reducing esters 3.39a/b with LiBH₄ to the corresponding alcohols 3.40a and 3.40b, obtained in 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 3.41a/b by treatment with MeOCH=PPh₃ under Wittig olefination conditions and subsequent hydrolysis afforded aldehyde substrates 3.42a/b in 4:1 ratio and 88% yield over two steps.¹⁸

Subjection of 3.41a/b to photothermal conditions (mesitylene, 350 nm, CO, 160 °C) gave a single complexed tricyclic compound 3.43 and its demetallation product 3.44 in 21% and 26% yields, respectively (eq 3.6). Complex 3.41a can cyclize directly to give the desired products, but 3.41b needs to be converted to 3.41a first via thermal equilibrium under the cyclization conditions, and then undergoes cyclization.¹⁶ Complex 3.43 was readily converted to pure organic compound 3.44 by demetallation with CuCl₂ in EtOH, and the combined yield for formation of 3.44 was 42% over two steps. A 1.6:1 mixture of known¹⁶ compounds 3.45a/b was also isolated in 17% yield, resulting from iron promoted decarbonylation of 3.41a/b, analogous to the decarbonylation observed during the cyclization of 2.44a/b (eq 3.4).
The stereochemistry of compound 3.44 was determined by 2D COSY and NOE difference spectra as shown in Figure 3.1. Since the chirality of C4 is established during the spirocyclization, the stronger NOE effect between H₄ and H₃a (5.6%) than between H₄ and H₃b (1.2%) indicates that H₄ and H₃b are *trans* on the 5-membered lactam ring. Then observation of NOE effect between H₃b and H₅b (3.8%) can distinguish H₅b from H₅a, which is very important to further determine the stereochemistry of C6 and C7. It turns out H₆ and H₅b are *cis* on the newly formed ring because H₆ and H₅b show stronger NOE effect (5.0%) than do H₆ and H₅a (3.1%). The observation of the NOE effect only between H₇ and H₅b instead of between H₇ and H₅a confirms H₇ is *cis* to H₅b on the newly formed ring.

**Figure 3.1.** Determination of the stereochemistry for compound 3.44
In order to directly compare this iron promoted carbonyl-diene reaction with the known nickel catalyzed carbonyl-diene coupling procedure, decomplexed aldehydes 3.46a/b were prepared in good yields from complexed alcohols 3.40a/b by demetallation and subsequent oxidation with Dess Martin reagent (Scheme 3.7). Treatment of 3.46a with Ni(acac)$_2$ and Et$_2$Zn in THF afforded two isomers in 9% and 52% yields, respectively. The major isomer was fully characterized as 3.47b by NMR and mass spectra. The stereochemistry at C7 is dictated by the molecular structure of starting material 3.46a in which cyclocoupling can proceed only on the top of the diene ring, but the stereochemistry at C6 was deduced from the known characteristics of this nickel
catalyzed reaction, in which the hydroxyl oxygen coordinates with metal catalyst in reaction intermediates. Similarly, the minor isomer was assigned as 3.47a. Subsequent oxidation of 3.47a and 3.47b with Dess Martin reagent gave two ketone isomers 3.48a and 3.48b, which further confirmed that 3.47a and 3.47b are a pair of regioisomers instead of two alcohol epimers. Similarly, 3.46b was also treated with Ni(acac)2 and Et2Zn in THF to afford 3.49a and 3.49b, each in 11% yield. Increased amount of Ni(acac)2 and Et2Zn, and prolonged reaction time caused loss of most material. Subsequent oxidation of 3.49a and 3.49b with Dess Martin reagent also afforded two ketone isomers 3.40a and 3.40b 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 3.42a/b was also investigated under both thermal and photothermal conditions and produced three regioisomers 3.51a-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 3.8. One carbonyl ligand dissociates from iron under the reaction conditions and then subsequent oxidative addition of the aldehyde leads to intermediate 3.52, on which decarbonylation occurs to give intermediate 3.53. Then reductive elimination forms π allyl complex 3.54, which can undergo a second reductive elimination and demetallation to afford 3.51b or 3.51c. Presumably 3.51a results from double bond migration on the initial products. Note that substrate 3.41 also gives products of decarbonylation (3.45) but there is no decarbonylative cyclization because this would require 4-membered ring formation.
In order to investigate alternate cyclization methods that can avoid decarbonylation, a 1:2.7 mixture of 3.55a/b was prepared in 57% yield by treating complexes 3.42a/b with Me₃NO in benzene (Scheme 3.9). Subsequent treatment of the 3.55a/b mixture with 2 N HCl led to 100% recovery of 3.55b and cyclization product 3.56 in 75% yield from its corresponding substrate 3.55a, which was completely consumed after the reaction (path a in Scheme 3.9). A better combined yield for formation of 3.56, 63% over two steps from 3.42a/b, was obtained by demetallation with CuCl₂ in EtOH, followed by direct treatment of the product mixture with 2 N HCl (path b in Scheme 3.9). These results indicate 3.56 is formed through a Prins reaction from demetallated compound 3.55a rather than a hetero Diels-Alder reaction. However, due to difficulty in forming a seven-membered
ring with the diene in 3.55b, this compound does not undergo Prins reaction and remains unchanged under the conditions used here.

\[
\begin{array}{c}
3.42a + 3.42b \xrightarrow{\text{Me$_3$NO, benzene}} 3.55a + 3.55b \\
\text{path a: } 60\% (75\%)^a \\
\text{path b: } 50\% (63\%)^a
\end{array}
\]

\[
\begin{array}{c}
\text{path b: } 19\% (95\%)^a \text{ (two steps)}
\end{array}
\]

\[3.55a \quad 3.55b\]

\[\text{N} \quad \text{O} \quad \text{Ph} \quad \text{N} \quad \text{O} \quad \text{Ph} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{O} \quad \text{Ph} \quad \text{H} \quad \text{H} \]

\[2 \text{ N HCl/THF(1/1)}
\]

\[3.56
\]

\[a\text{Parenthesized yields are based on the corresponding single aldehyde isomer.}

Scheme 3.9 Prins reaction from substrates 3.42a/b

In order to find an alternative reaction that might allow the formation of a six-membered ring, substrate 3.57 bearing a pendant oxime functional group was prepared from aldehyde 3.20a (Scheme 3.10). Under photothermal cyclization conditions (CO, 350 nm, PhH, 85 °C), 3.57 underwent dehydration to afford only nitrile 3.58 in 24% yield along with recovered starting material, and no expected cyclized product was observed. Thermal cyclization conditions (n-Bu$_2$O, CO, 142 °C) gave similar results. Subjection of nitrile 3.58 to more forcing conditions (CO, 350 nm, mesitylene, 160 °C) gave no cyclized product, either. Substrates 3.59 and 3.60 were also prepared from aldehyde
3.20a, and neither of them proceeds to a cyclization reaction under photothermal conditions. Both reactions gave a complex mixture with formation of many spots on analytical TLC plates, which were not isolated and characterized.

![Scheme 3.10](image)

Scheme 3.10 Investigations on new substrate systems
3.3 Conclusion

An intramolecular iron promoted aldehyde-diene coupling reaction was discovered and investigated to provide spirocyclic or tricyclic 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.

However, the new iron-promoted aldehyde-diene cyclocoupling reaction did not show any possibility for both spirocyclization and bicyclization to form a 6-membered ring. Most investigations on some potential alternative reactions also were not very productive, the best result being a cyclization reaction of 3.55a under Prins reaction conditions to give 3.56 with a 6-membered ring.
3.4 Future Work

Since \textbf{3.42a/b} underwent a decarbonylative cyclization reaction to give tricyclic compounds \textbf{3.51a-c} with formation of a five-membered ring instead of a six-membered ring as shown in Scheme 3.8, substrate \textbf{3.61a/b} with one more carbon on pendant side chain than \textbf{3.42a/b} might also proceed to give decarbonylative cyclization products \textbf{3.62a-c} with formation of a six-membered ring, which can be converted to one single compound \textbf{3.63} through some transformations (Scheme 3.11).

\begin{center}
\includegraphics[width=\textwidth]{scheme.png}
\end{center}

\textbf{Scheme 3.11} Future work
3.5 Experimental Section

Cyclization of 2.44a/b to give compounds 3.15, 3.16 and 3.17. According to the general procedure for the photothermally induced cyclization, a solution of aldehyde 2.44a/b (8.7 mg, 15.7 μmol) in mesitylene (2.4 mL) was heated at 165 °C for 9 h. Preparative TLC (Hex:EA/2:1) afforded 3.15 (1.2 mg, 19%). R_f = 0.20 (Hex:EA/1:1). ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.20 (5H), 7.07 (d, J = 4.8 Hz, 2H), 6.87 (d, J = 5.6 Hz, 2H), 6.05 (m, 1H), 5.91 (dd, J = 6.0, 3.6 Hz, 1H), 5.80 (dd, J = 6.8, 2.4 Hz, 1H), 5.35 (d, J = 6.4 Hz, 1H), 5.09 and 3.92 (ABq, J = 9.6 Hz, 2H), 3.82 (s, 3H), 3.64 (m, 1H), 3.42 (m, 1H), 3.25 (m, 1H), 3.12 (dd, J = 8.8, 3.6 Hz, 1H), 2.58 (dd, J = 8.8, 5.6 Hz, 1H), 2.64 (d, J = 4.0 Hz, 1H), 1.78 (m, 1H), 1.65 (m, 1H), 0.40 (d, J = 4.8 Hz, 3H). ^13C NMR (100 MHz, CDCl_3): δ 177.1, 159.5, 137.2, 130.3, 129.7, 128.9, 128.5, 127.3, 127.0, 124.5, 123.2, 122.9, 114.3, 81.8, 56.3, 55.5, 53.9, 52.2, 45.6, 44.7, 42.1, 40.6. HRMS (FAB) calcd for MH^+ (C_{27}H_{30}NO_3) 416.2225, found, 416.2220. The mixture of 3.16 and 3.17 (3.0 mg, 36%). R_f = 0.65 (Hex:EA/1:1). One isomer: ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.03 (7H), 6.83 (d, J = 5.6 Hz, 2H), 5.52 (dd, J = 4.0, 3.2 Hz, 1H), 5.28 (dd, J = 3.6, 3.2 Hz, 1H), 4.97 and 3.88 (ABq, J = 10.0 Hz, 2H), 3.80 (s, 3H), 3.33 (m, 1H), 3.17 (dd, J = 5.6, 3.2 Hz, 1H), 3.09 (dd, J = 8.8, 3.2 Hz, 1H), 2.76 (dd, J = 8.8, 5.6 Hz, 1H), 2.63 (d,
$J = 4.0$ Hz, 1H), 1.98 (dd, $J = 10.4$, 2.4 Hz, 1H), 1.92-1.87 (2H), 0.90-0.84 (2H), 0.31 (t, $J = 4.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 212.0, 159.3, 137.7, 129.7, 129.6, 128.9, 127.0, 114.2, 86.6, 85.8, 77.5, 62.1, 61.4, 60.4, 55.5, 51.6, 45.0, 44.1, 40.3, 29.9, 22.7, 11.4. HRMS (FAB) calcd for MH$^+$ (C$_{29}$FeH$_{30}$NO$_5$) 528.1474, found, 528.1456. The other isomer: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.30-7.26 (2H), 7.23-7.21 (m, 1H), 7.08 (d, $J = 5.6$ Hz, 2H), 7.03 (d, $J = 5.2$ Hz, 2H), 6.84 (d, $J = 6.0$ Hz, 2H), 5.69 (dd, $J = 3.6$, 3.6 Hz, 1H), 5.48 (dd, $J = 3.6$, 3.2 Hz, 1H), 4.89 and 3.84 (ABq, $J = 9.6$ Hz, 2H), 3.80 (s, 3H), 3.14-3.12 (2H), 2.95 (dd, $J = 8.8$, 3.2 Hz, 1H), 2.66 (d, $J = 8.8$ Hz, 1H), 2.43 (dd, $J = 8.8$, 6.4 Hz, 1H), 2.09-2.06 (m, 1H), 1.94 (dd, $J = 10.0$, 2.4 Hz, 1H), 1.71-1.67 (2H), 0.82-0.77 (m, H), 0.34 (t, $J = 4.8$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 211.9, 159.3, 137.6, 130.0, 129.8, 129.5, 128.9, 127.1, 114.3, 114.2, 88.6, 82.6, 77.5, 68.5, 63.8, 61.2, 55.5, 50.6, 46.8, 44.8, 40.3, 33.3, 23.5, 10.4. HRMS (FAB) calcd for MH$^+$ (C$_{29}$FeH$_{30}$NO$_5$) 528.1474, found, 528.1468.

(3-Methylcyclohexa-1,3-dienecarboxylic acid)tricarbonyliron (3.18b). To a solution of (methyl 3-methylcyclohexa-1,3-dienecarboxylate) tricarbonyliron (130 g, 0.45 mmol) in a mixture of dioxane (0.7 mL) and methanol (0.7 mL) which was purged with Ar for 10 min, was added 30% KOH solution (0.36 mL) which was also bubbled with Ar for 10 min before addition. After the reaction solution was stirred under Ar at rt for 24 h, 2N HCl was added to adjust to pH = 2-3. The aqueous solution was extracted with CH$_2$Cl$_2$ (3 mL x 3). The combined organic layer was washed with brine (2 mL x 2), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/2:1) afforded acid 3.18b (90
mg, 73%). Rf = 0.20 (Hex:EA/2:1). MP 182-185 °C. 1H NMR (400 MHz, DMSO): δ 12.30-12.15 (br, 1H), 5.96 (s, 1H), 3.40-3.40 (br, 1H), 2.07 (s, 3H), 2.00-1.90 (m, 1H), 190-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.35-1.28 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 211.6, 174.0, 103.5, 89.1, 67.4, 63.9, 26.0, 23.3, 22.0. HRMS (FAB) calcd for MH+(C11H11FeNO5) 278.9956, found, 278.9952.

**General procedure for the synthesis of amide complexes**

3.19a-c. Exemplified with [ethyl 2-(N-phenylcyclohexa-1,3-diene carboxamido)acetate]tricarbonyliron (3.19a). To a solution of complexed carboxylic acid 3.18a (170 mg, 0.64 mmol) and diisopropylethylamine (135 μL, 0.83 mmol) in freshly distilled CH2Cl2 (10 mL) under argon at 0 °C, was quickly added methanesulfonyl chloride (74 μL, 0.96 mmol). Stirring was continued at this temperature for 1 h. Diisopropylethylamine (233 μL, 1.41 mmol) was added, followed by a solution of ethyl 2-(phenylamino)acetate (184 mg, 1.03 mmol) in freshly distilled CH2Cl2 (2.0 mL). The temperature was allowed to reach 40 °C and then the reaction mixture was stirred for 24 h. After CH2Cl2 (20 mL) was added, the organic layer was washed with 1 N HCl (8 mL x 3) and brine (5mL x 2), dried (Na2SO4), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/4:1) afforded amide 3.19a (210 mg, 77%). Rf = 0.45 (Hex:EA/4:1). 1H NMR (400 MHz, CDCl3): δ 7.50-7.38 (5H), 5.45 (d, J = 4.0 Hz, 1H), 5.02 (dd, J = 9.6, 6.0 Hz, 1H), 4.49 and 4.14 (ABq, J = 16.8 Hz, 2H), 4.20-4.10 (2H), 3.23 (m, 1H), 1.99-1.92 (m, 1H), 1.83-1.75 (m, 1H), 1.64-1.58 (m, 1H), 1.40-1.33 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl3):
δ 173.2, 169.3, 144.2, 130.1, 128.0, 127.9, 86.7, 84.2, 70.6, 63.5, 61.3, 53.7, 26.3, 25.2, 14.3. HRMS (FAB) calcd for MH⁺ (C₂₀H₂₀FeNO₆) 426.0640, found, 426.0633.

[Ethyl 2-(3-methyl-N-phenylcyclohexa-1,3-dienecarboxamido)acetate|tricarbonyliron (3.19b). From 3.18b (600 mg, 2.16 mmol) was prepared 3.19b and purified by flash chromatography (Hex:EA/4:1) in 77% yield. Rf = 0.40 (Hex:EA/4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.31 (5H), 5.52 (s, 1H), 4.47 and 4.16 (ABq, J = 16.8, 2H), 4.21-4.10 (2H), 3.21 (dd, J = 3.2, 2.0 Hz, 1H), 1.92 (s, 3H), 1.78-1.68 (2H), 1.65-1.57 (m, 1H), 1.32-1.21 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 173.7, 169.4, 144.2, 130.0, 128.0, 101.8, 87.4, 66.6, 66.2, 61.3, 54.0, 26.6, 24.7, 22.0, 14.3. HRMS (FAB) calcd for MH⁺ (C₂₁H₂₂FeNO₆) 440.0797, found, 440.0792.

[Ethyl 2-(3-methoxy-N-phenylcyclohexa-1,3-dienecarboxamido)acetate|tricarbonyliron (3.19c). From 3.18c (500 mg, 1.7 mmol) was prepared 3.19c and purified by flash chromatography (Hex:EA/4:1). Rf = 0.40 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.35 (5H), 5.52 (d, J = 2.0 Hz, 1H), 4.46 and 4.17 (ABq, J = 16.8 Hz, 2H), 4.22-4.10 (2H), 3.49 (s, 3H), 3.44 (d, J = 2.4 Hz, 1H), 1.66-1.50 (3H), 1.25 (t, J = 7.2 Hz, 3H), 1.20-1.14 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 174.3, 169.4, 144.1, 138.5, 130.1, 128.2, 128.1, 69.3, 61.3, 59.2, 55.9, 54.3, 54.2, 26.9, 24.2, 14.3. HRMS (FAB) calcd for MH⁺ (C₂₁H₂₂FeNO₇) 456.0746, found, 456.0743.
General procedure for the synthesis of aldehyde complexes

3.20a-c. Exemplified with [N-(formylmethyl)-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (3.20a). To a solution of ester 3.19a (420 mg, 1.00 mmol) in freshly distilled CH₂Cl₂ (10 mL) under Ar at -78 °C, was slowly added DIBAl-H solution (1.5 M in toluene, 3.3 mL, 5.00 mmol). Stirring was continued for 1h at -78 °C, then the reaction was quenched by slow addition of MeOH (5 mL) at this temperature, followed by 1 N HCl (10 mL). The temperature was allowed to reach rt, then the reaction mixture was extracted with CH₂Cl₂ (10 mL x 3), washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Hex:EA/3:1) to afford 3.20a (285 mg, 75%) as a yellow oil. R₇ = 0.40 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 9.58 (s, 1H), 7.42-7.24 (5H), 5.42 (dd, J = 4.4, 1.2 Hz, 1H), 5.00-4.97 (m, 1H), 4.37 and 4.15 (ABq, J = 16.8 Hz, 2H), 3.21-3.19 (m, 1H), 1.90-1.80 (m, 1H), 1.76-1.65 (m,1H), 1.60-1.50 (m, 1H), 1.33-1.25 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 197.3, 173.5, 144.0, 130.4, 128.3, 127.6, 86.6, 84.5, 69.8, 63.7, 61.7, 26.2, 25.1. HRMS (FAB) calcd for MH⁺ (C₁₈H₁₆FeNO₅) 382.0378, found, 382.0376.

[N-(Formylmethyl)-3-methyl-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (3.20b). Ester 3.19b (200 mg, 0.45 mmol) was reduced by DIBAl-H (1.51 mL, 1.5 M in toluene) to afford aldehyde 3.20b (131 mg, 73%) purified by flash chromatography (Hex:EA/3:1). R₇ = 0.40 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 9.65 (s, 1H), 7.50-7.30 (5H), 5.54 (s, 1H), 4.42 and 4.21 (ABq, J = 17.6 Hz, 2H), 3.24
(d, J = 1.6 Hz, 1H), 1.94 (s, 3H), 1.76-1.68 (2H), 1.64-1.59 (m, 1H), 1.30-1.24 (m, 1H).

13C NMR (100 MHz, CDCl3): δ 197.5, 174.0, 144.0, 130.0, 128.3, 127.8, 102.2, 87.3, 66.4, 65.8, 62.0, 26.6, 24.6, 22.0. HRMS (FAB) calcd for MH+ (C19H18FeNO5) 396.0534, found, 396.0545.

**[N-(Formylmethyl)-3-methoxy-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyliron (3.20c).** Ester 3.19c (200 mg, 0.44 mmol) was reduced to aldehyde 3.20c (128 mg, 71%) purified by flash chromatography (Hex:EA/2:1). Rf = 0.35 (Hex:EA/2:1). 1H NMR (400 MHz, CDCl3): δ 9.66 (s, 1H), 7.49-7.30 (5H), 5.54 (d, J = 2.4 Hz, 1H), 4.42 and 4.21 (ABq, J = 17.6 Hz, 2H), 3.51 (s, 3H), 3.47 (d, J = 2.8 Hz, 1H), 1.70-1.50 (3H), 1.20-1.13 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 197.4, 174.6, 144.0, 138.8, 130.4, 128.4, 128.0, 69.2, 62.2, 58.6, 56.1, 54.4, 26.8, 24.1. HRMS (FAB) calcd for MH+ (C19H18FeNO6) 412.0484, found, 412.0487.

**[N-(2-Oxopropyl)-N-phenylcyclohexa-1,3-dienecarboxamide]tricarbonyl iron (3.21).** To a solution of aldehyde 3.20a (45.0 mg, 118.0 μmol) in THF (1.1 mL) under Ar at -78 °C, was added methylmagnesium bromide (1.4 M in toluene, 0.11 mL, 153 mmol). Stirring was continued at -78 °C for 2 h. After the temperature was raised to 0 °C, a solution of 1, 1′-(azodicarbonyl)-dipiperidine (33.0 mg, 130 μmol) in THF (0.4 mL) was added and the reaction was maintained at this temperature for 1 h and then at rt for 1 h. The solution was quenched with brine (3 mL), extracted with Et2O (5 mL x 3), dried (Na2SO4), filtered
and concentrated in vacuo. Pure ketone 3.21 (29 mg, 62%) was obtained by flash chromatography ((Hex:EA/3:1) followed by a second flash chromatography (1% THF in CH₂Cl₂). Rₐ = 0.40 (Hex:EA/2:1); Rₐ = 0.50 (1% THF in CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.32 (5H), 5.40 (d, J = 4.4 Hz, 1H), 5.00 (dd, J = 5.2, 5.6 Hz, 1H), 4.53 and 4.26 (ABq, J = 17.6 Hz, 2H), 3.30-3.20 (m, 1H), 2.13 (s, 3H), 1.99-1.92 (m, 1H), 1.82-1.76 (m, 1H), 1.63-1.55 (m, 1H), 1.42-1.35 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 202.5, 172.9, 144.2, 130.1, 128.0, 127.8, 86.5, 84.1, 70.8, 63.5, 61.4, 27.4, 26.2, 25.4. HRMS (FAB) calcd for MH⁺ (C₁₉H₁₈FeNO₅) 396.0534, found, 396.0537.

![Cyclization of 3.20a to afford 3.22a, 3.23a, 3.24a and 3.25a.](image)

Cyclization of 3.20a to afford 3.22a, 3.23a, 3.24a and 3.25a. According to the general procedure for the photothermally induced cyclization, a solution of aldehyde 3.20a (43 mg, 0.11 mmol) in toluene (22 mL) was heated at 100 °C for 12 h. Flash chromatography (Hex:EA/3:1) afforded 3.22a (20.2 mg, 47%) as a pale yellow solid. MP 189-191 °C. Rₐ = 0.60 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.57 (dd, J = 9.2, 1.6 Hz, 2H), 7.37-7.33 (2H), 7.13 (t, J = 7.2 Hz, 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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₁₈H₁₆FeNO₅) 382.0378, found, 382.0378. Purification of the remaining material by preparative TLC (2% MeOH...
in CH$_2$Cl$_2$) gave recovered starting material (7.0 mg, 8%) and afforded 3.24a (2.9 mg, 7%) as a pale yellow solid. MP 50 °C (decomposed). R$_f$ = 0.50 (2% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CH$_3$OD:CDCl$_3$/1:1): $\delta$ 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$_3$OD:CDCl$_3$/1:1): $\delta$ 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)$_3$]$_2$ (C$_{15}$H$_{16}$NO$_2$) 242.1181, found, 242.1173.

3.23a (1.6 mg, 6%). MP 155-157 °C. R$_f$ = 0.40 (2% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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), 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$_3$): $\delta$ 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$_2$) 244.1337, found, 244.1331.

3.25a (2.2 mg, 8%). MP 195-197 °C. R$_f$ = 0.30 (2% MeOH in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 175.7, 139.6, 135.8, 129.1, 124.8, 122.2, 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.
Demetallation of 3.22a to afford 3.23a. According to the general procedure B of demetallation, complex 3.22a (11 mg, 29 μmol) was treated with CuCl₂ in EtOH for 20h. The crude products were purified by preparative TLC to give 3.23a (5.5 mg, 79%).

Cyclization of 3.20b to afford 3.22b and 3.24b. According to the general procedure for the photothermally induced cyclization, a solution of aldehyde 3.20b (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 3.22b (4.5 mg, 20%) as a pale yellow solid. MP 158-160 °C. R_f = 0.70 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₁₀H₁₃FeNO₅) 396.0534, found, 396.0552. Further purification of the remaining material by preparative TLC (2% THF in CH₂Cl₂) gave recovered 3.20b (4.5 mg, 19%) and afforded 3.24b (1.2 mg, 5%). MP 170 °C (decomposed). R_f = 0.20 (2% THF in CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₁⁹H₁₈FeNO₅) 396.0534, found, 396.0542.

**Cyclization of 3.20c to afford 3.22c.** According to the general procedure for the photothermally induced cyclization, aldehyde 3.20c (29 mg, 0.07 mmol) in toluene (15 mL) was heated at 100 °C for 12 h. Preparative TLC (Hex:EA/2:1) afforded 3.22c (1.9 mg, 7%). Rf = 0.70 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₁⁹H₁₈FeNO₆) 412.0484, found, 412.0487.

**Cyclization of ketone 3.21 to give 3.26a and 3.26b.** According to the general procedure for the photothermally induced cyclization, a solution of ketone 3.21 (4.5 mg, 11.4 μmol) in mesitylene (1.3 mL) was heated at 160 °C for 9 h. Preparative TLC (Hex:EA/2:1) afforded 3.26a (1.1 mg, 24%). Rf = 0.20 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.31 (3H), 7.19 (d, J = 8.4 Hz, 2H), 5.44-5.41 (m, 1H), 5.36 (dd, J = 6.4, 5.2 Hz, 1H), 4.30 and 4.24 (ABq, J = 15.6 Hz, 2H), 3.04-3.01 (m, 1H), 2.89-2.80
(2H), 2.08 (s, 3H), 1.73-1.60 (2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 211.8, 202.3, 174.9, 142.8, 130.0, 128.7, 128.1, 86.6, 85.5, 60.8, 60.1, 59.8, 40.7, 30.2, 27.5. HRMS (FAB) calcd for MH$^+$ (C$_{19}$H$_{18}$FeNO$_5$) 396.0534, found, 396.0533. Further purification by preparative TLC (1% THF in CH$_2$Cl$_2$) afforded another isomer 3.26b (1.4 mg, 31%). $R_f$ = 0.50 (Hex:EA/2:1); $R_f$ = 0.6 (1% THF in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39-7.25 (5H), 5.54 (d, $J$ = 6.8 Hz, 1H), 4.61 and 4.55 (ABq, $J$ = 17.6 Hz, 2H), 3.03-2.98 (2H), 2.20 (s, 3H), 1.60-1.53 (m, 1H), 1.48-1.39 (m, 1H), 1.29-1.20 (m, 1H), 0.80-0.73 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 211.0, 201.8, 169.5, 144.1, 129.8, 128.3, 127.7, 97.4, 89.4, 63.2, 60.6, 60.1, 27.4, 24.1, 23.6. HRMS (FAB) calcd for MH$^+$ (C$_{19}$H$_{18}$FeNO$_5$) 396.0534, found, 396.0525.

**[N-(2-Formylethyl)-N-phenylcyclohexa-1,3-dienecarboxamide]**

**tricarbonyliron (3.33).** To a mixture of methoxytrimethylphosphonium chloride (310 mg, 0.91 mmol) in THF (6 mL) under Ar at -78 °C, was added KHMDS (0.5 M in toluene, 2.0 mL, 0.99 mmol). Stirring was continued at this temperature for 1h, then a solution of aldehyde 3.20a (230 mg, 0.60 mmol) in THF (2.0 mL) was added and the reaction was remained at -78 °C for 1h. The temperature was allowed to warm to rt and stirring was continued for 1h. The reaction mixture was carefully quenched with water (4 mL), extracted with Et$_2$O (6 mL x 3), washed with brine (3 mL x 2), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. A quick flash chromatography (Hex:EA/4:1) afforded a yellow oil. Then a solution of this oil in dioxane (6 mL) was treated with 2 N HCl (2 mL) at rt for 1.5 h. Et$_2$O (50 mL) was added, and the solution was washed with water (10 mL) and brine (10 mL), dried
(Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded pure **3.33** (164 mg, 69%) as a yellow oil. Rₖ = 0.50 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 9.74 (t, J = 1.6 Hz, 1H), 7.49-7.45 (2H), 7.39-7.35 (1H), 7.21 (d, J = 7.6 Hz, 2H), 5.31 (dd, J = 4.4, 0.8 Hz, 1H), 4.99-4.96 (m, 1H), 4.28-4.21 (m, 1H), 3.78-3.72 (m, 1H), 3.26-3.22 (m, 1H), 2.88-2.80 (m, 1H), 2.67-2.59 (m, 1H), 2.07-1.99 (m, 1H), 1.88-1.79 (m, 1H), 1.76-1.60 (m, 1H), 1.35-1.28 (m, 1H). ¹³C NMR (400 MHz, CDCl₃): δ 200.8, 173.4, 143.5, 130.3, 128.0, 127.6, 86.3, 84.1, 71.2, 63.7, 46.2, 42.4, 26.4, 25.3. HRMS (FAB) calcd for MH⁺ (C₁₉H₁₈FeNO₅) 396.0534, found, 396.0530.

**[N-Phenylcyclohexa-1,3-diene-carboxamide]tricarbonyliron** (**3.34**). According to the general procedure for the photothermally induced cyclization, a solution of aldehyde **3.33** (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 **3.34** (12 mg, 46%). Rₖ = 0.50 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (400 MHz, CDCl₃): 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⁺ (C₁₆H₁₄FeNO₄) 340.0272, found, 340.0272.

**tert-Butyl formylmethylphenylcarbamate** (**3.36**). To a solution of 2-(phenylamino)ethanol (**3.35**) (2.0 g, 14.6 mmol) in dioxane (26 mL) was added di-tert-butyl dicarbonate (3.82 g, 17.5 mmol). The reaction solution
was stirred at 50 °C for 36 h and concentrated in vacuo. Flash chromatography (Hex:EA/2:1) afforded tert-butyl 2-hydroxyethylphenylcarbamate (3.2 g, 94%) as a colorless solid. MP 74-76 °C. R<sub>f</sub> = 0.50 (Hex:EA/2:1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.38-7.31 (2H), 7.24-7.15 (3H), 3.82-3.74 (4H), 2.8-2.6 (br, 1H), 1.41 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 142.9, 129.1, 127.3, 126.6, 81.0, 62.0, 53.1, 28.5. HRMS (FAB) calcd for MH<sup>+</sup> (C<sub>13</sub>H<sub>20</sub>NO<sub>3</sub>) 238.1443, found, 238.1453.

To a solution of oxalyl chloride (1.72 mL, 19.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at -78 °C, was slowly added DMSO (2.78 mL, 39.2 mmol). After 5 min at this temperature, the reaction solution was allowed to warm to -60 °C over 30 min, whereupon a solution of tert-butyl 2-hydroxyethylphenylcarbamate (3.1 g, 13.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added slowly. The solution was warmed to -45 °C over 30 min and stirred at this temperature for 5 min. Then diisopropylethylamine (11.1 mL) was added slowly. After 5 min at this temperature, the cooling bath was removed and the solution was allowed to warm to 0 °C. The solution was quenched with 1N HCl (40 mL) and water (10 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 2), washed with brine (40 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/4:1) afforded 3.36 (2.9 g, 94%) as a colorless oil. R<sub>f</sub> = 0.50 (Hex:EA/4:1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.72 (t, J = 0.8 Hz, 1H), 7.36-7.30 (2H), 7.25-7.16 (3H), 4.33 (d, J = 0.8 Hz, 2H), 1.44 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 198.4, 142.7, 129.2, 126.7, 126.5, 81.7, 60.4, 28.4. HRMS (FAB) calcd for MH<sup>+</sup> (C<sub>13</sub>H<sub>18</sub>NO<sub>3</sub>) 236.1287, found, 236.1285.

(2E)-Ethyl 4-[N-tert-butoxycarbonyl-N-phenylamino]pent-2-enoate. To a solution of triethyl phosphonoacetate (4.20 g, 18.7 mmol)
in MeCN (100 mL) was added anhydrous lithium chloride (0.79 g, 18.7 mmol) and DBU (2.81 mL, 18.7 mmol). The mixture was stirred at rt for 20 min until all solid disappeared completely. After the reaction solution was cooled to 0 °C, a solution of aldehyde 3.36 (2.70 g, 11.4 mmol) in MeCN (10 mL) was added dropwise and stirring was continued at this temperature for 1.5 h. The reaction was quenched with 1 N HCl (50 mL), extracted with Et₂O (60 mL x 3), washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/8:1) afforded (2E)-Ethyl 4-[N-tert-butoxycarbonyl-N-phenylamino] pent-2-enoate (2.60 g, 75%) as a colorless oil. R_f = 0.65 (Hex:EA/4:1). ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.29 (2H), 7.22-7.15 (3H), 6.98 (dt, J = 15.6, 5.2 Hz, 1H), 5.94 (dt, J = 15.6, 1.6 Hz, 1H), 4.38 (dd, J = 5.6, 2.0 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.44 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.3, 154.5, 144.3, 142.7, 129.0, 126.3, 126.2, 122.4, 81.1, 60.7, 51.5, 28.5, 14.4. HRMS (FAB) calcd for MH⁺ (C₁₇H₂₄NO₄) 306.1705, found, 306.1699.

(2E)-Ethyl 4-phenylaminopent-2-enoate (3.37). (2E)-Ethyl 4-[N-tert-butoxycarbonyl-N-phenylamino]pent-2-enoate (1.81 g, 5.9 mmol) was dissolved in dry CH₂Cl₂ (30 mL) and cooled to 0 °C. TFA (15 mL) was added slowly to the reaction solution, which was then stirred at the same temperature for 1 h, carefully quenched by aq sat NaHCO₃ solution (140 mL) at 0 °C (pH = 8-9), and extracted with CH₂Cl₂ (30 mL x 3). The combined organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product 3.37 (1.19 g, 98%) was used in the next reaction without further purification. R_f = 0.40 (Hex:EA/4:1). ¹H NMR
(400 MHz, CDCl$_3$): $\delta$ 7.21-7.16 (2H), 7.03 (dt, $J = 15.6$, 5.2 Hz, 1H), 6.76-6.70 (1H), 6.61-6.58 (2H), 6.05 (dt, $J = 15.6$, 1.6 Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.96 (dd, $J = 4.4$, 2.0 Hz, 2H), 3.94-3.88 (br, 1H), 1.27 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.6, 147.5 145.8, 129.6, 122.0, 118.2, 113.1, 60.7, 45.0, 14.5. HRMS (FAB) calcd for MH$^+$ (C$_{12}$H$_{16}$NO$_2$) 206.1181, found, 206.1180.

$^{[(2E)-Ethyl~4-(N-phenylcyclohexa-1,3-dienecarboxamido)}$ but-2-enolate$|$tricarbonyliron (3.38). According to the procedure for preparation of amide complexes, complexed acid 3.18a (100 mg, 0.38 mmol) was coupled with amine 3.37 (123 mg, 0.60 mmol) for 16 h at rt to give ester 3.38 (130 mg, 76%), which was purified by flash chromatography (Hex:EA/4:1). $R_f$ = 0.50 (Hex:EA/4:1). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.46-7.42 (2H), 7.37-7.33 (1H), 7.21-7.19 (2H), 6.91 (dt, $J = 16.0$, 6.0 Hz, 1H), 5.83 (dt, $J = 16.0$, 1.6 Hz, 1H), 5.37 (dd, $J = 4.4$, 1.2 Hz, 1H), 5.01-4.98 (m, 1H), 4.53 (ddd, $J = 16.0$, 6.0, 2.0 Hz, 1H), 4.31 (ddd, $J = 16.0$, 6.4, 1.6 Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.26-3.22 (m, 1H), 2.06-1.98 (m, 1H), 1.87-1.78 (m, 1H), 1.68-1.57 (m, 1H), 1.38-1.31 (m, 1H). 1.25 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.0, 166.2, 143.6, 142.9, 130.2, 128.0, 127.5, 123.6, 86.4, 84.2, 71.1, 63.6, 60.6, 52.9, 26.4, 25.4, 14.4. HRMS (FAB) calcd for MH$^+$ (C$_{22}$H$_{22}$FeNO$_6$) 452.0797, found, 452.0801.

$^{[Ethyl~2-[6,9,\eta-2-phenyl-1-oxo-2-azaspiro[4.5]}$ deca-6,8-dien-4-yl]acetate$|$tricarbonyliron (3.39a and 3.39b). According to the general procedure for
the photothermally induced cyclization, complex 3.38 (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 an inseparable mixture of two diastereomers 3.39a and 3.39b (81 mg, 78%) in 1.7:1 ratio. Rf = 0.50 (Hex:EA/4:1). 1H NMR (400 MHz, CDCl3): δ 7.62 -7.56 (4H, two isomers), 7.37-7.32 (4H, two isomers), 7.15-7.10 (2H, two 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). 13C NMR (100 MHz, CDCl3): 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+ (C22H22FeNO6) 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 (3.40a and 3.40b). To a solution of esters 3.39a and 3.39b (451.0 mg, 1.0 mmol) in Et2O (28 mL) under Ar was added LiBH4 (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 Et2O (25 mL x 3), washed with brine (15 mL x 2),
dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/4:1) afforded an inseparable mixture of two diastereomers 3.40a and 3.40b (337.0 mg, 82%) in 1.4:1 ratio. R<sub>f</sub> = 0.30 (Hex:EA/2:1). <sup>1</sup>H NMR (400 MHz, CDCl₃): 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). <sup>13</sup>C NMR (100 MHz, CDCl₃): 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<sup>+</sup> (C₂₀H₂₀FeNO₅) 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 (3.41a and 3.41b). To a solution of alcohol 3.40a/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 Et₂O (10 mL x 2), washed with a mixture of brine and water (1:1, 5 mL x 2), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded 3.41a and 3.41b (118 mg, 76% combined yield) in 3.5:1 ratio. 3.41a (91.7 mg, 59%): Rᵥ = 0.50 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₂₀H₂₈FeNO₅) 408.0534, found, 408.0531. 3.41b (26.2 mg, 17%): Rᵥ = 0.40 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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 (dd, J = 10.8, 6.0, 1.2 Hz, 1H), 3.43-3.32 (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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₂₀H₂₈FeNO₅) 408.0534, found, 408.0527.

[2-[6,9,η-2-Phenyl-1-oxo-2-azaspiro[4.5]
deca-6,8-dien-4-y]propionaldehyde]tricarbonyl iron (3.42a and 3.42b). 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 3.41a/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 1h. The mixture was allowed to warm to rt and stirring was continued for 1h. The reaction mixture was carefully quenched with brine (10 mL), extracted with Et₂O (7 mL x 3), washed with brine (8 mL x 2), dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was dissolved in dioxane (3.0 mL) and treated with 2N HCl (1.0 mL) for 3 h. Et₂O (50 mL) was added, then the solution was washed with water (10 mL) and brine (10 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded inseparable 3.42a and 3.42b (120 mg, 88%) in 4:1 ratio. R_f = 0.60 (Hex:EA/2:1). \(^1\)H NMR (400 MHz, CDCl₃): 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), 2.60-2.20 (6H, two isomers), 2.11-2.03 (4H, two isomers), 1.91-1.71 (4H, two isomers). \(^1\)C NMR (100 MHz, CDCl₃): 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⁺ (C₂₁H₂₀FeNO₅) 422.0691, found, 422.0711.
Cyclization of 3.41a/b to afford compounds

**3.43 and 3.44.** According to the general procedure for the photothermally induced cyclization, aldehydes 3.41a/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 3.45a/b (2.4 mg, 17%), cyclization product 3.43 (3.2 mg, 21% from 1H NMR, with some impurity) and demetallated product 3.44 (2.6 mg, 26%). According to the general demetallation procedure B, 3.43 was decomplexed by CuCl₂ in EtOH to afford 3.44 in 74% yield (42% combined yield over two steps). 3.44: MP 138-140 °C. R₇ = 0.40 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): 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), 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). ¹³C NMR (100 MHz, CDCl₃): 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⁺ (C₁₇H₁₈NO₂) 268.1338, found, 268.1332.

2-[2-Phenyl-1-oxo-2-azaspiro[4.5]deca-6,8-dien-4-yl]acetaldehyde (3.46a and 3.46b). According to the general demetallation procedure B, 3.40a/b (38.0 mg, 92.9 μmol) was treated with sat. ethanolic CuCl₂ (2.0 mL) at rt for 12 h. The products were used in the next step immediately after flash chromatography.
(Hex:EA/2:1). To a solution of the above products in CH₂Cl₂ (0.8 mL) under Ar at 0 °C, was added Dess-Martin reagent (56.0 mg, 134 μmol). Stirring was continued for 1.5 h, then the temperature was raised to rt and the reaction was maintained at this temperature for 1.5 h. The reaction mixture was quenched with a solution of Na₂S₂O₃ (0.2 g in 1.2 mL water) and sat. NaHCO₃ (1.2 mL), then the mixture was stirred for 15 min, extracted with Et₂O (3 mL x 3), washed with brine (2 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/3:1) afforded 3.46a and 3.46b (14.2 mg, 58% combined yield over two steps). 3.46a (7.5 mg, 31%): Rᵥ = 0.45 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.38-7.36 (2H), 7.17-7.14 (m, 1H), 6.14 (dd, J = 9.6, 5.2 Hz, 1H), 5.97-5.92 (m, 1H), 5.80-5.73 (m, 1H), 5.68 (d, J = 9.6 Hz, 1H), 3.99 (dd, J = 10.0, 7.6 Hz, 1H), 3.48 (dd, J = 9.2, 9.6 Hz, 1H), 2.93 (dd, J = 17.6, 4.0 Hz, 1H), 2.75-2.60 (2H), 2.54 (dd, J = 18.0, 10.4 Hz, 1H), 2.39 (dd, J = 18.0, 5.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 200.6, 178.0, 140.0, 129.1, 126.6, 126.2, 124.9, 124.2, 123.8, 119.9, 49.8, 49.0, 43.6, 38.2, 26.3. HRMS (FAB) calcd for MH⁺ (C₁₇H₁₈NO₂) 268.1338, found, 268.1336. 3.46b (6.7 mg, 27%): Rᵥ = 0.50 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 9.79 (s, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.39-7.35 (2H), 7.17-7.14 (m, 1H), 6.21 (dd, J = 10.0, 3.2 Hz, 1H), 5.94-5.90 (2H), 5.50 (d, J = 9.6 Hz, 1H), 4.00 (dd, J = 10.0, 7.2 Hz, 1H), 3.44 (dd, J = 10.0, 8.4 Hz, 1H), 3.16 (d, J = 18.4 Hz, 1H), 2.97 (dd, J = 16.8, 2.8 Hz, 1H), 2.72-2.62 (2H), 2.23 (dd, J = 17.6, 5.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 176.5, 139.6, 129.1, 127.8, 126.3, 124.9, 122.9, 122.5, 120.0, 50.4, 48.7, 43.7, 38.8, 31.6. HRMS (FAB) calcd for MH⁺ (C₁₇H₁₈NO₂) 268.1337, found, 268.1335.
Ni(acac)$_2$ catalyzed cyclization of 3.46a to afford 3.47a and 3.47b. To a solution of aldehyde 3.46a (9.0 mg, 34 μmol) and Ni(acac)$_2$ (0.9 mg, 4 μmol) in dry THF (0.3 mL) was added diethylzinc (1 M in hexanes, 0.08 mL, 82 μmol). The reaction solution was maintained at rt for 30 min under Ar and then quenched with 1 N HCl (1.0 mL), extracted with EtOAc (2 mL x 3), washed with sat. NaHCO$_3$ (2 mL) and brine (2 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Preparative TLC (5% THF in CH$_2$Cl$_2$) afforded two pure isomers 3.47a and 3.47b in 61% combined yield. 3.47a (0.8 mg, 9%): R$_f$ = 0.45 (5% THF in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.58-7.56 (2H), 7.32-7.28 (2H), 7.09-7.05 (m, 1H), 5.90-5.87 (2H), 4.00-3.94 (m, 1H), 3.69 (dd, $J$ = 11.2, 9.2 Hz, 1H), 3.61 (dd, $J$ = 9.2, 8.0 Hz, 1H), 2.40-2.00 (4H), 1.87-1.81 (2H), 1.68 (dd, $J$ = 12.8, 2.4 Hz, 1H), 1.57-1.52 (m, 1H), 1.45-1.35 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.4, 130.4, 129.1, 128.5, 124.5, 119.7, 69.9, 49.3, 44.4, 40.0, 33.3 28.5, 27.0, 23.2. 3.47b (4.7 mg, 52%): R$_f$ = 0.50 (5% THF in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.58-7.54 (2H), 7.32-7.28 (2H), 7.09-7.05 (m, 1H), 6.01 (ddd, $J$ = 10.0, 4.0, 2.4 Hz, 1H), 5.68-5.64 (m, 1H), 3.92-3.87 (m, 1H), 3.62-3.53 (2H), 2.89-2.83 (m, 1H), 8.55-8.54 (m, 1H), 2.39 (dd, $J$ = 17.2, 8.0 Hz, 1H), 1.90-1.83 (2H), 1.80-1.69 (2H), 1.58 (dd, $J$ = 12.8, 1.6 Hz, 1H), 1.35-1.33 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.0, 140.0, 130.4, 129.1, 124.6, 124.5, 119.7, 69.3, 49.4, 43.0, 40.7, 36.8, 34.8, 29.4, 29.0. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.0, 140.0, 130.4, 129.1, 124.6, 124.5, 119.7, 69.3, 49.4, 43.0, 40.7, 36.8, 34.7, 29.4, 29.0.
Ni(acac)$_2$ catalyzed cyclization of 3.46b to afford 3.49a and 3.49b. According to the above procedure, a solution of aldehyde 3.46b (3.0 mg, 11 μmol) and Ni(acac)$_2$ (0.3 mg, 1 μmol) in dry THF (0.1 mL) was treated with diethylzinc (1 M in hexanes, 0.03 mL, 30 μmol) at rt for 30 min under Ar. Preparative TLC (5% THF in CH$_2$Cl$_2$) afforded two pure isomers 3.49a and 3.49b in 22% combined yield. 3.49a (0.4 mg, 11%): R$_f$ = 0.55 (5% THF in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.62-7.59 (2H), 7.32-7.28 (2H), 7.10-7.06 (m, 1H), 6.14-6.10 (m, 1H), 5.78-5.74 (m, 1H), 4.26-4.23 (m, 1H), 4.04 (dd, $J$ = 10.0, 8.0 Hz, 1H), 3.45 (dd, $J$ = 10.0, 1.6 Hz, 1H), 2.84-2.81 (m, 1H), 2.67-2.61 (m, 1H), 2.35-2.25 (m, 1H), 2.14-2.08 (m, 1H), 2.04-1.95 (m, 1H), 1.93-1.87 (m, 1H), 1.64-1.57 (2H), 1.55-1.48 (br, 1H). 3.49b (0.4 mg, 11%): R$_f$ = 0.45 (5% THF in CH$_2$Cl$_2$). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.60-7.57 (2H), 7.34-7.29 (2H), 7.11-7.07 (m, 1H), 5.89-5.85 (m, 1H), 5.74-5.71 (m, 1H), 4.33-4.31 (m, 1H), 3.96 (dd, $J$ = 10.0, 6.8 Hz, 1H), 3.47 (dd, $J$ = 10.0, 1.2 Hz, 1H), 2.62-2.50 (m, 1H), 2.50-2.45 (m, 1H), 2.30-2.00 (5H), 1.75 (ddd, $J$ = 14.0, 7.2, 4.8 Hz, 1H), 1.50-1.45 (br, 1H).

Oxidation of 3.47a/b and 3.49a/b to 3.48a/b and 3.50a/b, respectively. According to the procedure for preparation of 3.46a/b, 3.47a (0.5 mg, 2 μmol) was
oxidized by Dess-Martin reagent (1.6 mg, 4 μmol) to the ketone isomer **3.48a** (0.5 mg, 100%). \( R_f = 0.50 \) (Hex:EA/2:1, two developments). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.66-7.63 (2H), 7.41-7.37 (2H), 7.21-7.15 (m, 1H), 5.94-5.90 (m, 1H), 5.86-5.82 (m, 1H), 4.06 (dd, \( J = 9.6, 8.0 \) Hz, 1H), 3.70 (dd, \( J = 8.8, 10.0 \) Hz, 1H), 2.75-2.66 (3H), 2.50-2.29 (4H), 2.12-2.04 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 214.2, 176.1, 130.0, 129.2, 129.0, 125.1, 120.0, 53.2, 45.9, 41.0, 40.1, 37.9, 29.6, 27.3. HRMS (FAB) calcd for MH\(^+\) (C\(_{17}\)H\(_{18}\)NO\(_2\)) 268.1337, found, 268.1330. **3.47b** (2.8 mg, 10 μmol) was oxidized by Dess-Martin reagent (8.8 mg, 20 μmol) to the ketone isomer **3.48b** (2.3 mg, 83%). \( R_f = 0.55 \) (Hex:EA/2:1, two development). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.64-7.61 (2H), 7.25-7.14 (2H), 6.12-6.08 (m, 1H), 5.77-5.72 (m, 1H), 3.89 (dd, \( J = 10.0, 8.4 \) Hz, 1H), 3.56 (dd, \( J = 10.0, 8.8 \) Hz, 1H), 3.08-3.02 (2H), 2.87 (dd, \( J = 16.4, 8.0 \) Hz, 1H), 2.79-2.72 (m, 1H), 2.32 (dd, \( J = 16.8, 4.0 \) Hz, 1H), 2.17-2.05 (3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 208.9, 176.2, 139.3, 130.5, 129.2, 125.1, 124.8, 119.9, 51.2, 46.8, 43.5, 39.1, 37.8, 35.4, 28.9. HRMS (FAB) calcd for MH\(^+\) (C\(_{17}\)H\(_{18}\)NO\(_2\)) 268.1337, found, 268.1355. **3.49a** (1.4 mg, 5 μmol) was oxidized by Dess-Martin reagent (4.4 mg, 10 μmol) to the corresponding ketone isomer of **3.50a** (1.3 mg, 93%). \( R_f = 0.50 \) (Hex:EA/2:1, two developments). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.65-7.61 (2H), 7.41-7.36 (2H), 7.21-7.16 (m, 1H), 5.96-5.92 (m, 1H), 5.73-5.69 (m, 1H), 4.17 (dd, \( J = 10.4, 6.0 \) Hz, 1H), 3.65-3.63 (m, 1H), 3.34-3.30 (m, 1H), 2.85-2.72 (2H), 2.38-2.20 (2H), 2.16-2.04 (m, 1H), 1.94-1.86 (m, 1H), 1.84-1.77 (m, 1H). HRMS (FAB) calcd for MH\(^+\) (C\(_{17}\)H\(_{18}\)NO\(_2\)) 268.1337, found, 268.1334. **3.49b** (1.6 mg, 6 μmol) was oxidized by Dess-Martin reagent (5.0 mg, 12 μmol) to corresponding ketone isomer of **3.50b** (1.2 mg, 76%). \( R_f = 0.50 \) (Hex:EA/2:1, two developments). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.67-7.64 (2H), 7.41-7.37 (2H), 7.20-7.16
(m, 1H), 5.90-5.85 (2H), 4.14 (dd, J = 10.4, 9.6 Hz, 1H), 3.63 (dd, J = 10.0, 4.0 Hz, 1H), 2.85-2.81 (m, 1H), 2.74-2.60 (2H), 2.54-2.46 (2H), 2.37-2.24 (2H), 2.20-2.14 (m, 1H). HRMS (FAB) calcd for MH⁺ (C₁₇H₁₈NO₂) 268.1337, found, 268.1332.

**Cyclization of 3.42a/b to afford compounds 3.51a, 3.51b and 3.51c.** According to the general procedure for the photothermally induced cyclization, the mixture of aldehydes 3.42a/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 3.51a (1.4 mg, 12%), inseparable 3.51b and 3.51c (3.8 mg, 32% combined yield) in 1:5 ratio. 3.51a: Rᶠ = 0.35 (Hex:EA/8:1). ¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (150 MHz, CDCl₃): 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⁺ (C₁₇H₂₀NO) 254.1545, found, 254.1546. 3.51b and 3.51c: Rᶠ = 0.40 (Hex:EA/8:1). ¹H NMR (400 MHz, CDCl₃): 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\(_3\)): \( \delta \) 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.

Demetallation of 3.42a/b to afford 3.55a and 3.55b. 3.42a/b (23.0 mg, 55 \( \mu \)mol) in benzene (1.2 mL)
was treated with Me\(_3\)NO (143 mg, 1.91 mmol) at rt for 5h. The reaction mixture was diluted with diethyl ether (8 mL),
filtered through Celite, washed with brine (1.5 mL x 3), dried (Na\(_2\)SO\(_4\)), filtered and
concentrated in vacuo. Flash chromatography (Hex:EA/2:1) afforded an inseparable
mixture of 3.55a and 3.55b (8.5 mg, 57% combined yield). \( R_f = 0.40 \) (Hex:EA/2:1). \(^1\)H
NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.78 (t, \( J = 1.2 \) Hz, 2H, two isomers), 7.67-7.63 (4H, two
isomers), 5.97-5.87 (3H, two isomers), 5.79-5.75 (m, 1H, minor isomer), 5.65 (d, \( J = 9.6 \)
Hz, 1H, minor isomer), 5.47 (d, \( J = 9.6 \) Hz, 1H, major isomer), 3.77 (dd, \( J = 9.2, 7.6 \) Hz,
1H, major isomer), 3.72 (dd, \( J = 9.6, 7.2 \) Hz, 1H, minor isomer), 3.5-3.47 (2H, two
isomers), 3.25-3.19 (m, 1H, major isomer), 2.68-2.62 (m, 1H, minor isomer), 2.56-2.44
(4H, two isomers), 2.24-1.99 (6H, two isomers), 1.87-1.69 (2H, two isomers). \(^{13}\)C NMR
(100 MHz, CDCl\(_3\)): \( \delta \) 201.6, 201.5, 178.0, 177.0, 139.7, 139.5, 129.1, 127.3, 127.0, 126.2,
126.0, 124.9, 124.2, 123.9, 122.6, 122.1, 120.0, 50.4, 50.0, 49.6, 49.5, 45.6, 43.9, 42.5,
42.4, 32.0, 26.0, 21.3, 21.2. HRMS (FAB) calcd for MH\(^{+}\) (C\(_{18}\)H\(_{20}\)NO\(_2\)) 282.1494, found,
282.1496.
Cyclization of 3.55a/b mixture to afford 3.56. The solution of 3.55a/b (4.5 mg, 16.0 μmol) in THF (0.6 mL) was treated with 2 N HCl (0.6 mL) at rt for 6 h. The reaction solution was extracted with diethyl ether (3 mL x 4), washed with brine (3 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Preparative TLC (Hex:EA/2:1) afforded recovered 3.55b (0.9 mg) and afforded cyclization product 3.56 (2.7 mg, 75% calculated from the corresponding single isomer 3.55a). Rf = 0.30 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.68-7.64 (2H), 7.39-7.34 (2H), 7.15-7.11 (m, 1H), 6.56 (ddd, J = 8.0, 5.6, 1.2 Hz, 1H), 6.40 (ddd, J = 7.2, 6.8, 1.2 Hz, 1H), 4.62 (dd, J = 5.2, 4.8 Hz, 1H), 4.31 (dd, J = 11.2, 9.2 Hz, 1H), 3.62 (dd, J = 9.2, 7.6 Hz, 1H), 3.45 (d, J = 4.0 Hz 1H), 2.44-2.37 (2H), 2.23-2.17 (m, 1H), 2.09 (dd, J = 12.8, 1.2 Hz, 1H), 2.07-2.01 (m, 1H), 1.91 (dd, J = 12.8, 4.8 Hz, 1H), 1.66-1.57 (2H). ¹³C NMR (100 MHz, CDCl₃): δ 177.0, 140.3, 133.5, 132.5, 129.1, 124.3, 119.3, 69.2, 67.8, 48.1, 42.0, 38.7, 38.6, 35.6, 25.9, 15.9. HRMS (FAB) calcd for MH⁺ (C₁₈H₂₀NO₂) 282.1494, found, 282.1493. Single isomer 3.55b: ¹H NMR (400 MHz, CDCl₃): δ 9.79 (t, J = 1.2 Hz, 1H), 7.63-7.61 (2H), 7.39-7.34 (2H), 7.17-7.12 (m, 1H), 6.18 (dd, J = 10.0, 3.2 Hz, 1H), 6.00-5.96 (m, 1H), 5.80-5.75 (m, 1H), 5.65 (d, J = 10.0 Hz, 1H), 3.72 (dd, J = 9.6, 7.6 Hz, 1H), 3.52 (dd, J = 9.6, 9.6 Hz, 1H), 2.68-2.42 (4H), 2.22-2.17 (m, 1H), 2.05-1.98 (m, 1H), 1.79-1.1.73 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 201.3, 177.9, 139.3, 128.9, 126.8, 125.9, 124.6, 123.7, 119.7, 49.7, 49.4, 43.7, 42.1, 25.8, 21.0. HRMS (FAB) calcd for MH⁺ (C₁₈H₂₀NO₂) 282.1494, found, 282.1496.

Formation of 3.56 through path b. According to the general demetallation procedure B, the 4:1 mixture of 3.42a/b (21.0 mg, 50.0 μmol) was treated with sat. ethanolic CuCl₂ (1.0 mL) at rt for 3 h. The crude product without further purification was
dissolved in THF (0.8 mL) and 2N HCl (0.8 mL) was added. Stirring was continued for 6 h. The reaction solution was extracted with diethyl ether (6 mL x 3), washed with brine (5 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Preparative TLC (Hex:EA/2:1) afforded unreacted 3.55b (2.7 mg, 95% calculated from the corresponding single isomer 3.42b) and cyclization products 3.56 (7.0 mg, 63% over two steps calculated from the corresponding single isomer 3.42a).

**Preparation of oxime 3.57.** To a solution of aldehyde 3.20a (40.0 mg, 105 μmol) in EtOH (1.0 mL) and water (0.3 mL), was added hydroxylamine hydrochloride salt (24.8 mg, 473 μmol) and sodium bicarbonate (8.4 mg). The solution was stirred for 3 h at rt. The solvent was removed in vacuo, then CH₂Cl₂ (8 mL) was added to the residue and shaken two minutes. The organic layer was washed with water (3 mL x 3), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/2:1) afforded 3.57 (40.0 mg, 96%) as a 1:1 mixture of two isomers. Rₐ = 0.45 (Hex:EA/2:1).

$^{1}$H NMR (400 MHz, CDCl₃): δ 7.53 (dd, $J = 6.4$, 4.2 Hz, 1H, one isomer), 7.49-7.44 (3H, two isomers), 7.39-7.34 (2H, two isomers), 7.27-7.00 (4H, two isomers), 6.88-6.84 m, 1H, one isomer), 6.86 (s, 1H, one isomer), 5.39-5.37 (2H, two isomers), 5.03-4.99 (2H, two isomers), 4.65 (dd, $J = 17.2$, 4.0 Hz, 1H, one isomer), 4.54-4.49 (2H, two isomers), 4.25 (dd, $J = 14.8$, 6.4 Hz, 1H, one isomer), 3.28-3.23 (2H, two isomers), 1.88-1.78 (2H, two isomers), 1.68-1.59 (2H, two isomers), 1.40-1.24 (2H, two isomers). $^{13}$C NMR (100 MHz, CDCl₃): δ 173.6, 173.4, 149.7, 147.6, 144.0, 143.3, 130.4, 130.3, 128.1, 128.0, 127.6, 127.2, 86.3, 86.2, 84.3, 84.2, 70.8, 70.5, 63.8, 63.5, 50.7, 47.7, 26.4, 25.3, 25.2.
Cyclization of 3.57 to afford nitrile 3.58. According to the general procedure for the photothermally induced cyclization, oxime 3.57 (15.0 mg, 38 μmol) in benzene (4.0 mL) was heated under CO at 85 °C for 9 h. Preparative TLC (Hex:EA/3:1) afforded nitrile 3.45a/b (3.6 mg, 24%). Rf = 0.60 (Hex:EA/2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.55-7.50 (2H), 7.47-7.43 (m, 1H), 7.33-7.26 (2H), 5.52 (d, J = 3.6 Hz, 1H), 5.08 (dd, J = 5.6, 4.8 Hz, 1H), 4.61 and 4.34 (ABq, J = 16.8 Hz, 2H), 3.31-3.27 (m, 1H), 1.97-1.90 (m, 1H), 1.84-1.75 (m, 1H), 1.64-1.55 (m, 1H), 1.33-1.25 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 142.4, 130.8, 129.2, 127.5, 110.0, 86.7, 85.0, 68.4, 64.0, 40.1, 26.3, 24.7.

Preparation of imine 3.59. To a solution of aldehyde 3.20a (36.0 mg, 94 μL) in CH₂Cl₂ (0.5 mL), was added benzylamine (10.1 mg, 94 μL) and magnesium sulfate (8.4 mg). The solution was stirred for 24 h at rt, then solvent was evaporated in vacuo. The crude product (hydrolyzed on both silica gel and basic alumina columns) was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 7.81 (dd, J = 4.4, 4.8 Hz, 1H), 7.39-7.11 (10H), 5.46 (br, 1H), 4.65 (dd, J = 12.8, 4.4 Hz, 1H), 4.56 and 4.50 (ABq, J = 16.8 Hz, 2H), 4.30 (dd, J = 4.8, 16.4 Hz, 1H), 3.23-3.22 (m, 1H), 1.90-1.70 (2H), 1.65-1.58 (m, 1H), 1.30-1.20 (m, 1H).

Preparation of imine 3.60. To a solution of aldehyde 3.20a (17.0 mg, 45 μL) in MeOH (0.25 mL), was added phenylhydrazine (4.8 mg, 45 μL). The solution was stirred for 24
h at rt, then solvent was evaporated in vacuo. The crude product (hydrolyzed on both silica gel and basic alumina columns) was used for the next step without further purification. $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.49 (dd, $J =$ 7.6, 7.6 Hz, 2H), 7.39 (dd, $J =$ 7.2, 7.6 Hz, 1H), 7.32 (d, $J =$ 7.2 Hz, 2H), 7.14-7.07 (3H), 6.83 (d, $J =$ 7.6 Hz, 2H), 6.68 (dd, $J =$ 7.2, 7.2 Hz, 1H), 5.35 (d, $J =$ 4.4 Hz, 1H), 5.11 (dd, $J =$ 5.6, 5.6 Hz, 1H), 4.6 (br, 1H), 4.57 (dd, $J =$ 14.8, 4.4 Hz, 1H), 4.35 (dd, $J =$ 15.2, 5.6 Hz, 1H), 3.30-3.25 (m, 1H), 2.15-2.07 (m, 1H), 1.92-1.85 (m, 1H), 1.71-1.65 (m, 1H), 1.50-1.43 (m, 1H).
3.6 Literature References


CHAPTER FOUR

Preliminary Studies on Iron Tricarbonyl
Promoted All-Carbon Double Cyclization Reaction
4.1 Introduction

Previous researchers in our laboratory have also investigated spirocyclization of cyclohexadiene-Fe(CO)₃ complexes with pendant alkenyl ketones (Table 1.1 in chapter 1) or with a pendant all-carbon olefin (eq 4.1 and Scheme 4.1). Generally, only those substrates with an unsubstituted olefin can undergo spirocyclization in satisfactory yields.

Scheme 4.1 Spirocyclization of all-carbon substrates 4.4a/b
Substrate 4.1 can not directly undergo cyclocoupling and needs to be converted to intermediate 4.2, via a diene double bond migration under cyclization conditions, which cyclizes to afford products 4.3a/b with formation of a five-membered ring as shown in equation 4.1.

Cyclization of substrates 4.4a/b with introduction a chiral center on the pendant side chain has also been investigated and afforded four diastereomers 4.6a-c as products (Scheme 4.1). So far, no further studies have been carried out for this type of substrate.

![Scheme 4.2 Retrosynthetic analysis for Elisabethin A](image)

The tricyclic framework as shown in compound 4.10 is found in many natural molecules, among which Elisabethin A is most attractive as a synthetic target. Retrosynthetic analysis (Scheme 4.2) indicated that Elisabethin A might be reached from intermediate 4.10 which might be accessible through an Fe(CO)$_3$ mediated all-carbon double spirocyclization reaction similar to the reaction shown in Scheme 4.3. So, the potential applications of this methodology in the syntheses of complex molecules make the research on all-carbon double cyclization reactions more compelling.

Substrate 4.13 with a pendant diene was designed for a novel all-carbon double cyclization that is expected to afford tricyclic product 4.14 as shown in Scheme 4.3.
4.2 Iron tricarbonyl Promoted All-Carbon Double Cyclization Reaction

The first objective was to prepare the key intermediate, methyl nona-5,8-dienoate (4.12). The required cyclohexadienyliron cation salt 4.11 was obtained according to reported methods. Treatment of 5-hexynoic acid (4.15) with n-BuLi followed by addition of allyl iodide gave acid 4.16, which was esterified to afford methyl non-8-en-5-ynoate (4.17) in 75% yield as illustrated in Scheme 4.4. Attempts to hydrogenate 4.17 using Lindlar catalyst afforded the expected product 4.12, but this was accompanied by formation of an overhydrogenated product cis-4.18 in over 15% yield. These two products were inseparable and expected to be problematic for the study of later
cyclization reactions, so much effort was expended to optimize the reaction conditions by changing reaction time, amount of catalyst, solvents, amount of quinoline or even the pressure of hydrogen. Unfortunately, none of them eliminated the formation of overhydrogenated product \textit{cis-4.18}.

Metal/ammonia (Li/NH\textsubscript{3}) conditions were also tested for this hydrogenation to obtain intermediate \textit{trans-4.12}, but it turned out that formation of overhydrogenated product \textit{4.18} still could not be avoided as shown in Scheme 4.5.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme4.4}
\caption{Scheme 4.4 Preparation of diene \textit{cis-4.12}}
\end{figure}
Scheme 4.5 Attempt to prepare trans-4.12

Scheme 4.6 Preparation and attempted cyclization of substrate 4.13
Finally, intermediate cis-4.12 was prepared via a Wittig olefination reaction, from aldehyde 4.20, which was derived from δ-valerolactone according to a published procedure.\(^6\) The enolate of cis-4.12 was coupled with cation salt 4.11 to give cyclohexadieneiron tricarbonyl complex 4.21 in 50% yield. Subsequent reduction of 4.21 with DIBAL-H followed by protection of the resulting hydroxyl group with TBDPSCI afforded the substrate 4.13 in 73% yield over two steps. However, no expected double cyclization product 4.14 was obtained under either thermal or photothermal conditions. Prolonged reaction time, change of solvents (n-Bu\(_2\)O, ethoxyethyl ether, decalin, benzene, toluene and mesitylene) or higher temperature (80°C – 185 °C) also failed to give the expected product and generally caused decomposition of starting material.

![Scheme 4.7 Attempted cyclization of substrate 4.24](image)

Based on the supposition that five-membered ring formation would be more facile, substrate 4.24 was prepared through the same procedure as for 4.13 and similar results were obtained after subjecting it to both thermal and photothermal conditions (Scheme 4.7).

Based on the mechanism of this cyclization reaction,\(^1,\,^7\) compounds 4.23 and 4.25 are expected to be important intermediates for the cyclization of substrates 4.13 and 4.24,
respectively, but neither of them could be observed under cyclization conditions by analyzing NMR spectra. So the failure of the cyclization of both 4.13 and 4.24 might be due to the failure of the requisite cyclohexadiene double bond migration to form intermediates 4.23 and 4.25.
4.3 Conclusions and outlook

In order to investigate an all-carbon double cyclization reaction, substrates 4.13 and 4.24 were prepared, but they could not proceed to give the anticipated cyclized products, perhaps owing to the failure to induce the requisite cyclohexadiene double bond migration before the cyclization step.

![Scheme 4.8 Preparation and cyclization of substrates 4.23](image-url)
Considering the possible reason for the failure of the reactions mentioned above, we propose a pathway for preparation of the direct cyclization intermediate 4.23 starting with 2-phenylacetic acid (4.27). We expect that would undergo a cyclization reaction more easily to give the tricyclic product 4.14 (Scheme 4.8). Cyclohexadiene 4.29 was obtained from 2-phenylacetic acid (4.27) through Birch reduction followed by esterification. Subsequent complexation with iron pentacarbonyl under thermal conditions gave a 4:3 mixture of complexes 4.30 and 4.31 in 72% combined yield, which were separated by flash chromatography. Conversion of 4.30 to substrate 4.23 will be investigated by another student.

Scheme 4.9 A stepwise all-carbon double cyclization
According to previous work showing that a pendant electron deficient double bond facilitated the cyclization,\(^9\),\(^{10}\) a stepwise approach, based on starting material 4.33, can be designed (Scheme 4.9). The introduction of a methyl carboxylate onto the end of the pendant double bond in substrate 4.33 is expected to facilitate the coordination between the double bond and iron, and then further facilitate the spirocyclization. After the first cyclization, the ester can be converted to a second double bond as shown in 4.36a/b and then the second cyclization is expected to proceed more easily.
4.4 Experimental section

**Non-8-en-5-ynoic acid (4.16).** To a solution of 5-hexynoic acid (4.15) (1.0 g, 8.9 mmol) in THF (30 mL), was added n-BuLi solution (2.5 M in Hexanes, 8.0 mL, 20.1 mmol) at -78 °C. After the reaction solution was stirred for 30 min, it was warmed to 0 °C for 10 min, and then cooled to -78 °C. Allyl iodide (4.6 g, 27.3 mmol) was added to the reaction solution, which was then warmed to rt and stirred overnight. The reaction mixture was quenched with sulfuric acid (2 M, 25 mL) and extracted with diethyl ether (30 mL x 4). The combined organic phase was washed with NH₄Cl solution (2%, 15 mL x 2), brine (20 mL x 2), dried (MgSO₄), and concentrated in vacuo. Flash chromatography (Hex:EA/7:3) afforded 4.16 (1.2 g, 89%) as a light yellow oil. Rₙ = 0.40 (Hex:EA/7:3). ¹H NMR (200 MHz, CDCl₃): δ 11.5 (br, 1H), 5.90-5.70 (m, 1H), 5.40-5.20 (m, 1H), 5.15-5.00 (m, 1H), 2.96-2.90 (m, 1H), 2.51 (t, J = 7.2 Hz, 1H), 2.34-2.20 (m, 1H), 1.88-1.78 (m, 1H).

**Methyl non-8-en-5-ynoate (4.17).** To a solution of acid 4.16 (0.46 g, 3.00 mmol) in anhydrous CH₂Cl₂ (6.0 mL), was added oxalyl chloride (0.76 g, 6.0 mmol) and pyridine (0.28 g, 3.6 mmol) under argon. The reaction mixture was stirred at rt for 30 min. After the solvent was evaporated in vacuo, the resulting oil was kept under vacuum (0.40 mmHg) for 20 min. Then a solution of pyridine (0.47 g, 6.0 mmol) in methanol (5.0 mL) was slowly added under argon. The
stirring was continued at rt for 24 h, then the solvent was evaporated in vacuo and the resulting residue was dissolved in CH₂Cl₂ (30 mL). The organic phase was washed with 1 N HCl (10 mL x 3) and cold water (10 mL x 3), dried (MgSO₄), and concentrated in vacuo. Flash chromatography (Hex:EA/19:1) afforded 4.17 (0.35 g, 70%) as a colorless oil. R_f = 0.15 (Hex:EA/19:1). ^1H NMR (200 MHz, CDCl₃): δ 5.93-5.72 (m, 1H), 5.39-5.25 (m, 1H), 5.14-5.05 (m, H), 3.68 (s, 3H), 2.96-2.90 (m, 1H), 2.45 (t, J = 7.2 Hz, 1H), 2.30-2.22 (m, 1H), 1.91-1.75 (m, 1H).

(Z)-Methyl nona-5,8-dienoate (cis-4.12) and (Z)-methyl non-5-enoate (cis 4.18). Compound 4.17 (0.22 g, 1.32 mmol) was dissolved in the mixed solvent of hexanes (7.0 mL) and ethyl acetate (3.0 mL). After Lindlar’s catalyst (0.06 g) and quinoline (1 small drop) were added, the reaction mixture was stirred in the atmosphere of H₂ at rt for 12 h. The reaction was monitored by ^1H NMR. Filtration of the catalyst and evaporation of the solvent gave a light yellow oil containing two inseparable products, the expected product cis-4.12 (85%) and overhydrogenated product cis-4.18 (15%). cis-4.12 R_f = 0.30 (Hex:EA/12:1). ^1H NMR (200 MHz, CDCl₃): δ 5.84-5.73 (m, 1H), 5.47-5.40 (2H), 5.06-4.95 (2H), 3.66 (s, 3H), 2.78-2.76 (2H), 2.31 (t, J = 10.0 Hz, 1H), 2.12-2.05 (2H), 1.75-1.65 (2H). cis-4.18 R_f = 0.30 (Hex:EA/12:1). ^1H NMR (200 MHz, CDCl₃): δ 5.50-5.25 (2H), 3.65 (s, 3H), 2.35-2.22 (2H), 2.12-1.88 (4H), 1.75-1.55 (2H), 1.42-1.20 (3H), 1.00-0.85 (2H). ^13C NMR (50 MHz, CDCl₃): δ 174.1, 136.8, 129.7, 127.9, 114.7, 51.5, 33.4, 31.5, 26.5, 24.8.
Preparation of cis-4.12 from aldehyde 4.20. To a mixture of (but-3-enyl)triphenylphosphonium bromide (7.0 g, 17.6 mmol) in HMPA (11.1 mL, 64 mmol) and THF (52 mL), was slowly added LDA (2 M, 8.0 mL, 16.0 mmol) at -40 °C. The reaction mixture was stirred at this temperature for 1 h and then cooled to -78 °C. A solution of aldehyde 4.20 (1.91 g, 14.7 mmol) in THF (10 mL) was added to the reaction mixture, which was stirred at this temperature for 2 h, then warmed to rt for 4 h, diluted with diethyl ether (250 mL), washed with NH₄Cl (20%, 100 mL) and water (30 mL x 2), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/15:1) afforded cis-4.12 (1.78 g, 74%) as a colorless oil. Rₐ = 0.60 (Hex:EA/8:1).

(E)-Methyl nona-5,8-dienoate (trans-4.12) and (E)-methyl non-5-enoate (trans-4.18). To a solution of non-8-en-5-ynoic acid (4.16) (0.6 g, 3.9 mmol) in ethanol (0.5 mL) and liquid ammonia (10 mL), was added lithium (0.08 g, 12 mmol) in small portions at – 78 °C. When a blue color persisted for 30 min, the reaction mixture was quenched with NH₄Cl and the flask was left open to allow ammonia to evaporate. The resulting residue was dissolved in water (25 mL) and extracted with CH₂Cl₂ (10 mL x 2). The aqueous solution was acidified to pH = 2-3 with 1 N HCl (20 mL) and extracted with CH₂Cl₂ (15 mL x 3). Then the combined organic phase was washed with brine (10 mL x 2), dried (Na₂SO₄), and concentrated in vacuo. A light yellow oil (0.48 g, 80%) was obtained and used in the next step without further purification.
According to the procedure for the preparation of 4.17, the above residue was esterified to give inseparable products **trans-4.12** (0.37 g, 70%) and **trans-4.18** (0.09 g, 18%).

![Image of 4.21](attachment:image.png)

**[(5E)-Methyl 2-((R)-cyclohexa-2,4-dienyl)nona-5,8-dienoate]tricarbonyliron (4.21).** To a solution of ester **cis-4.12** (0.10 g, 0.60 mmol) in THF (3 mL), was slowly added LDA (2.0 M, 0.33 mL, 0.66 mmol) at -78 °C under Ar. After stirring was continued for 1 h, cation salt **4.11** (0.28 g, 0.77 mmol) was added. The reaction mixture was stirred at this temperature for 1 h, then warmed to rt for 5.5 h, quenched with NH₄Cl (15%, 17 mL) and extracted with diethyl ether (30 mL x 3). The combined organic phase was washed with water (15 mL x 3), dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/15:1) afforded two inseparable isomers **4.21** (0.11 g, 50%). R_f = 0.65 (Hex:EA/8:1). ¹H NMR (200 MHz, CDCl₃): δ 5.90-5.70 (2H, two isomers), 5.45-5.25 (8H, two isomers), 5.10-4.93 (4H, two isomers), 3.70 (s, 3H, one isomer), 3.66 (s, 3H, one isomer), 3.10-2.85 (4H, two isomers), 2.80-2.68 (4H, two isomers), 2.40-2.25 (2H, two isomers), 2.18-1.30 (16H, two isomers). ¹³C NMR (50 MHz, CDCl₃): δ 211.8, 211.7, 175.3, 175.2, 137.2, 130.3, 130.2, 130.2, 130.1, 128.8, 115.0, 85.8, 85.6, 85.2, 84.7, 62.8, 62.6, 59.7, 59.1, 53.5, 52.3, 51.5, 51.5, 51.4, 40.9, 40.3, 36.7, 31.0, 30.7, 30.6, 30.1, 28.8, 28.2.
[(5E)-2-((R)-Cyclohexa-2,4-dienyl)nona-5,8-dien-1-ol]tricarbonyliron (4.22). To a solution of 4.21 (0.16 g, 0.42 mmol) in CH₂Cl₂ (5 mL), was slowly added DIBAl-H (1.5 M in toluene, 1.0 mL) under Ar at – 78 °C. Reaction solution was stirred at this temperature for 2 h, then warmed to rt for 2 h, quenched with cold water (8 mL) and extracted with CH₂Cl₂ (8 mL x 2). The organic phase was dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/4:1) afforded two inseparable isomers 4.22 (0.13 g, 87%). Rf = 0.70 (Hex:EA/2:1). ¹H NMR (200 MHz, CDCl₃): δ 5.91-5.70 (2H, two isomers), 5.50-5.28 (8H, two isomers), 5.10-4.92 (4H, two isomers), 3.68-3.35 (4H, two isomers), 3.10-3.00 (4H, two isomers), 2.80-2.68 (4H, two isomers), 2.40-2.20 (2H, two isomers), 2.10-1.10 (18H, two isomers).

[((5E)-2-((R)-Cyclohexa-2,4-dienyl)nona-5,8-dienyloxy)(tert-butyl)diphenylsilane]tricarbonyliron (4.13). Alcohol 4.22 (125 mg, 0.35 mmol), DMAP (7.0 mg, 0.06 mmol), imidazole (57 mg, 0.84 mmol) and one drop of DMF were dissolved in CH₂Cl₂ (1.0 mL) at 0 °C, and then t-butylidiphenylsilyl chloride (0.12 mL, 0.46 mmol) was added slowly. The reaction mixture was stirred at rt for 1 h, filtered through celite, washed with sat. NH₄Claq and water, dried (Na₂SO₄), filtered and concentrated in vacuo. Flash chromatography (Hex:EA/19:1) afforded an inseparable mixture of isomers 4.13 (0.17 g, 84%). Rf = 0.50 (Hex:EA/19:1). ¹H NMR (200 MHz, CDCl₃): δ 7.75-7.62 (8H, two isomers), 7.50-7.35
(12H, two isomers), 5.95-5.75 (2H, two isomers), 5.42-5.20 (8H, two isomers), 5.10-4.95 (4H, two isomers), 3.70-3.40 (4H, two isomers), 3.10-2.92 (4H, two isomers), 2.80-2.70 (4H, two isomers), 2.55-2.40 (2H, two isomers), 2.05-1.80 (8H, two isomers), 1.40-1.15 (14H, two isomers), 1.07 (s, 9H, two isomers). 13C NMR (50 MHz, CDCl3): δ 212.4, 137.0, 135.8, 135.7, 133.8, 133.7, 131.0, 129.7, 127.7, 127.0, 114.7, 85.8, 85.5, 84.9, 65.2, 64.6, 64.5, 63.9, 60.2, 46.9, 46.0, 39.6, 39.2, 31.6, 28.4, 28.2, 27.4, 27.0, 25.3, 25.2, 19.4, 19.3.

[(2-((R)-Cyclohexa-2,4-dienyl)octa-5,7-dienyloxy)(tert-butyl)diphenylsilane]tricarbonyliron (4.24). According to the procedure for the preparation of 4.13, 4.24 was prepared in 72% yield. Rf = 0.60 (Hex:EA/8:1). 1H NMR (200 MHz, CDCl3): δ 7.70-7.55 (16H, four isomers), 7.50-7.30 (24H, four isomers), 6.60-6.20 (4H, four isomers), 6.10-5.92 (4H, four isomers), 5.70-4.95 (20H, four isomers), 3.70-3.38 (8H, four isomers), 3.05-2.88 (8H, four isomers), 2.50-2.35 (4H, four isomers), 2.15-1.78 (12H, four isomers), 1.40-1.18 (16H, four isomers), 1.02 (s, 36H, four isomers).

2-(Cyclohexa-1,4-dienyl)acetic acid (4.28). To a solution of 2-phenylacetic acid (4.27) (4.0 g, 29.4 mmol) in ethanol (8.6 mL) and liquid ammonia (200 mL), was added lithium (0.62 g, 88.2 mmol) in small portions until a blue color persisted 20 min. The reaction solution was quenched with NH₄Cl, and then the flask was left open to evaporate the solvent. The
resulting residue was dissolved in cold water (150 mL) and 2 N HCl(aq) was added to adjust pH = 2-3. The mixture was extracted with CH₂Cl₂ (100 mL x 3), and the combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo to give a white solid 4.28 (3.8 g, 95%), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 12.00 (br, 1H), 5.69-5.68 (2H), 5.63-5.62 (m, 1H), 3.02 (s, 3H), 2.74-2.70 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 178.7, 128.0, 124.2, 124.0, 123.9, 43.1, 29.2, 27.1.

**Methyl 2-(cyclohexa-1,4-dienyl)acetate (4.29).**

According to the procedure for the preparation of 4.17, acid 4.28 (3.3 g, 23.9 mmol) was esterified to give product 4.29 (2.8 g, 78%) purified by flash chromatography (Hex:EA/15:1). Rᵣ = 0.50 (Hex:EA/10:1). ¹H NMR (400 MHz, CDCl₃): δ 5.69-5.68 (2H), 5.59-5.58 (m, 1H), 3.68 (s, 3H), 2.99 (s, 3H), 2.74-2.66 (4H). ¹³C NMR (100 MHz, CDCl₃): δ 172.3, 128.6, 124.1, 123.9, 123.5, 52.0, 43.2, 29.2, 27.1.

![Methyl 2-(cyclohexa-1,3-dienyl)acetate|tricarbonyliron (4.30) and [methyl 2-(cyclohexa-1,5-dienyl)acetate|tricarbonyliron (4.31).](image)

[Methyl 2-(cyclohexa-1,3-dienyl)acetate|tricarbonyliron (4.30) and [methyl 2-(cyclohexa-1,5-dienyl)acetate|tricarbonyliron (4.31). A solution of ester 4.29 (3.0 g, 19.7 mmol) and iron pentacarbonyl (8.3 g, 59.2 mmol) in n-Bu₂O (20 mL) was heated under Ar at 145 °C for 48 h. After reaction mixture was filtered through Celite, the solvent was evaporated in vacuo. The resulting residue was purified by a slow flash
chromatography (Hex:DCM/1.5:1) to give 4.30 and 4.31 (4.5 g, 72% combined yield).

4.30 (2.5 g, 40%): Rf = 0.40 (Hex:DCM/1.5:1) $^1$H NMR (400 MHz, CDCl$_3$): δ 5.38 (d, $J$ = 4.4 Hz, 1H), 5.21 (dd, $J$ = 6.0, 6.0 Hz, 1H), 3.70 (s, 3H), 3.17-3.14 (m, 1H), 2.80 and 2.77 (ABq, $J$ = 15.2 Hz, 2H), 1.90-1.75 (2H), 1.69-1.64 (m, 1H), 1.56-1.51 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 212.1, 171.5, 88.5, 82.9, 73.6, 62.0, 52.0, 44.8, 27.8, 25.0.

4.31 (2.0 g, 32%): Rf = 0.45 (Hex:DCM/1.5:1) $^1$H NMR (400 MHz, CDCl$_3$): δ 5.32 (d, $J$ = 4.8 Hz, 1H), 3.74 (s, 3H), 3.28-3.12 (4H), 1.76-1.60 (4H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 211.9, 171.3, 98.4, 86.8, 65.2, 60.1, 52.4, 41.9, 24.6, 24.0.
4.5 Literature references


APPENDIX

$^1$H, $^{13}$C NMR and Other Spectra of New Compounds
2.15a or 2.15b
the other isomer
NOESY

2.19a  2.19b
9 : 1

Pulse sequence: gCOSY
Solvent: CDCl3
Chemical shift: ppm
Temperature: 298 K
Polarizer delay: 0.000 sec
Acq. time: 8.688 sec
Field strength: 240.1 MHz
Experimental setup for gCOSY
Data processing
F2: FFT, INVERSE, Z-SCORE
F1: DATA PROCESSING
Total time: 2 hrs, 16 min, 1 sec

2.19b  2.19d
9 : 1

gCOSY
Pulse Sequence: gCOSY
Solenoid: CECI3
Ambient temperature
Sample: 450 MHz
Relax delay: 1.400 sec
Data time: 3.00 sec
1H: 4.001 MHz
2D: 8991.0 Hz
time constant
Data processing
S1: 1000:1:1:1:16
S2: 1:1:1:1:16
Total time 2 min, 58 sec

2.20

gCOSY

2.21a

- 200 -
product from reduction of 2.22

- 204 -
2.23 (400 MHz, $^{19}$F NMR)

-25560 -26000 -26500 -27000 -27500 -28000 -28500 Hz

Rulse Sequence: 256p1
2.30a
gCOSY
Catalyst: + rotamers

2.34a + 2.34b

amides from racemic amine

four rotamers
2.37 one isomer

2.37, the other isomer
2.38 one isomer

2.38, the other isomer
2.38, the other isomer

product from reduction of 2.40
2.51
gCOSY
\[ \text{CH}_3\text{OH} / \text{CDCl}_3 = 1 / 9 \]

Pulse Sequence: yCONY
Solvent: CD3OD
Ampl.: Temperature

Delay: 1.000 sec
Acq. time: 0.100 sec

Sample

Data

Processing

Total time: 5 min, 14 sec

3.24a
\[ \xi \leftrightarrow C' \quad \eta \leftrightarrow C'' \]

\[ \delta \leftrightarrow C' \quad \epsilon \leftrightarrow C'' \]
Pulse Sequence: al2pul
Solute: CDCl3
Ambient temperature
{

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.125 sec
Width 3512.96 Hz
5000 repetitions
Chemshift CL2, 100.515722 MHz
Endowed XL, 399.7487328 MHz
Sweep 46 Hz
continuously on
MAINS-18 modulated
DATA PROCESSING
Line broadening 1.0 Hz
PT size 65536
Total time 3 hr, 4 min, 1 sec

3.47b

3.47D
BIBLIOGRAPHY


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