Catalytic Iron-Mediated Enediene Carbocyclizations: Investigations into the Stereoselective Formation of Bicyclic Ring Systems

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Trienes in which the requisite 1,3-diene and allylic ether moieties are appended to a pre-existing ring system afford bicyclic ring systems upon iron-catalyzed cyclization. The efficiency and stereoselectivity of the cyclization are dramatically influenced by the nature of the ring system to which the diene and alkene subunits are appended. Certain bicyclic ring systems are formed in good yield; most notably, substrates bearing a basic nitrogen are well-tolerated and certain indolizidine and quinolizidine ring systems are accessible using this methodology. The efficiency and stereoselectivity of the cyclization is also markedly dependent on the ligand used to modify the iron catalyst, and in this regard, a bisoxazoline-modified iron catalyst system is generally superior to what was the standard bipyridine-modified catalyst. In the course of these studies a difference spin polarization transfer (DSPT) experiment proved very useful for the stereochemical analysis of compounds that exhibit very crowded high field NMR spectra.

Introduction

A growing number of methodologies for the construction of synthetically interesting ring systems exploit the catalytic or stoichiometric transition metal-mediated carbon–carbon bond construction between two or more centers of unsaturation. While the precise mechanistic details for most of these cyclizations have yet to be rigorously established, most if not all can reasonably be grouped into one of two general mechanistic pathways. The first is illustrated schematically in Scheme 1A for the cyclization of the α,ω-diene **1**. The cyclization is initiated by complexation (templating or chelating) of the two unsaturated moieties within the substrate molecule about the metal center. Subsequent oxidative coupling of these π-bonded ligands (oxidative cyclization, in the case of the intramolecular coupling) effects the crucial carbon–carbon bond formation. Thus, the ring-forming event in this case occurs via the oxidative cyclization of metal chelate **2** to metallacycle **3**. The chemistry of these latter intermediates is proving to be rich, and a number of fates can await metallacycle **3**. These include (a) metal-mediated atom transfer, usually hydrogen atom transfer effecting some net cycloisomerization reaction; (b) reductive elimination to form a second carbon–carbon bond, effecting a net cycloaddition; (c) migratory insertion into another (intra- or intermolecular) unsaturated group; or (d) as illustrated in Scheme 1A, reaction with some X–Y trapping reagent. A variety of novel metal-mediated carbocyclizations have been realized via this oxidative cyclization strategy. Representative examples include cyclizations of α,ω-dienes,[1,2] enynes,[3] diynes,[4,5] enedienes,[6] dienynes,[7–9] endiynes,[10] triynes,[11] and bisdienes.[12,13]

The second general strategy, illustrated by Scheme 1B, involves the initial formation of a carbon–metal σ-bonded (in some cases, an η^3-allyl bonded) intermediate (*i.e.*, **7**) via the hydro- or carbometalation of an alkene or an alkyne (*e.g.*, **5** to **7**) or via oxidative addition of a reduced metal center to an appropriate C–X bond (*e.g.*, **6** to **7**). The crucial carbon–carbon bond-forming event occurs via insertion of a π-bonded ligand (*i.e.*, a coordinated alkene, alkyne, diene, etc.) into the carbon–metal σ-bond. This migratory insertion reaction generates an intermediate (*e.g.*, **8**) possessing a new carbon–metal σ-bond, and this latter functionality proves useful for further chemistry. Typically, **8** may undergo (a) further intra- or intermolecular insertions with additional unsaturated functional groups; (b) reaction with electrophile to afford for example **9**; or (c) β-hydride elimination. Again, a variety of novel metal-mediated carbocyclizations have been realized via this ligand insertion strategy. Representative examples include insertions of alkenes, dienes, and alkynes into metal–carbon σ-bonded (or η^3-allyl bonded) intermediates generated via the oxidative addition of a low oxidation state metal complex into a vinyl, aryl, or allylic C–X bond[14–18] (wherein X = halogen or pseudohalogen) or generated via the carbometalation[19,20] or hydrometalation[21] of an alkene or alkyne.

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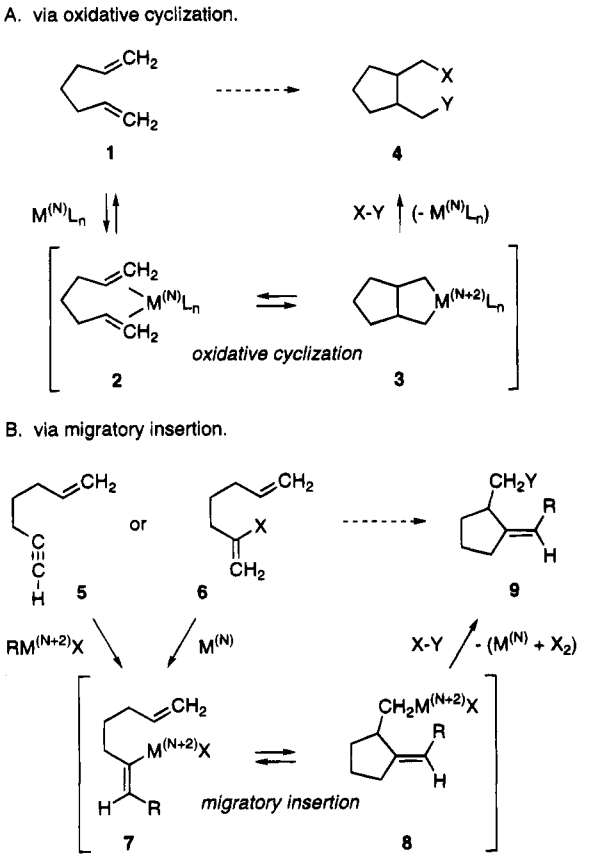
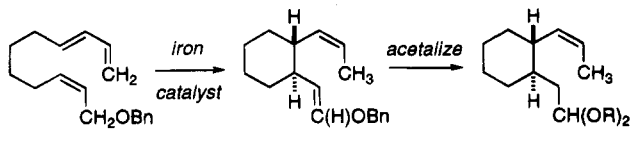
Scheme 1. Two General Strategies for Catalytic Metal-Mediated Carbocyclizations



Acyclic triene substrates bearing a 1,3-diene subunit and an allylic ether subunit at the two termini can undergo efficient, stereoselective iron-catalyzed carbocyclization to afford five- and six-membered carbocycles and heterocycles.[6,22-27] For example, enediene **10** is converted to a mixture of cyclized enol ethers upon treatment with a reduced iron–catalyst (0.1 equiv of [$Fe(acac)_3$/1.1 2,2′-bipyridine (bpy)/3.1 Et_3Al], toluene, rt, 6 h). Subsequent acid-catalyzed formation of the ethylene acetal by reaction with ethylene glycol affords **11** in good overall yield (68%). All of the results obtained to date suggest that this iron-catalyzed carbocyclization proceeds via an oxidative cyclization pathway.[28]



10 **11 (68 %)**

Considering possible synthetic applications that would exploit this bond construction, it is apparent that targets of even modest complexity would require the cyclization of a more highly constrained substrate than typified by the acyclic enedienes studied to date. The metal triene complex and the metallacyclic intermediate key to the oxidative cyclization mechanism are expected to impose significant structural requirements, and at the onset of our studies, it was not clear whether these requirements could generally be met in bicyclic or polycyclic ring systems. We therefore investigated the iron-catalyzed cyclizations of several simple model enedienes and cyclizations that lead to the stereoselective formation of bicyclic ring systems and now report the full details of those investigations.[27]

Results and Discussion

We prepared enedienes **12a** and **12b** via the route outlined in Scheme 2 and examined their iron-catalyzed carbocyclizations. Enedienes **12a** and **b** will lead to the formation of a new six-membered ring upon cyclization, and prior work in our labs has shown that an (*E*)-1,3-diene and a (*Z*)-alkene functionalities are the preferred reacting partners for such cyclizations.[24] The cis/trans relative disposition of the diene and alkene moieties about the pre-existing ring was identified as one of the potentially important factors controlling the facility of the iron-catalyzed cyclization. Diels–Alder cycloaddition of the (*E*)-enoate **14** with 2-(trimethylsiloxy)-1,3-butadiene sets the trans relative stereochemistry between the side chains in the derived cyclohexanone **15**. **14** also bears the *Z*-allylic ether functionality that will serve as the alkene partner in the iron-catalyzed cyclization. Subsequent ketalization of **15** and elaboration of the 1,3-diene subunit completes the synthesis of **12a**. Alternatively, reduction of **15** and protection of the secondary hydroxyl affords intermediate **18**. Elaboration of the primary alcohol to the diene side chain via Swern oxidation[29] followed by dienylation with allyldiphenylphosphine oxide[30] affords the desired enediene **12b**.

Compared to the acyclic enediene substrates reported to date, the ring system in **12a** will significantly restrict the conformations that the diene and alkene moieties can adopt in complexing about the iron. We find that the iron-catalyzed cyclization of **12a** requires more stringent reaction conditions than does the acyclic enediene **10**. Furthermore, while treatment with 0.25 equiv of the reduced iron catalyst [$Fe(acac)_3$/1.1 bpy/3.1 Et_3Al] at 80 °C in benzene[31] affords the substituted *trans*-decalin **19a** in high diastereomeric purity, the chemical yield is only 31%. About 20% unreacted starting material was recovered from the reaction mixture along with several partially reduced, noncyclized compounds.[32] Enediene **12b** is somewhat more reactive, and cyclization at ambient temperature affords a somewhat cleaner reaction. However, the reaction again failed to go to comple-

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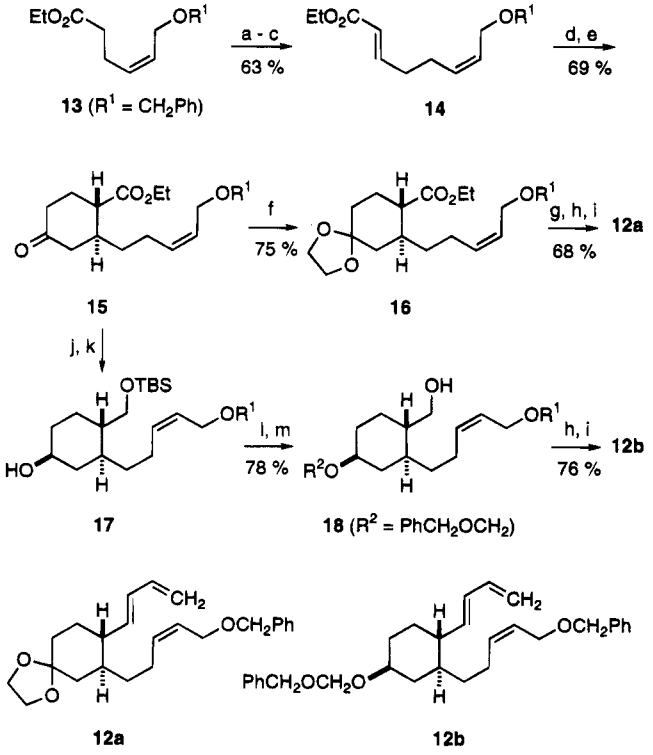
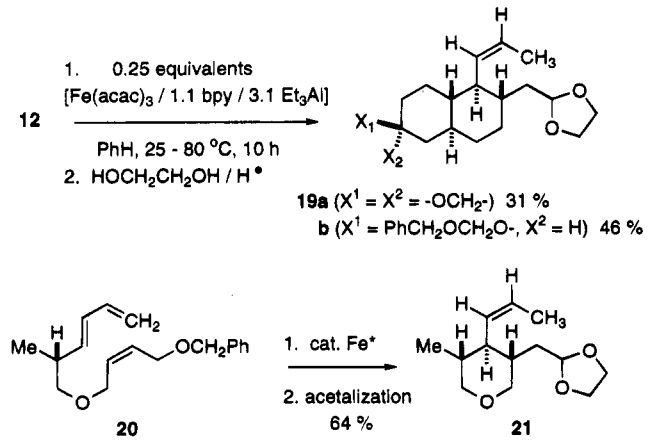
(30) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029–4032.
(31) Benzene was originally employed as the reaction solvent of choice; however, we find that toluene usually affords comparable results and we now recommend its use in place of benzene.
(32) Included among the reduced side products are compounds in which the benzyl group has been cleaved. This is an unusual side reaction in iron-catalyzed cyclization and perhaps could be overcome through the use of silyl or alkyl ethers[6] in place of the benzyl group.

Scheme 2. Syntheses of Triene Substrates 12a and 12b[a]



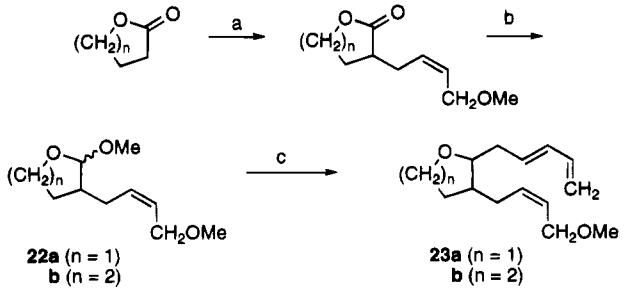
[a] Conditions: (a) 2.1 DIBAL-H, THF, 0 °C (95%); (b) $(COCl)_2$, DMSO, Et_3N, DCM (99%); (c) $Li[(EtO)_2P(O)C(H)CO_2Et]$, THF (67%); (d) CH_2=CHC(OTMS)=CH_2, $EtAlCl_2$, PhMe, reflux (99%); (e) 10% aqueous HCl, acetone, 0 °C (70%); (f) $(HOCH_2)_2$, p-TsOH, PhH, 70 °C (75%); (g) 2.1 DIBAL-H, THF, 0 °C (98%); (h) $(COCl)_2$, DMSO, Et_3N, DCM (91–93%); (i) $Li[Ph_2P(O)CHCH{=}CH_2]$, THF, HMPA (75% **12a**, 83% **12b**); (j) $LiAlH_4$, THF (93%); (k) TBDMSCl, imidazole, DMF (74%); (l) $PhCH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, DCM (97%); (m) p-TsOH, MeOH (80%).

tion under the conditions employed. 33% of the unreacted starting material was recovered. A single substituted *trans*-decalin **19b** was isolated in 32% yield (46% based on the amount of recovered starting material). We attribute the low yields of product obtained in these two cyclizations to the added constraints imposed by the ring system. We find that the standard bipyridine-modified catalyst system slowly precipitates iron metal,[25] and when substrates react slowly, competing catalyst decomposition presents a problem.



Substrates **12a** and **b** contain two nearby stereogenic centers that influence the stereochemical course of the

Scheme 3. Syntheses of Triene Substrates 23a and 23b[a]



[a] Conditions: (a) 1. LDA, THF, HMPA 2. (Z)-$MeOCH_2$-CH=$CHCH_2Br$ (**a**, 60%; **b**, 81%); (b) 1. DIBAL-H, DCM, −78 °C 2. MeOH, p-TsOH (**a**, 61%; **b**, 65%); (c) $TMSCH_2CH{=}CHCH{=}CH_2$, BF_3–OEt_2, −78 °C, DCM (**a**, 86%; **b**, 91%).

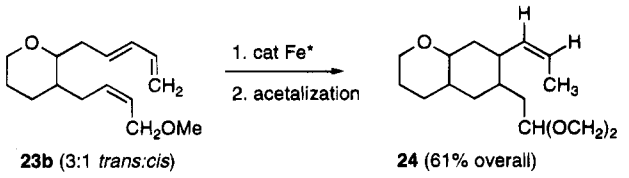
cyclization. From the perspective of the newly forming six-membered ring, these two resident chiral centers are positioned in 1,2- and 1,3-relationships to the newly forming C–C bond. In general, we find that substituents positioned in a 1,2-relationship to the newly forming carbon–carbon bond impose a significant bias in the diastereomeric cyclization pathways, and 1,2-stereoinduction is usually quite high. In contrast, the level of 1,3-stereoinduction is usually low (*vide infra*).[6] The stereochemistry indicated in structures **19a** and **19b** was established on the basis of the relevant vicinal proton coupling constants, and the sense of 1,2-stereoinduction is consistent with that observed in the cyclization of a simple acyclic chiral enediene such as **20**. Iron-catalyzed cyclization of **20** affords the trans,trans-trisubstituted tetrahydropyran **21**.[23]

Given the limited success realized in the cyclizations of **12** we next turned our attention to enediene substrates bearing a slightly different substitution pattern, one that we expected would offer greater conformational freedom to the diene and alkene bearing side chains. The substituted acetals **22a** and **b** were prepared from γ-butyrolactone and δ-valerolactone, respectively, via generation of the enolate and alkylation with (*E*)-1-bromo-4-methoxy-2-butene.[6] Half reduction using DIBAL-H and acetalization in acidic methanol affords the acetals. BF_3-catalyzed addition of pentadienyltrimethylsilane[33,34] to the five-membered ring acetal **22a** proceeds with good diastereoselectivity (10:1) to afford furan **23a**. Addition to the six-membered ring acetal **22b** affords a disappointing 3:1 trans:cis mixture of pyrans **23b**, a mixture that we were unable to efficiently separate by chromatography (Scheme 3).

Treatment of the furan substrate **23a** with the reduced iron catalyst (0.1 equiv of $[Fe(acac)_3$/1.1 bpy/3.1 $Et_3Al]$) under our standard cyclization conditions (toluene, 50 °C, 10 h) surprisingly showed no evidence of cyclization. In contrast, the mixture of *trans*- and *cis*-pyrans **23b** cyclized smoothly upon exposure to the same catalyst affording a mixture of products **24** (61% yield) bearing the bicyclo[4.4.0] ring skeleton. While the improved chemical yield for cyclization of the pyran substrate was gratifying, the 3:1 mixture of *trans*- and *cis*-pyran isomers made it impossible to convincingly sort out the stereoselectivity of the cyclization reaction. We therefore needed an alternative pyran synthesis, one that would

(33) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 3783–3786.
(34) Seyferth, D.; Pornet, J.; Weinstein, R. M. *Organometallics* **1982**, *1*, 1651–1658.

permit us to individually examine the cyclizations of both the trans-disubstituted and the cis-disubstituted pyran substrates.

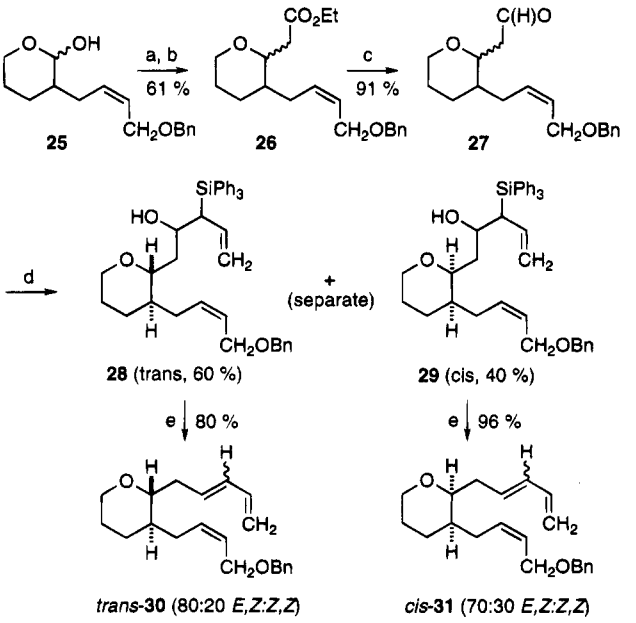


23b (3:1 *trans:cis*) **24** (61% overall)

Lactol **25** was prepared via alkylation of δ-valerolactone with (*Z*)-1-bromo-4-(benzyloxy)-2-butene[6] followed by half reduction of the lactone using DIBAL-H. Phosphonate Wittig olefination under the Masamune–Roush conditions[35] affords a 2:1 cis:trans mixture of pyrans **26**. The isomers could be easily separated at this stage; however, a later synthetic intermediate suffers cis/trans equilibration making separation at this stage pointless. The mixture of esters is converted to a 3:1 cis:trans mixture of aldehydes **27** via DIBAL-H reduction and Swern oxidation.[29] Condensation of the aldehydes with allyltriphenylsilane under the conditions of Yamamoto,[36] conditions under which allyltriphenylsilane is treated sequentially with *n*-BuLi, $(i\text{-PrO})_4$Ti, and then aldehyde, affords a mixture of four diastereomeric β-hydroxysilanes. The trans-disubstituted pyrans **28** and the cis-disubstituted pyrans **29** were isolated from the mixture in 60% and 40% yields, respectively. Unfortunately, while we succeeded in obtaining clean trans- and cis-relative stereochemistry between the side chain substituents, **28** and **29** are each a mixture of *syn* and *anti* β-hydroxysilanes. Upon acid-catalyzed elimination, each leads to an *E*/*Z* mixture of dienes that proved difficult to separate. **28** yields the trans-disubstituted pyran **30** as an 80:20 *E*:*Z* mixture of 1,3-dienes, and **29** affords a mixture of *cis*-pyrans **31** (70:30 *E*:*Z* about the 1,3-diene). Several alternative methods for this crucial dienylation were examined. The allyldiphenylphosphine oxide[30] dienylation procedure was unsuccessful. Apparently the intermediate anion is too basic and promotes the β-elimination of aldehyde **27**. The use of allyltrimethylsilane or allyl(dimethylphenyl)silane,[36] in place of allyltriphenylsilane, afforded no better stereoselectivity. Similarly, neither the use of $(i\text{-PrO})_3$TiCl[37] nor Cp_2TiCl[38] as the titanium addend improved the reaction, so we carried on with the *E*/*Z* mixtures generated according to Scheme 4.

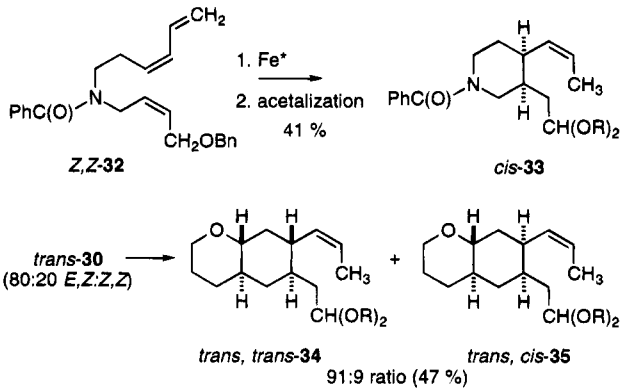
Carrying the *Z*-diene isomer into the iron-catalyzed cyclization somewhat complicates the investigation. Prior studies in our labs showed that while *Z*-alkenes are good, *Z*-dienes are generally poor substrates for iron-catalyzed cyclization. Furthermore, *Z*-dienes lead to a diastereomeric cis- rather than trans-disubstituted six-membered ring cyclization product.[24] For example, compare the cyclization of *E*,*Z*-triene **10** (described above) to the cyclization of the *Z*,*Z*-triene **32**. The former affords the trans-disubstituted cyclohexane **11** (68%); the latter leads to a mixture of cis-disubstituted products in only 41% yield. Compound **33** is the major isomer obtained from

Scheme 4. Synthesis of Cis- and Trans-Substituted Pyran Substrates 30 and 31[a]



[a] Conditions: (a) $Ph_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN (62%); (b) 2.1 equiv of DIBAL-H, THF, 0 °C (99%); (c) $(COCl)_2$, DMSO, Et_3N, DCM (91%); (d) $Ph_3SiCH_2CH{=}CH_2$, n-BuLi, $Ti(OiPr)_4$ (60% **28**, 40% **29**); (e) H_2SO_4, THF, 65 °C, 10 h (80% **30**, 96% **31**).

the reaction of (*Z*,*Z*)-**32**. Thus, while the mixtures **30** and **31** are acceptable for establishing the diastereoselectivity of the cyclizations, the isolated yields are likely lower than if isomerically pure *E*,*Z*-triene were to be employed, and we can expect to see minor amounts of cis (i.e., *Z*-diene derived) products. These expectations are borne out in the laboratory.



The iron-catalyzed carbocyclization of the mixture of trans-substituted pyrans (*E*,*Z*)-**30** and (*Z*,*Z*)-**30** affords a 91:9 mixture of two diastereomeric products (*trans*, *trans*-**34** and *trans*,*cis*-**35**, 47% yield). The minor isomer **35** has the new propenyl and acetal-bearing side chains formed with the cis relationship. This cis relative stereochemistry is analogous to that found in product **33** and is therefore consistent with arising from the minor (*Z*,*Z*)-**30** isomer. The major isomer **34** is that expected from the cyclization of (*E*,*Z*)-**30**. The all-equatorial disposition of substituents in **34** defines the propenyl and acetal-bearing side chains as trans. It should be noted that there are two possible trans,trans-diastereomers: one where the newly formed propenyl- and acetal-bearing side chains are diequatorial (as in **34**) and one where they

(35) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

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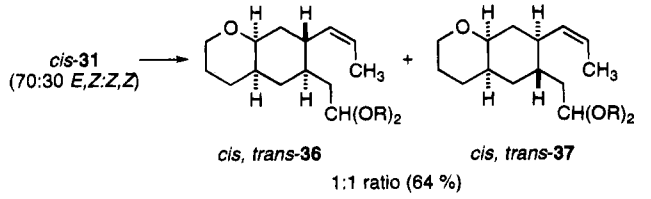
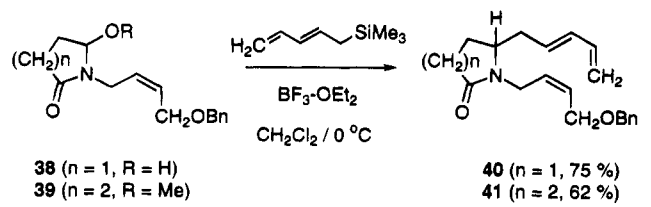
are oriented diaxial. Of the two possibilities, only the observed diequatorial arrangement can accommodate the simultaneous bonding of the side chains to the metal as required by the oxidative cyclization mechanism.

The mixture of cis-substituted pyrans (*E,Z*)-**31** and (*Z,Z*)-**31** cyclizes to a 50:50 mixture of diastereomers *cis,trans*-**36** and *cis,trans*-**37**. Both diastereomers possess the trans relationship between the propenyl- and acetal-bearing side chains and, as such, would seem to be derived from only the (*E,Z*)-**31** isomer. We were surprised by the absence of products derived from the 30% of (*Z,Z*)-**31** present in the starting mixture. We isolated a small amount of highly enriched (*Z,Z*)-**31** and found that it indeed fails to cyclize upon treatment with the standard iron catalyst system. Taking this fact into account, products **36** and **37** were isolated in a respectable 64% yield (*i.e.*, based upon the actual amount of (*E,Z*)-**31** present in the starting mixture), a yield comparable to that obtained from the cyclization of **23b**.

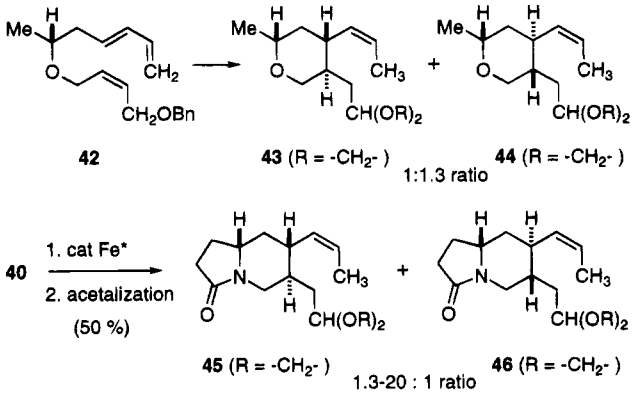


The 50:50 mixture of diastereomers obtained from the cyclization of *cis*-**31** is not surprising given the conformational mobility of the cis-substituted pyran ring system. During attempts to optimize the cyclization conditions it was noted that the **36**:**37** ratio varied within a modest range. The 50:50 ratio described above is obtained with the standard iron catalyst system (0.1 equiv of [Fe(acac)$_3$/1.1 bpy/3.1 Et$_3$Al], benzene, rt, 7 h). As we previously reported,[25] furan addends are occasionally added to the reaction mixture to suppress precipitation of the iron catalyst. In the presence of 4−5 equiv of 2-methylfuran, iron-catalyzed cyclization of *cis*-**31** affords a 70:30 **36**:**37** mixture. In retrospect, this variation in the stereoselectivity as a function of addends was a foreshadowing of an important ligand effect (*vide infra*).

Continuing our survey of substrates leading to bicyclic ring systems, we next turned our attention to the enediene substrates that would lead to the formation of bicyclic amides and amines. Amide substrates **40** and **41** were prepared via the addition of pentadienyltrimethylsilane to the *N*-acyliminium ion generated in situ by the action of BF$_3$−Et$_2$O on **38** and **39**, respectively.[39] Precursors to the latter compounds were prepared in a straightforward manner by N-alkylation of the appropriate imide with (*Z*)-1-chloro-4-(benzyloxy)-2-butene[40] followed by half-reduction of the imide with LiEt$_3$BH.[41]



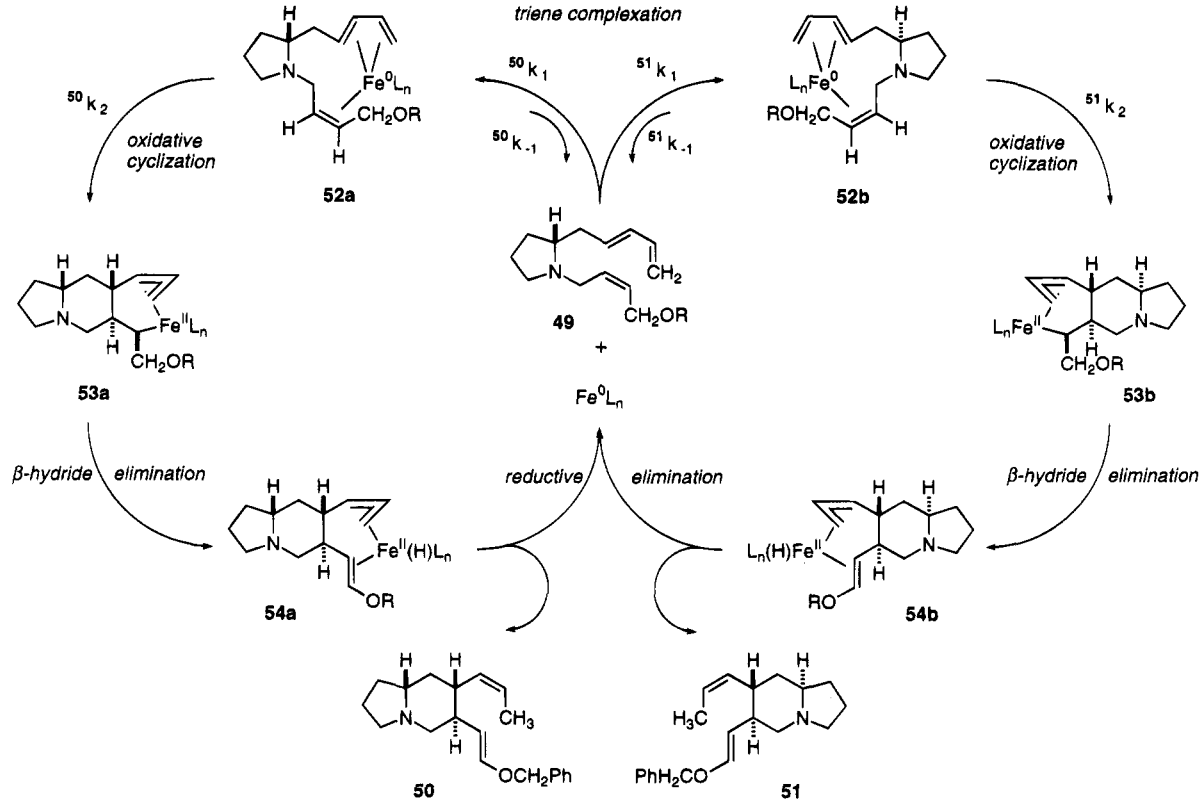
Amides **40** and **41** each contain a stereogenic center, and as such, iron-catalyzed cyclization can potentially proceed with stereoinduction from that pre-existing center. However, that single center resides in a 1,3-relationship with respect to the newly forming carbon−carbon bond, and generally, substituents so placed fail to impose a significant bias between the two diastereomeric cyclization pathways.[6] For example, consider the cyclization of the chiral acyclic enediene **42**. In contrast to the highly stereoselective cyclization of enediene **20** (described above), treatment of tetrahydropyran **42** with the standard bipyridine-modified iron catalyst system (0.2 equiv of [Fe(acac)$_3$/1.1 bpy/3.3 Et$_3$Al]) affords a 1:1.3 mixture of **43**:**44**. Treatment of amide **40** with the same bipyridine-modified catalyst system (toluene, 50 °C, 12 h) affords after acetalization a 1.3:1 mixture of bicyclic products **45**:**46** in 50% chemical yield. Within each of the diastereomers the relative stereochemistry between the propenyl- and acetal-bearing side chains is trans, a result again consistent with those obtained from prior six-membered ring-forming cyclizations. **45** and **46** differ only with respect to the relative stereochemistry between the two newly formed centers and the resident stereocenter. As anticipated, the resident stereocenter in substrate **40** indeed fails to impose a significant stereochemical bias on the course of the carbon−carbon bond construction. However, we find the level of stereoinduction improves dramatically when ligands other than bipyridine are employed.



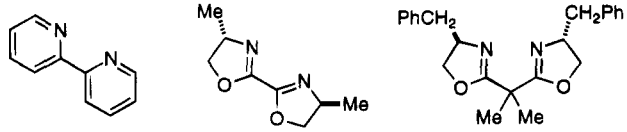
All of the examples discussed above employ what was the standard bipyridine-modified catalyst system. Bipyridine was chosen as the standard ligand based on the results of early studies on intermolecular coupling reactions. A variety of ligand types were screened, and bipyridine was found to be optimal for those couplings.[42] Other ligand systems have been used with iron catalysts. Among these the most notable are the 1,4-diazadiene ligands employed by tom Dieck and co-workers[43,44] for iron-catalyzed diene cycloaddition reactions. In connection with other studies, we had the chiral bisoxazolines[45] **47** and **48** available in our laboratories. We examined these two ligands as chiral analogues of bipyridine in an attempt to both improve the stability of the iron catalyst[25] and modify its stereoselectivity in the cyclization. Curiously, bisoxazoline **47** failed to give an active iron catalyst

(39) Takacs, J. M.; Weidner, J. J. *J. Org. Chem.* **1994**, *59*, 6480−3.
(40) CAS registry number 107691-95-2. For a preparation, see: Yadav, J. S.; Reddy, P. S. *Synth. Commun.* **1986**, *16*, 1119−31.
(41) Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215−233.
(42) Takacs, J. M.; Anderson, L. G.; BinduMadhavan, G. V.; Seely, F. L. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1013−5.
(43) tom Dieck, H.; Dietrich, J. *Chem. Ber.* **1984**, *117*, 694−701.
(44) tom Dieck, H.; Dietrich, J.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 781−783.
(45) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257−259.

Scheme 5. Working Model for the Catalytic Cycle and a Possible Origin for the Enhanced Stereoselectivity with Bisoxazoline-Modified Catalyst Systems

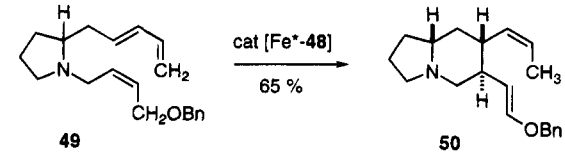


under the conditions employed; however, treatment of amide **40** with an iron catalyst modified by the bisoxazoline ligand **48** affords cyclized product in 45% yield after acetalization. The product obtained shows no optical rotation indicating a racemic product, but the diastereomer ratio **45**:**46** is dramatically improved from 1.3:1 with the bipyridine-modified catalyst to greater than 20:1 with the bisoxazoline **48**-modified catalyst system!



2,2'-bipyridine **47** **48**

We are interested in applying iron-catalyzed cyclization to the synthesis of some polycyclic alkaloids, yet none of the cyclizations that we had investigated involved substrates bearing a basic nitrogen. There are relatively few reports of catalytic metal-mediated carbocyclizations involving such substrates in the literature,[46-49] other than reactions that employ amines as nucleophiles. Early studies in our labs had revealed that the iron catalyst is quite sensitive to the presence of excess ligand,[42] so there was reason to suspect that such amine substrates might act as poisons for the iron catalyst system.[50] Nonetheless, we prepared the tertiary amine substrate **49** via the $LiAlH_4$ reduction of amide **40** (60%), and contrary to our concerns, the amine substrate **49** cyclizes even more readily than the corresponding amide **40**. Some problems were encountered in the acetalization step so we isolated products at the intermediate enol ether stage. The bipyridine-modified catalyst system affords a 3:1 mixture of diastereomeric cyclized products **50** and **51** (analogous to the amides **45** and **46**), each as a mixture of *E*- and *Z*-enol ethers in a combined 58% yield. Again, employing bisoxazoline **48**, in place of bipyridine, affords a much more stereoselective catalyst system. The bisoxazoline-modified catalyst affords exclusively the *E*-enol ether isomer of **50** (65% yield, >20:1 **50**:**51** diastereoselectivity).



49 **50**

It is tempting to speculate on how the bisoxazoline ligand influences the stereochemistry of the cyclization, particularly, in that its apparent role is to enhance the degree of 1,3-stereoinduction from the resident stereocenter.[51] Our working model for the catalytic cycle is illustrated in Scheme 5 for the cyclization of enediene

(46) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053-4.

(47) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478-80.

(48) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028-9.

(49) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, *50*, 359-70.

(50) It should be noted that ynamines were found to be suitable basic nitrogen-containing substrates for iron-catalyzed cycloadditions. See: Genet, J. P.; Ficini, J. *Tetrahedron Lett.* **1979**, 1499-1502.

(51) The fact that the products obtained from bisoxazoline-modified catalysts are racemic shows that the ligand effect is not the result of efficient asymmetric catalysis. In the context of a short enantioselective synthesis of a simple tetrahydroisoquinoline homologue of (−)-protoemetinol, we have shown that the chirality of the bisoxazoline ligand is irrelevant. The chemical nature of the ligand, not its stereochemical nature, is important. An achiral bisoxazoline functions similarly: Takacs, J. M.; Boito, S. C. *Tetrahedron Lett.*, in press.

49. The two competing diastereomeric pathways (*i.e.*, one leading to **50**, the other to **51**) are illustrated. Literature precedents[52] suggest that the cyclization is initiated by complexation of the unsaturated functionalities (*i.e.*, diene and alkene) about the metal center (*e.g.*, formation of triene complex **52**) followed by oxidative cyclization to form an intermediate iron metallacycle **53**. Iron-mediated hydride transfer via sequential β-hydride elimination (*e.g.*, formation of **54**) and reductive elimination would complete the observed synthetic transformation and regenerate the iron catalyst. Our previously reported mechanistic studies are fully consistent with this postulated catalytic cycle;[28] however, as noted by a reviewer the change to the bisoxazoline ligand could also change the mechanism. Nonetheless, in reflecting upon the remarkable effect of the bisoxazoline ligand, it appeared to us perhaps more surprising that the bipyridine-modified catalyst system is so relatively nonselective than that the bisoxazoline catalyst strongly favored **50** over **51**. After all, product **50** has all of the substituents pseudoequatorial with respect to the piperidine ring and is the product that would likely be favored on the basis of relative stability.

Consider the model presented in Scheme 5. Note that all of the stereochemistry relevant to carbon–carbon bond formation is determined in the complexation and/or oxidative cyclization steps. With a relatively remote stereocenter influencing the cyclization as is the case in **49**, it is reasonable to assume relatively indiscriminate complexation ($^{50}k_1 \approx {}^{51}k_1$) and the formation of comparable amounts of the diastereomeric triene complexes **52a** and **52b**. We postulate that the origin of the unusual ligand stereoenhancing effect is tied to a ligand dependency for the relative rates of decomplexation (k_{-1}) versus oxidative cyclization (k_2) in the two diastereomeric pathways. When decomplexation (k_{-1}) is slow relative to the diastereomeric modes of oxidative cyclization (k_2), then the product ratio **50**:**51** is largely determined by the indiscriminate complexation step ($^{50}k_1 \approx {}^{51}k_1$). This scenario would explain the results obtained when the bipyridine-modified catalyst is employed for the cyclization of **49**. With the bisoxazoline-modified catalyst we speculate that decomplexation (k_{-1}) is fast relative to oxidative cyclization (k_2), perhaps due to the bulky substituents adjacent to nitrogen. Consequently, the relative rates of the diastereomeric oxidative cyclizations (*e.g.*, $^{50}k_2/^{51}k_2$) determine the **50**:**51** product ratio;[53] the cyclization proceeds with high selectivity favoring the ring system wherein all of the substituents about the piperidine ring are pseudoequatorial (>20:1 **50**:**51**).

Returning to the formation of bicyclic heterocycles, we also investigated the reaction of the six-membered ring amide substrate **41**. Recall the surprising lack of reactivity of the tetrahydrofuran substrate **23a**. We again find that structural constraints imposed by the pre-existing ring system markedly influence the facility of the iron-catalyzed cyclization. In contrast to the five-membered ring amide **40**, the six-membered ring amide substrate

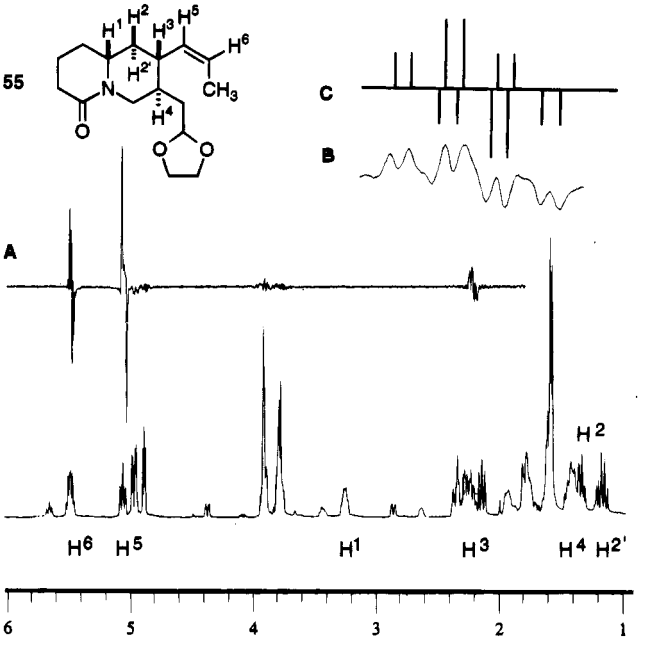
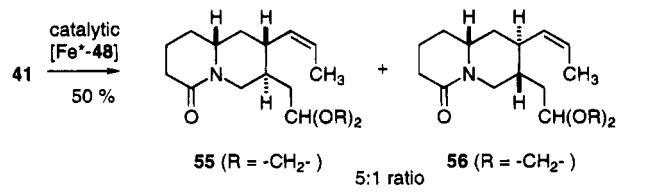


Figure 1. The partial (1–6 ppm) ^{1}H NMR spectrum of the 5:1 **55**:**56** mixture and the stereochemical analysis of **56** based on the DSPT NMR experiment.

41 does not cyclize to an appreciable extent with the bipyridine-modified catalyst system. The bisoxazoline-modified catalyst solutions appear to be more stable toward precipitating iron metal, and treatment of **41** with the bisoxazoline-modified catalyst system affords a modest yield (40% after acetalization) of cyclized products as a 5:1 **55**:**56** mixture.



Before describing the results of our investigations with the amine substrate derived from **41**, it is worthwhile to comment on the spectroscopic method by which the structure of **55** (as well as other of the products described in this study) is determined. Often these products exhibit very crowded high-field NMR spectra making the analysis of the relevant scalar coupling constants difficult. For example, Figure 1 shows the relevant 500 MHz ^{1}H NMR spectrum of the 5:1 **55**:**56** mixture. From the splitting pattern it is easy to establish that H^1 (δ 3.2 ppm) must be pseudoaxial with respect to the piperidine ring. To finish the stereochemical assignment of **55** as shown we need to establish that H^3 and H^4 are trans diaxial. Unfortunately, H^3 is buried under the δ 2.1–2.4 ppm multiplets and H^4 is buried under the δ 1.2–1.5 ppm multiplets. Several spectroscopic techniques, most commonly the relatively cumbersome 2D phase sensitive DQCOSY experiment, could in principle be used to extract the appropriate coupling constants. We find that a difference spin polarization transfer (DSPT) experiment[54–56] often provides a quick and convenient

(52) Akiyama, T.; Grevels, F.-W.; Reuvers, J. G. A.; Ritterskamp, P. *Organometallics* **1983**, *2*, 157–160.

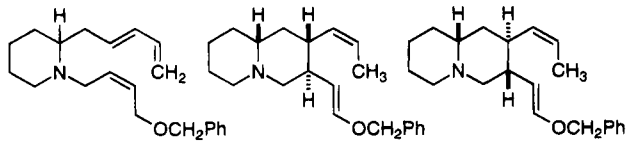
(53) We have no evidence as to the reversibility of oxidative cyclization under these reaction conditions and recognize that β-hydride elimination, rather than oxidative cyclization, could in principle be the stereochemically determining step in the cycle. However, the arguments regarding the role of the bisoxazoline ligand in differentiating the diastereomeric reaction pathways leading to **50** or **51**, essentially a Curtin–Hammett argument, are unchanged if oxidative cyclization is rapidly reversible relative to the rate of β-hydride elimination.

(54) The DSPT spectrum is also described as a selective population transfer difference spectrum. See: Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy: A Guide for Chemists*, 2nd ed.; Oxford University Press: New York, 1993.

method for such analyses.[57] This relatively powerful one-dimensional NMR experiment is quite simple, yet it is infrequently used by synthetic chemists.

In the case of compound **55** the DSPT spectrum is obtained by recording a spectrum after applying a soft pulse at the downfield side of the δ 5.05 doublet of doublets corresponding to the vinyl hydrogen H^5 and then subtracting the spectrum obtained after applying a soft pulse at the upfield side of the same resonance. Inset A (Figure 1) shows the DSPT spectrum in the region 1.8–6.0 ppm. Only the hydrogens that are scalar coupled to H^5 (*i.e.*, H^3 and H^6) appear in the DSPT spectrum. They appear as difference patterns for those hydrogens and preserve the coupling constant information. Inset B (Figure 1) shows the expanded difference pattern obtained for H^3, and inset C shows its interpretation as two overlapping doublet-of-doublet-of-doublets (ddd). H^3 has four scalar couplings ($J_{2,3}$, $J_{2',3}$, $J_{3,4}$, and $J_{3,5}$), each of which is relatively easily obtained from the difference pattern. The active coupling in the DSPT experiment ($J_{3,5}$ = 10.5 Hz) is measured from the center of the positive ddd to the center of the negative ddd. The positive (or negative) ddd pattern arises from one small ($J_{2,3}$ = 4.0 Hz) and two large ($J_{2',3} \approx J_{3,4} \approx$ 11.5 Hz) coupling constants, a pattern that is only consistent with the H^3–H^4 trans diaxial relationship depicted in structure **55**.

Returning to the cyclization of the six-membered ring amine substrate, substrate **57** is obtained by $LiAlH_4$ reduction of **41** (63%). In contrast to amide **41**, amine **57** cyclizes upon treatment with the bipyridine-modified iron catalyst, and the chemical yield is good (70%). Apparently, the added conformational flexibility afforded to the amine **57** over the amide **41** is enough to enable the former to interact productively with the iron catalyst whereas the latter is quite unreactive. A 3:2 mixture of diastereomers **58**:**59** (each as a mixture of *E*- and *Z*-enol ethers) is obtained. The bisoxazoline-modified catalyst effects the cyclization of amine **57** in comparable yield (70%), but with improved stereoselectivity affording a 6:1 **58**:**59** mixture. Each is formed with exclusively the *E*-enol ether geometry.



57 **58** **59**

Conclusions. We investigated the iron-catalyzed reactions of several simple model enedienes that lead to the formation of bicyclic ring systems and find that the efficacy and stereoselectivity of the cyclization are dramatically influenced by the nature of the ring system to which the diene and alkene subunits are appended and by the nature of the ligand employed. Our working model for the iron-catalyzed cyclization proceeds via an oxidative cyclization mechanism, and as such, iron triene complex and metallacycle structures presumably play important roles in the catalytic cycle. Their unique structural requirements apparently dictate the facility and stereoselectivity of the cyclization with these more highly constrained substrates. Enediene substrates **12**, **23a**, and **41** are relatively unreactive under the conditions employed, and typically, catalyst decomposition competes with cyclization. Nonetheless, we find that certain bicyclic ring systems are formed in good yield. Most notably, substrates bearing a basic nitrogen (*i.e.*, **49** and **57**) are well-tolerated and certain indolizidine and quinolizidine ring systems are readily accessible using this chemistry. The cyclizations often proceed with good stereoselectivity. Both the chemical efficiency and stereoselectivity are markedly dependent on the ligand used to modify the iron catalyst. In this regard we find that a bisoxazoline-modified catalyst system is generally superior to what was the standard bipyridine-modified catalyst. In the course of these studies we have made rather extensive use of a difference spin polarization transfer (DSPT) experiment. DSPT spectra can be very useful for the stereochemical analysis of compounds such as these that exhibit very crowded high-field NMR spectra. Further studies and synthetic applications of this chemistry are in progress.

Experimental Section

General Procedures.[58] Extra care was taken to ensure that the toluene used in the catalytic iron chemistry was dry and oxygen free. Toluene was distilled from sodium metal and then redistilled from purple (blue often proved unacceptable) sodium–benzophenone ketyl. Dichloromethane (DCM) was passed through a column of activity I alumina immediately prior to use. Ferric acetylacetonate ($Fe(acac)_3$) was purified by recrystallization from ethanol and/or (preferably) by sublimation (0.01 mm, 150 °C). 2,2′-Bipyridine (bpy) was purified by sublimation (0.01 mm, 80 °C). Triethylaluminum (Et_3Al) was used as a 1.9 M solution in toluene. After several months of use, stock solutions of Et_3Al were replaced. All temperatures are reported in degrees Celsius and unless otherwise noted were externally measured. Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen. Combustion analyses were performed by M-H-W Analytical Labs, Phoenix, AZ. High-resolution mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, Lincoln, NE.

Preparation of (Z)-Ethyl 6-(Benzyloxy)-4-hexenoate (13). To a stirred, cooled (−78 °C) solution of $(i\text{-Pr})_2NH$ (4.0 mL, 28.5 mmol) and HMPA (9.8 mL, 56.3 mmol) in dry THF (175 mL) was added *n*-BuLi (11.3 mL, 28.3 mmol) followed by EtOAc (2.5 mL, 25.7 mmol). To the resulting clear solution was added a solution of (*Z*)-1-(benzyloxy)-4-bromo-2-butene[6] (6.5 g, 27.0 mmol) in THF (5 mL) via cannula. After being slowly warmed to rt overnight, the reaction mixture was diluted with ether (250 mL) and then washed with water (150 mL) and with brine (150 mL). The organic layer was diluted with hexanes (150 mL) and then washed with brine (3 × 150 mL), dried ($MgSO_4$), filtered, and concentrated to give an orange-red oil. Chromatography on silica (60–200 mesh, 90:10 Hex:EtOAc) yielded 4.9 g (77%) of **13** as a clear liquid: TLC analysis (70:30 Hex:EtOAc) R_f 0.48; capillary GC analysis (DB-5, 100–250 °C at 5 °C/min) 9.7 (2.0%), 15.9 min (98.0%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.33 (m, 5 H), 5.57–5.67 (m, 2 H), 4.51 (s, 2 H), 4.08–4.15 (m, 4 H), 2.36 (s, 4 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.8, 138.2, 131.1, 128.3, 127.7, 127.5, 72.1, 65.5, 60.3, 33.9, 23.0, 14.1; IR (neat) 1735 (s, C=O); HRMS analysis (EI, rt, $C_{15}H_{19}O_3$ (M − H) = 247.1335) found m/z 247.1323.

Preparation of (Z)-6-(Benzyloxy)-4-hexen-1-ol. To a stirred, cooled (0 °C) solution of **13** (12.8 g, 51.7 mmol) in THF (300 mL) was added DIBAL-H (79.3 mL, 119.0 mmol). After being warmed to rt (4 h), the reaction mixture was carefully

(55) Sanders, J. K. M.; Mersh, J. D. *Prog. N.M.R. Spectrosc.* **1982**, *15*, 353–400.
(56) Hallenga, K.; Hull, W. E. *J. Magn. Reson.* **1982**, *47*, 174–9.
(57) Takacs, J. M.; Chandramouli, S. V.; Shoemaker, R. *Tetrahedron Lett.* **1994**, *35*, 9161–4.

(58) For more details on the general experimental procedures, analytical methods, and purification of reagents, see ref 6.

quenched by the addition of excess $Na_2SO_4(H_2O)_{10}$ (ca. 10 g), ether (200 mL), and Celite (ca. 7 g). The resulting slurry was stirred (3 h) and then dried (anhyd Na_2SO_4, ca. 2 g), filtered, and concentrated to yield 10.1 g (95%) of (*Z*)-6-(benzyloxy)-4-hexen-1-ol as a clear oil that was used without further purification: GC analysis (DB-5, 100−250 °C at 5 °C/min) 9.7 (2.1%), 13.3 min (97.9%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.35 (m, 5 H), 5.58−5.67 (m, 2 H), 4.51 (s, 2 H), 4.05 (d, 2 H, J = 5.6 Hz), 3.55 (t, 2 H, J = 6.4 Hz), 2.45 (br s, 1 H), 2.14 (dt, 2 H, J = 6.8, 7.1 Hz), 1.59 (dt, 2 H, J = 6.9, 6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 133.6, 128.3, 127.8, 127.6, 126.2, 72.2, 65.3, 61.4, 31.8, 23.6; IR (neat) 3400 (br s, OH); combustion analysis ($C_{13}H_{18}O_2$: 75.37 C, 9.02 H) found 75.69 C, 8.79 H.

Preparation of (2*E*,6*Z*)-Ethyl 8-(Benzyloxy)-2,6-octadieneoate (14). To a cooled (−55 °C, internally measured), stirred solution of oxalyl chloride (1.90 mL, 21.8 mmol) in DCM (250 mL) was added DMSO (3.10 mL, 43.7 mmol) dropwise. After 2 min, a solution of (*Z*)-6-(benzyloxy)-4-hexen-1-ol (4.13 g, 20.0 mmol) in DCM (10 mL) was added. The resulting clear reaction mixture was stirred for 15 min (−55 °C) at which point Et_3N (14.0 mL, 100 mmol) was added. The resulting milky white reaction mixture was stirred for 5 min (−55 °C) and then the ice bath removed. Upon being warmed to rt, the reaction mixture was partitioned with water (150 mL). The aqueous layer was back-extracted with DCM (100 mL). The combined organic extracts were washed with brine (3 × 150 mL) and then dried ($MgSO_4$), filtered, and concentrated. The resulting oil (which contained some solid) was filtered through a plug of silica (70:30 Hex:EtOAc) and concentrated to yield 4.0 g (99%) of the aldehyde as a pale yellow liquid, which was used without further purification.

To a cooled (0 °C), stirred solution of triethyl phosphonoacetate (2.20 mL, 11.2 mmol) in dry THF (150 mL) was added *n*-BuLi (5.00 mL, 12.5 mmol). To the resulting solution was added a solution of the crude aldehyde (2.1 g, 10.3 mmol) in THF (5 mL). After being warmed to ambient temperature (3 h), the reaction was quenched by the addition of saturated aqueous NH_4Cl (1−2 mL) and concentrated. The resulting oil was diluted with ether (150 mL), washed with brine (3 × 100 mL), and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260−400 mesh, 90:10 Hex:EtOAc) yielded 1.90 g (67%) of **14** as a clear oil: TLC analysis (70:30 Hex:EtOAc) R_f 0.53; GC analysis (DB-5, 100−250 °C at 5 °C/min) 9.7 (4.0%), 20.7 (96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16−7.25 (m, 5 H), 6.82 (dt, 1 H, J = 15.7, 6.7 Hz), 5.71 (d, 1 H, J = 15.6 Hz), 5.45−5.58 (m, 2 H), 4.40 (s, 2 H), 4.07 (q, 2 H, J = 7.1 Hz), 3.95 (d, 2 H, J = 5.7 Hz), 2.07−2.17 (m, 4 H), 1.17 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4, 147.8, 138.1, 131.6, 128.3, 128.0, 127.7, 127.5, 127.2, 121.8, 72.1, 65.5, 60.1, 31.9, 26.0, 14.2; IR (neat) 1720 (s, C=O); combustion analysis ($C_{17}H_{22}O_3$: 74.42 C, 8.08 H) found 74.24 C, 8.28 H.

Cycloaddition Reaction of Enoate 14 with 2-[(Trimethylsilyl)oxy]-1,3-butadiene. To a stirred solution of **14** (1.34 g, 4.88 mmol) in toluene (15 mL) was added $EtAlCl_2$ (2.7 mL of a 1.8 M solution in toluene, 4.9 mmol) and 2-[(trimethylsilyl)oxy]-1,3-butadiene (7.2 mL, 41 mmol). The resulting yellow solution was refluxed (115 °C, 10 h) and then cooled (rt) and quenched by the addition of $Na_2SO_4(H_2O)_{10}$ (ca. 2 g), Celite (ca. 3 g), and ether (ca. 20 mL). The resulting slurry was stirred (1.5 h) and then dried (anhydrous Na_2SO_4), filtered, and concentrated. The resulting oil was filtered through silica (60-200 mesh, 70:30 Hex:EtOAc) to yield 2.10 g of crude cycloadduct which was used without further purification: TLC analysis (70:30 Hex:EtOAc) R_f 0.32 (ketone), 0.67 (silyl enol ether).

a. Preparation of *trans*-5-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-carbethoxycyclohexanone (15). To a stirred, cooled (0 °C) acetone solution (100 mL) of the crude cycloadduct derived from **14** (6.1 g, 22 mmol) as described above was added 10% aqueous HCl (ca. 5 drops). The reaction was stirred (45 min) and then diluted with ether (150 mL) and washed with saturated aqueous $NaHCO_3$ (4 × 100 mL) and brine (100 mL). The organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60−200 mesh, 70:30 Hex:EtOAc) yielded 5.25 g (70%) of keto ester **15**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26−7.36 (m, 5 H), 5.51−5.63 (m, 2 H), 4.50 (s, 2 H), 4.16 (q, 2 H, J = 7.1 Hz), 4.05 (d, 2 H, J = 5.8 Hz), 1.95−2.58 (m, 10 H), 1.32−1.55 (m, 2 H), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 209.2, 174.2, 138.1, 132.2, 128.2, 127.6, 127.4, 126.7, 72.0, 65.4, 60.5, 46.8, 44.6, 39.3, 39.0, 34.0, 27.6, 24.0, 14.1; FT-IR (ATR) 1715 (s, C=O); HRMS analysis (EI, rt, $C_{21}H_{28}O_4$ = 344.1988) found m/z 344.1990.

b. Preparation of *trans*-5-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-carbethoxy-1,1-(ethylenedioxy)cyclohexane (16). To a stirred solution of the crude cycloadduct derived from **14** (1.34 g, 4.88 mmol) in benzene (20 mL) was added excess ethylene glycol (2 mL) and a catalytic amount of *p*-TsOH (5−10 mg). The reaction mixture was stirred (70 °C, 4 h) and then heated to ca. 85 °C and 10 mL of benzene and benzene−water azeotrope collected by distillation. The reaction was cooled (rt), diluted with ether (150 mL), and washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60−200 mesh, 70:30 Hex:EtOAc) yielded 1.40 g (75% from **14**) of **16** as a pale yellow oil: TLC analysis (70:30 Hex:EtOAc) R_f 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5 H), 5.58 (m, 2 H), 4.50 (s, 2 H), 4.12 (q, 2 H, J = 6.6 Hz), 4.05 (d, 2 H, J = 5.6 Hz), 3.92 (s, 4 H), 1.75−2.08 (m, 8 H), 1.43−1.49 (m, 2 H), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3, 138.3, 133.0, 128.2, 127.7, 127.5, 126.2, 108.1, 71.9, 65.6, 64.3, 64.2, 60.1, 48.7, 39.0, 36.5, 33.9, 33.7, 27.1, 24.2, 14.2; IR (neat) 1730 (s, C=O); combustion analysis ($C_{23}H_{32}O_5$: 71.11 C, 8.30 H) found 71.14 C, 8.56 H.

Preparation of *trans*-5-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-1,1-(ethylenedioxy)-4-(hydroxymethyl)cyclohexane. To a cooled (0 °C), stirred solution of **16** (3.00 g, 7.72 mmol) in THF (200 mL) was added DIBAL-H (11.3 mL, 17.0 mmol). The reaction was stirred (0 °C, 4 h) and then warmed to rt and carefully quenched by the addition of $Na_2SO_4(H_2O)_{10}$ (ca. 10 g), ether (200 mL), and Celite (ca. 7 g). The resulting slurry was stirred (3 h) and then dried (anhydrous Na_2SO_4, ca. 2 g), filtered, and concentrated to yield 2.50 g (98%) of the alcohol as a clear oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5 H), 5.58 (s, 2 H), 4.50 (s, 2 H), 4.05 (d, 2 H, J = 5.0 Hz), 3.91 (s, 4 H), 3.80 (m, 1 H), 3.47 (m, 1 H), 1.20−2.16 (m, 13 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 133.5, 128.2, 127.6, 127.4, 125.9, 108.8, 72.0, 65.5, 64.7, 64.2, 64.1, 42.9, 39.6, 35.5, 34.1, 32.7, 36.8, 24.1; IR (neat) 3450 (br s, OH). A portion was purified by chromatography on silica: combustion analysis ($C_{21}H_{30}O_4$: 72.80 C, 8.73 H) found 73.13 C, 8.92 H.

Preparation of *trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-((*E*)-1,3-butadienyl)-1,1-(ethylenedioxy)cyclohexane (12a). To a cooled (−55 °C, internally measured), stirred solution of oxalyl chloride (0.74 mL, 8.50 mmol) and DMSO (1.20 mL, 17.0 mmol) in DCM (100 mL) was added a solution of *trans* 5-[(*Z*)-5-(benzyloxy)-3-pentenyl]-1,1-(ethylenedioxy)-4-(hydroxymethyl)cyclohexane (2.80 g, 7.72 mmol) in DCM (10 mL). The clear reaction mixture was stirred for 15 min (−55 °C) at which point Et_3N (5.40 mL, 38.6 mmol) was added. The resulting milky white reaction mixture was stirred for 5 min (−55 °C) and then the cold bath removed and the reaction warmed to rt. The resulting reaction mixture was partitioned with water (100 mL) and the aqueous layer back-extracted with DCM (75 mL). The combined organic extracts were washed with brine (3 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a plug of silica (70:30 Hex:EtOAc) and concentrated to yield 2.50 g (93%) of the crude aldehyde as a pale yellow liquid, which was used without further purification.

To a cooled (−78 °C), stirred solution of allyldiphenylphosphine oxide (1.60 g, 6.7 mmol) and HMPA (2.60 mL, 14.7 mmol) in dry THF (175 mL) was added *n*-BuLi (3.0 mL, 7.4 mmol). A solution of crude aldehyde (2.30 g, 6.7 mmol) in THF (5 mL) was added to the resulting deep red solution. The resulting reaction mixture was slowly warmed to rt (gradually turning from red to orange) and after 5 h (rt) was quenched by the addition of saturated aqueous NH_4Cl (1−2 mL). The mixture was then concentrated via rotovap and partitioned between ether (200 mL)-water (120 mL). The organic layer

was diluted with 130 mL of hexanes, washed with brine (3 × 120 mL), and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60–200 mesh, 80:20 Hex:EtOAc) yielded 1.80 g (75%) of enediene **12a** as a clear oil: HPLC analysis (SiO_2, 90:10 Hex:EtOAc at 1.5 mL/min) 7.1 (3.3%), 7.9 (96.7%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5 H), 6.28 (m, 1 H), 6.02 (dd, 1 H, J = 10.3, 15.1 Hz), 5.43–5.57 (m, 3 H), 5.08 (d, 1 H, J = 16.9 Hz), 4.65 (d, 1 H, J = 10.0 Hz), 4.48 (s, 2 H), 4.04 (d, 2 H, J = 5.3 Hz), 3.91 (s, 4 H), 1.40–2.10 (m, 10 H), 1.05–1.26 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.6, 137.0, 133.4, 131.1, 128.1, 127.6, 127.4, 125.9, 115.0, 108.7, 72.0, 65.6, 64.2, 64.1, 46.0, 39.7, 38.9, 34.2, 33.9, 30.6, 24.3; IR (neat) 1450 (m); HRMS analysis (EI, 100 °C, $C_{24}H_{32}O_3$ = 368.2353) found m/z 368.2353.

Iron-Catalyzed Cyclization of *trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-((*E*)-1,3-butadienyl)-1,1-(ethylenedioxy)cyclohexane (12a). To a cooled (0–5 °C), stirred solution of $Fe(acac)_3$ (96 mg, 0.27 mmol), bpy (42 mg, 0.27 mmol), and **12a** (360 mg, 0.98 mmol) in dry oxygen-free benzene (10 mL) was added Et_3Al (0.46 mL, 0.88 mmol) dropwise. The resulting dark blue solution was removed from the ice bath and refluxed for 8 h. The mixture was filtered through silica (80:20 Hex:EtOAc) and concentrated to yield 300 mg of the crude *Z*- and *E*-enol ethers which were immediately acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between ether (75 mL)–saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260–400 mesh, 90:10 Hex:EtOAc) yielded 96 mg (31%) of **19a**: TLC analysis (70:30 Hex:EtOAc) R_f 0.47; ^1H NMR (300 MHz, C_6D_6) δ 5.53 (m, 1 H), 5.03 (dd, 1 H, J = 1.7, 10.7 Hz), 4.91 (m, 1 H), 3.35–3.62 (m, 8 H), 2.07–2.16 (m, 2 H), 1.71–1.87 (m, 4 H), 1.25–1.55 (m, 9 H), 0.89–1.12 (m, 2 H), 0.51–0.65 (m, 1 H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 134.8, 125.3, 109.3, 104.2, 64.7, 64.5, 64.2, 46.6, 46.2, 43.0, 39.4, 39.0, 38.8, 35.6, 33.5, 32.0, 28.9, 13.7; FT-IR (neat) 1446 (m); HRMS (EI, rt, $C_{19}H_{30}O_4$ = 322.2145) found m/z 322.2141.

Preparation of 3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-(hydroxymethyl)cyclohexanol. To a stirred, cooled (0 °C) solution of **15** (0.44 g, 1.28 mmol) in THF (25 mL) was added $LiAlH_4$ (0.05 g, 1.32 mmol). The reaction mixture was stirred (1 h, rt) and then quenched by the addition of $Na_2SO_4(H_2O)_{10}$ (0.05 g), Celite (ca. 1 g), and ether (50 mL). The resulting slurry was stirred (2 h) and then filtered and the filtrate concentrated to yield 0.42 g (93%) of crude diol that was used without further purification: HPLC analysis (SiO_2, EtOAc at 1.5 mL/min) 5.0 (80%, equatorial alcohol), 5.7 (20%, axial alcohol); ^1H NMR (200 MHz, $CDCl_3$) δ 7.27–7.36 (m, 5 H), 5.58 (m, 2 H), 4.50 (s, 2 H), 4.05 (d, 2 H, J = 4.8 Hz), 3.35–3.69 (m, 3 H), 2.33 (br s, 2 H), 1.51–2.11 (m, 7H), 0.85–1.31 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.15, 138.1, 138.0, 133.9, 133.7, 128.2, 127.7, 127.5, 125.9, 125.6, 72.1, 72.0, 70.2, 66.1, 65.5, 65.4, 64.7, 64.4, 43.1, 42.5, 40.5, 37.0, 36.1, 35.0, 32.6, 32.5, 31.7, 27.7, 24.3, 24.1, 22.7; FT-IR (ATR) 3370 (br m, OH); HRMS analysis (FAB, rt, $C_{19}H_{29}O_3$ [M + H] = 305.2118) found m/z 305.2119.

Preparation of 3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-[(*tert*-butyldimethylsiloxy)methyl]cyclohexanol (17). To a stirred, cooled (0 °C) solution of 3-[(*Z*)-5-(benzyloxy)-3-pentenyl]-4-(hydroxymethyl)cyclohexanol (3.40 g, 11.2 mmol) and imidazole (1.20 g, 16.8 mmol) in DMF (100 mL) was added a solution of *tert*-butyldimethylchlorosilane (1.70 g, 11.2 mmol) in DMF (20 mL) dropwise. After being stirred overnight, the reaction mixture was partitioned between ether (200 mL)–saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed with brine (100 mL) and then dried ($MgSO_4$), filtered, and concentrated. TLC analysis (50:50 Hex:EtOAc) showed four components: R_f 0.69 (bis silyl ether); 0.29 (axial alcohol); 0.21 (**17**, equatorial alcohol); and origin (diol). Chromatography on silica (260–400 mesh, 80:20 Hex:EtOAc) yielded 2.70 g (74% based on recovered diol) of the combined axial and equatorial alcohols and 26% of recovered diol. A portion of the equatorial alcohol **17** was characterized as follows: ^1H NMR (200 MHz, $CDCl_3$) δ 7.24–7.34 (m, 5 H), 5.53–5.59 (m, 2 H), 4.49 (s, 2 H), 4.05 (d, 2 H, J = 4.9 Hz), 3.40–3.62 (m, 3 H), 1.51–2.10 (m, 7 H), 1.09–1.32 (m, 5 H), 0.86 (s, 9 H), 0.0 (s, 6 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.3, 133.7, 128.3, 127.7, 127.5, 126.0, 72.1, 70.6, 65.7, 64.8, 43.2, 40.7, 36.1, 35.3, 32.7, 28.1, 25.9, 24.3, 18.2; FT-IR (ATR) 3365 (br m, OH), 1471 (m), 1462 (m), 1452 (m); HRMS analysis (EI, 200 °C, $C_{25}H_{42}O_3Si$ = 418.2905) found m/z 418.2896.

Preparation of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-[(*tert*-butyldimethylsiloxy)methyl]-1-[(benzyloxy)methoxy]cyclohexane. To a stirred solution (rt) of **17** (2.10 g, 5.11 mmol) and diisopropylethylamine (1.30 mL, 7.67 mmol) in DCM (60 mL) was added benzyl chloromethyl ether (0.85 mL, 6.13 mmol). The reaction mixture was stirred (rt, 10 h) and then partitioned between ether (100 mL)–water (100 mL). The organics were washed with brine (100 mL) and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60–200 mesh, 90:10 Hex:EtOAc) yielded 2.70 g (97%) of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(benzyloxy)-3-pentenyl]-4-[(*tert*-butyldimethylsiloxy)methyl]-1-[(benzyloxy)methyl]cyclohexane: ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.33 (m, 10 H), 5.56 (m, 2 H), 4.80 (s, 2 H), 4.60 (s, 2 H), 4.47 (s, 2 H), 4.04 (s, 2 H), 3.42–3.62 (m, 3 H), 1.45–2.11 (m, 6 H), 1.11–1.32 (m, 6 H), 0.86 (s, 9 H), 0.0 (s, 6 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.4, 138.0, 133.7, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 126.0, 92.7, 75.9, 72.1, 69.3, 65.7, 64.7, 43.4, 37.9, 36.2, 32.8, 32.5, 28.1, 25.9, 24.4, 18.2; FT-IR (ATR) 1470 (m), 1461 (m), 1453 (m); HRMS analysis (EI, 250 °C, $C_{33}H_{50}O_4Si$ = 538.3480) found m/z 538.3450.

Preparation of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-(hydroxymethyl)-1-[(benzyloxy)methoxy]cyclohexane (18). To a stirred solution (rt) of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(benzyloxy)-3-pentenyl]-4-[(*tert*-butyldimethylsiloxy)methyl]-1-[(benzyloxy)methyl]cyclohexane (2.50 g, 4.74 mmol) in MeOH (50 mL) was added a catalytic amount of *p*-TsOH (1–2 mg). After 4 h (rt), the reaction mixture was concentrated and the residue partitioned between ether (150 mL)–saturated aqueous $NaHCO_3$ (100 mL). The organics were washed with brine (100 mL) and then dried ($MgSO_4$), filtered, and concentrated. The residue was passed through a plug of silica to yield 1.60 g (80%) of **18**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.35 (m, 10 H), 5.57 (m, 2 H), 4.81 (s, 2 H), 4.62 (s, 2 H), 4.49 (s, 2 H), 4.04 (d, 2 H, J = 5.0 Hz), 3.41–3.62 (m, 3 H), 1.49–2.12 (m, 6 H), 0.99–1.36 (m, 6 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.2, 137.9, 133.6, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 126.0, 92.6, 76.4, 75.6, 72.0, 69.2, 65.5, 64.6, 43.2, 37.8, 36.3, 32.8, 32.3, 27.7, 24.2; FT-IR (ATR) 3454 (br s, OH), 1496 (m), 1452 (m); HRMS analysis (FAB, rt, $C_{27}H_{37}O_4$ [M + H] = 425.2693) found m/z 425.2685.

Preparation of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-((*E*)-1,3-butadienyl)-1-[(benzyloxy)methoxy]cyclohexane (12b). To a cooled (−55 °C, internally measured), stirred solution of oxalyl chloride (0.34 mL, 3.88 mmol) and DMSO (0.55 mL, 7.77 mmol) in DCM (50 mL) was added alcohol **18** (1.50 g, 3.53 mmol) in DCM (10 mL) dropwise. The resulting clear reaction mixture was stirred for 15 min (−55 °C) at which point Et_3N (2.50 mL, 17.7 mmol) was added. The resulting milky white reaction mixture was stirred for 5 min (−55 °C) and then the cold bath removed. Upon being warmed to rt, the reaction mixture was partitioned with water (100 mL) and the aqueous layer back-extracted with DCM (75 mL). The combined organic extracts were washed with brine (3 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a plug of silica (70:30 Hex:EtOAc) and concentrated to yield 1.35 g (91%) of the crude aldehyde as a pale yellow liquid that was used without further purification.

To a stirred, cooled (−78 °C) solution of allyldiphenylphosphine oxide (0.77 g, 3.19 mmol) and HMPA (1.2 mL, 7.0 mmol) in dry THF (125 mL) was added *n*-BuLi (1.40 mL, 3.51 mmol) dropwise. A solution of crude aldehyde (1.35 g, 3.19 mmol) in THF (5 mL) was added to the resulting red solution, and the resulting reaction mixture was slowly warmed to rt (gradually turning orange). After 5 h (rt) the mixture was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The solvent was evaporated via rotovap, and the resultant orange oil was partitioned between ether (200 mL)–water (100 mL). The

organic layer was diluted with hexanes (75 mL), washed with brine (3 × 120 mL), and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60–200 mesh, 80:20 Hex:EtOAc) yielded 1.20 g (83%) of **12b** as a clear oil: HPLC analysis (SiO_2, 90:10 Hex:EtOAc at 1.5 mL/min) 4.5 min (100%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.35 (m, 10 H), 6.28 (ddd, 1 H, J = 10.2, 10.2, 16.8 Hz), 6.01 (dd, 1 H, J = 15.0, 10.3 Hz), 5.36–5.58 (m, 3 H), 5.08 (d, 1 H, J = 16.9 Hz), 4.96 (d, 1 H, J = 10.2 Hz), 4.82 (s, 2 H), 4.62 (s, 2 H), 4.48 (s, 2 H), 4.03 (d, 2 H, J = 5.1 Hz), 3.56 (m, 1 H), 0.95–2.12 (m, 12 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.7, 138.4, 138.0, 137.1, 133.6, 131.2, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 126.1, 115.1, 92.7, 75.5, 72.0, 69.3, 65.7, 46.3, 40.0, 37.7, 34.0, 32.3, 31.6, 24.4; HRMS analysis (FAB, rt, $C_{30}H_{39}O_3$ [M + H] = 447.2900) found m/z 447.2896.

Iron-Catalyzed Cyclization of 1,3-*cis*-3,4-*trans*-3-[(*Z*)-5-(Benzyloxy)-3-pentenyl]-4-((*E*)-1,3-butadienyl)-1-[(benzyloxy)methoxy]cyclohexane (12b). To a cooled (0–5 °C), stirred solution of $Fe(acac)_3$ (49.4 mg, 0.14 mmol), bpy (21.9 mg, 0.14 mmol), and **12b** (250 mg, 0.56 mmol) in dry oxygen-free benzene (12 mL) was added Et_3Al (0.24 mL, 0.46 mmol) dropwise. The resulting dark blue solution was removed from the ice bath and stirred at rt (10 h). The mixture was filtered through silica (80:20 Hex:EtOAc) and concentrated to yield the crude *Z*- and *E*-enol ethers which were immediately acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between ether (75 mL)–saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine (2 × 50 mL), and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260–400 mesh, 75:25 Hex:EtOAc) yielded 74 mg (32%) of **19b** (46% yield based on the amount of recovered starting material): HPLC analysis (silica, 90:10 Hex:EtOAc at 1.5 mL/min) 9.5 min (100%); ^1H NMR (360 MHz, $CDCl_3$) δ 5.51–5.65 (m, 1 H), 5.00 (t, 1 H, J = 10.4 Hz), 4.86 (m, 1 H), 4.80 (s, 2 H), 4.60 (s, 2 H), 3.75–3.95 (m, 4 H), 3.58 (m, 1 H), 1.92–2.08 (m, 3 H), 1.82–1.89 (m, 2 H), 1.71 (dd, 1 H, J = 10, 10 Hz), 1.60 (s, 1 H), 1.55 (d, 3 H, J = 6.8 Hz), 1.01–1.32 (m, 8 H), 0.63–0.90 (m, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.0, 133.9, 128.3, 127.8, 127.5, 125.2, 103.8, 92.5, 75.6, 69.2, 64.7, 64.4, 46.4, 46.2, 40.3, 40.2, 38.5, 38.3, 33.1, 32.9, 31.7, 29.4, 13.6; FT-IR (ATR) 1452 (m); HRMS analysis (EI, 75 °C, $C_{25}H_{36}O_4$ = 400.2615) found m/z 400.2612.

Preparation of 3-[(*Z*)-4-(Benzyloxy)-2-butenyl]tetrahydropyran-2-one. To a cooled (−78 °C), stirred solution of $(i\text{-}Pr)_2NH$ (9.0 mL, 64 mmol) and HMPA (22.3 mL, 128 mmol) in dry THF (175 mL) was added *n*-BuLi (25.6 mL, 64.0 mmol) followed by a solution of δ-valerolactone (5.40 mL, 58.2 mmol) in THF (20 mL). After 10 min (−78 °C), a solution of (*Z*)-1-(benzyloxy)-4-bromobut-2-ene[6] (14.0 g, 58.2 mmol) in THF (15 mL) was added dropwise. The reaction mixture was slowly warmed to rt where it was stirred (5 h) and then quenched by the addition of saturated aqueous NH_4Cl (ca. 1 mL). The resulting mixture was concentrated via rotovap and the residue partitioned between ether (300 mL)–water (150 mL). The organic layer was diluted with hexanes (90 mL) and washed with brine (3 × 200 mL) and then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (60–200 mesh, 70:30 Hex:EtOAc) yielded 10.9 g (72%) of 3-[(*Z*)-4-(benzyloxy)-2-butenyl]tetrahydropyran-2-one as a pale yellow liquid: GC analysis (DB-5, 100–250 °C at 5 °C/min) 23.8 min (100%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5 H), 5.53–5.78 (m, 2 H), 4.51 (s, 2 H), 4.27 (t, 2 H, J = 5.4), 4.09 (d, 2 H, J = 6.2 Hz), 2.29–2.65 (m, 3 H), 1.80–2.09 (m, 3 H), 1.40–1.60 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.7, 138.1, 129.6, 128.7, 128.2, 127.7, 127.5, 72.2, 68.3, 65.6, 39.5, 29.0, 24.1, 21.9; FT-IR (neat) 1739 (s, C=O), 1454 (m); combustion analysis ($C_{16}H_{20}O_3$: 73.82 C, 7.74 H) found 73.99 C, 7.54 H.

Preparation of 3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-hydroxytetrahydropyran (25). To a cooled (−78 °C), stirred solution of 3-[(*Z*)-4-(benzyloxy)-2-butenyl]tetrahydropyran-2-one (10.8 g, 41.7 mmol) in dry THF (250 mL) was added DIBAL-H (27.8 mL, 41.7 mmol) via syringe pump (0.74 mL/min). After the addition was complete, the reaction mixture was stirred (1 h, −78 °C) and then quenched by the addition of MeOH (2 mL, stirred 2 h, rt) and saturated aqueous potassium sodium tartrate (Rochelle salt, 300 mL). The biphasic mixture was stirred (6 h, rt) and then extracted with ether (300 mL). The organic layer was washed with brine (200 mL) and then dried ($MgSO_4$), filtered, and concentrated to yield 10.8 g (99%) of lactol **25** as a clear oil, that was used without further purification: TLC analysis (70:30 Hex:EtOAc) R_f 0.20; GC analysis (DB-5, 100–250 °C at 5 °C/min) 17.2 (3.1%), 17.9 (2.0%), 21.4 (94.8%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5 H), 5.54–5.70 (m, 2 H), 4.36–4.51 (m, 3 H), 3.87–4.12 (m, 3 H), 3.37–3.57 (m, 2 H), 1.82–2.40 (m, 3 H), 1.40–1.69 (m, 3 H), 1.10–1.29 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.2, 131.4, 130.8, 128.3, 127.8, 127.65, 127.6, 127.4, 98.8, 93.3, 72.2, 65.6, 59.7, 41.8, 40.0, 29.1, 26.8, 25.3, 24.7, 23.6; FT-IR (neat) 3384 (br s, OH), 1452 (m); combustion analysis ($C_{16}H_{22}O_3$: 73.25 C, 8.45 H) found 73.18 C, 8.16 H.

Preparation of 3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(carbethoxymethyl)tetrahydropyran (26). To a stirred (rt) solution of LiCl (2.10 g, 49.4 mmol) and triethyl phosphonoacetate (9.8 mL, 49 mmol) in acetonitrile (400 mL) was added DBU (7.4 mL, 49 mmol). To the resulting solution was added a solution of lactol **25** (10.8 g, 41.2 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at rt (2 h) and then heated (45 °C, 7 h) during which time a precipitate formed. The reaction mixture was cooled and concentrated and the resulting residue taken up in ether (400 mL). The ether solution was washed with brine (3 × 200 mL) and then dried ($MgSO_4$), filtered, and concentrated. GC analysis of the crude product (DB-5, 100–250 °C at 5 °C/min) showed components at 7.5 (27.8%, trans) and 7.7 min (72.2%, cis). Chromatography on silica (60–200 mesh, 60:40 Hex:EtOAc) yielded 6.10 g of a mixture of *cis*- and *trans*-pyrans and 2.30 g of pure *cis*-pyran **26** (combined yield = 62%). Pyran *cis*-**26**: TLC analysis (70:30 Hex:EtOAc) R_f 0.48; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5 H), 5.45–5.78 (m, 2 H), 4.51 (s, 2 H), 3.86–4.20 (m, 6 H), 3.42–3.56 (m, 1 H), 2.56 (dd, 1 H, J = 9.1, 15.1 Hz), 2.27 (dd, 1 H, J = 4.6, 15.1 Hz), 2.02–2.32 (m, 3 H), 1.57–1.78 (m, 4 H), 1.25 (dd, 3 H, J = 7.1, 7.1 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.4, 138.2, 131.8, 128.2, 127.7, 127.5, 127.4, 76.4, 72.2, 68.1, 65.7, 60.3, 37.9, 37.0, 26.4, 24.1, 21.0, 14.1; FT-IR (neat) 1736 (s, C=O), 1454 (m); combustion analysis ($C_{20}H_{28}O_4$: 72.24 C, 8.49 H) found 72.39 C, 8.92 H.

Preparation of 3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(2-hydroxyethyl)tetrahydropyran. To a stirred, cooled (0 °C) solution of **26** (3.30 g, 9.87 mmol, 2:1 cis:trans) in THF (100 mL) was added DIBAL-H (14.5 mL, 21.7 mmol). After being slowly warmed to rt (2 h), the reaction mixture was carefully quenched by the addition of MeOH (1 mL) and concentrated via rotovap. The residue was stirred (4 h) with a mixture of ether (200 mL) and saturated aqueous potassium sodium tartrate (Rochelle salt, 200 mL). The organic layer was washed with brine (200 mL) and then dried ($MgSO_4$), filtered, and concentrated to yield 2.90 g (99%) of 3-[(*Z*)-4-(benzyloxy)-2-butenyl]-2-(2-hydroxyethyl)tetrahydropyran as a clear oil that was used without further purification: GC analysis (DB-5, 200–250 °C at 5 °C/min) 7.0 (33%, trans), 7.2 (67%, cis). A portion was chromatographed on silica to yield predominantly *cis*-pyran (>12.5:1, cis:trans) which was characterized as follows: ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5 H), 5.48–5.78 (m, 2 H), 4.52 (s, 2 H), 4.10 (d, 2 H, J = 6.1 Hz), 3.92 (d, 1 H), 3.64–3.77 (m, 3 H), 3.49 (m, 1 H), 2.76 (br s, 1 H), 2.10–2.35 (m, 2 H), 1.22–1.96 (m, 7 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.2, 132.3, 128.3, 127.7, 127.5, 127.2, 80.2, 72.3, 68.1, 65.8, 61.7, 37.5, 34.5, 26.5, 24.0, 21.1; FT-IR (neat) 3393 (br m, OH), 1453 (m); HRMS analysis (EI, 100 °C, $C_{18}H_{26}O_3$ = 290.1883) found m/z 290.1881.

Preparation of the Intermediate β-Hydroxsilanes *trans*-28 and *cis*-29 via Aldehyde 27. To a cooled (−55 °C, internally measured), stirred solution of oxalyl chloride (1.50 mL, 17.8 mmol) and DMSO (2.50 mL, 35.6 mmol) in DCM (240 mL) was added a solution of 3-[(*Z*)-4-(benzyloxy)-2-butenyl]-2-(2-hydroxyethyl)tetrahydropyran (4.70 g, 16.2 mmol, 9.9:1 cis:trans) in DCM (10 mL) dropwise. The resulting clear reaction mixture was stirred for 15 min (−55 °C) at which point Et_3N (11.3 mL, 80.9 mmol) was added. After 5 min the cold bath was removed. Upon being warmed to rt, the reaction was

poured into a separatory funnel and washed with water (150 mL). The aqueous layer was back-extracted with DCM (100 mL). The combined organic extracts were washed with brine (3 × 150 mL) and then dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a plug of silica (70:30 Hex:EtOAc) and concentrated to yield 4.50 g (97%) of a mixture of isomeric aldehydes **27** that was used without further purification. GC analysis (DB-5, 200–250 °C at 5 °C/min) showed components at 6.3 (24%, *trans*-pyran) and 6.4 min (76%, *cis*-pyran).

To a cooled (0 °C), stirred solution of allyltriphenylsilane[36] (6.50 g, 21.8 mmol) in dry THF (100 mL) was added dropwise a solution of *n*-BuLi (7.80 mL, 19.5 mmol). The resulting solution was stirred (1 h, 0 °C) and then cooled (−78 °C) and titanium tetraisopropoxide (6.30 mL, 21.1 mmol) added. The resulting solution was stirred (0.5 h, −78 °C), and then a solution of aldehydes **27** (4.5 g, 15.6 mmol, 3.1:1 cis:trans) in THF (5 mL) was added dropwise. The resulting yellow solution was stirred (0.5 h, −78 °C) and then quenched by the addition of 10% aqueous HCl (1–2 mL) and the mixture brought to rt. The reaction mixture was partitioned between ether (200 mL)–saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed with brine (2 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated to a thick oil. HPLC analysis (SiO_2, 90:10 Hex:EtOAc at 1.5 mL/min) showed three components: 2.2 (31%, allyltriphenylsilane); 3.8 (41%, *trans*-pyran); and 6.0 min (28%, *cis*-pyran). Chromatography on silica (60–200 mesh, 90:10 Hex:EtOAc) yielded 5.7 g of pyran *trans*-**28** (60% overall from 3-[(*Z*)-4-(benzyloxy)-2-butenyl]-2-(2-hydroxyethyl)tetrahydropyran) and 3.8 g of pyran *cis*-**29** (40% overall) as thick viscous oils.

Characterization of *trans*-28: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58–7.63 (m, 5 H), 7.22–7.39 (m, 15 H), 6.0 (ddd, 1 H, J = 10.5, 10.5, 17.1 Hz), 5.35–5.68 (m, 2 H), 5.01 (dd, 1 H, J = 2.0, 10.3 Hz), 4.87 (dd, 1 H, J = 2.0, 17.0 Hz), 4.49 (s, 2 H), 4.19 (m, 1 H), 4.05 (d, 2 H, J = 6.4 Hz), 3.85 (m, 1 H), 3.31–3.61 (m, 3 H), 2.48 (d, 1 H, J = 10.7 Hz), 1.42–2.31 (m, 7 H), 1.14–1.21 (m, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.2, 136.5, 135.3, 134.4, 132.2, 129.1, 128.3, 127.7, 127.5, 127.3, 116.4, 81.1, 72.3, 71.5, 68.1, 65.8, 41.5, 39.0, 37.7, 26.4, 24.0; 20.9; FT-IR (ATR) 3470 (br m, OH), 1623 (m, C=C), 1485 (m), 1452 (m), 1427 (s); HRMS analysis (FAB, $C_{39}H_{44}O_3SiLi$ [M + Li] = 595.2471) found m/z 595.3216.

Characterization of *cis*-29: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58–7.63 (m, 5 H), 7.22–7.39 (m, 15 H), 6.0 (ddd, 1 H, J = 10.5, 10.5, 17.1 Hz), 5.35–5.68 (m, 2 H), 5.10 (dd, 1 H, J = 1.9, 13 Hz), 4.99 (dd, 1 H, J = 1.9, 9 Hz), 4.49 (s, 2 H), 4.27 (m, 1 H), 4.03 (d, 2 H, J = 6.4 Hz), 3.58–3.78 (m, 2 H), 3.28–3.39 (m,1 H), 2.61 (dd, 1 H, J = 3.7, 10.5 Hz), 2.02–2.18 (m, 1 H), 1.83–1.92 (m, 1 H), 1.18–1.72 (m, 6 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.3, 136.3, 135.0, 134.0, 132.3, 129.4, 128.3, 127.7, 127.5, 127.0, 117.6, 76.3, 72.2, 67.7, 67.5, 65.9, 41.2, 39.4, 37.7, 26.5, 24.4, 21.7; FT-IR (ATR) 3572 (m, OH), 3446 (br m, OH), 1624 (m, C=C); HRMS analysis (FAB, $C_{39}H_{43}O_3Si$ = 587.2983) found m/z 587.2993.

Preparation of *trans*-3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(2,4-pentadienyl)tetrahydropyran (30). To a stirred solution (rt) of **28** (2.70 g, 4.6 mmol) in THF (50 mL) was added concentrated H_2SO_4 (4 drops). The resulting solution was refluxed (65 °C, 10 h) and then cooled (rt), neutralized with $NaHCO_3$ (ca. 0.2 g), and concentrated via rotovap. The residue was partitioned between ether (200 mL)–saturated aqueous $NaHCO_3$ (80 mL) and the organic layer dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (260–400 mesh, 90:10 Hex:EtOAc) yielded 1.00 g (80%) of *trans*-**30** as a clear oil: HPLC analysis (SiO_2, 90:10 Hex:EtOAc at 1.5 mL/min) 4.2 min (100%); ^{1}H NMR (200 MHz, $CDCl_3$, shows an 80:20 *E*:*Z* mixture of dienes) δ 7.23–7.35 (m, 5 H), 6.60 (m, 0.2 H, *Z*-diene), 6.32 (ddd, 0.8 H, J = 16.9, 10.2, 10.2 Hz, *E*-diene), 6.07 (dd, 1 H, J = 10.3, 15.0 Hz), 5.78 (m, 1 H), 5.64 (m, 1 H), 5.56 (m, 1 H), 5.08 (dd, 1 H, J = 1.7, 17.2 Hz), 4.98 (dd, 1 H, J = 1.7, 10.0 Hz), 4.50 (s, 2 H), 4.04 (d, 2 H, J = 5.7 Hz), 3.93 (ddd, 1 H, J = 1.5, 2.1, 11.1 Hz), 3.31 (ddd, 1 H, J = 3.5, 11.4, 11.4 Hz), 3.08 (ddd, 1 H, J = 3.1, 6.2, 9.2 Hz), 2.45 (ddd, 1 H, J = 3.1, 6.5, 14.4), 2.20 (ddd, 1 H, J = 6.5, 7.9, 14.7 Hz), 2.10–2.15 (m, 1 H), 1.78–1.89 (m, 2 H), 1.52–1.60 (m, 2 H), 1.38–1.43 (m, 1 H), 1.11 (ddd, 1 H, J = 4.9, 12.1, 12.1); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.2, 137.1, 132.6, 132.0, 131.3, 130.5, 128.2, 127.6, 127.55, 127.5, 117.2 (*Z*-diene), 115.0 (*E*-diene), 81.2, 72.1, 68.1, 65.6, 39.7, 36.2, 29.9, 29.0, 26.2; FTIR (ATR) 3028 (m, C_{sp2}-H), 1454 (m); HRMS analysis (EI, 125 °C, $C_{21}H_{28}O_2$ = 312.209) found m/z 312.208.

Iron-Catalyzed Cyclizations of *trans*-3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(2,4-pentadienyl)tetrahydropyran (30). To a cooled (0–5 °C), stirred solution of $Fe(acac)_3$ (42.4 mg, 0.12 mmol), bpy (18.7 mg, 0.12 mmol), and *trans*-pyran **30** (250 mg, 0.80 mmol) in dry oxygen-free benzene (12 mL) was added Et_3Al (0.29 mL, 0.38 mmol) dropwise. The resulting dark blue solution was removed from the ice bath and stirred at 35 °C (6 h). The reaction mixture was filtered through silica (80:20 Hex:EtOAc) and concentrated to yield a mixture of *Z*- and *E*-enol ethers which were immediately acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between ether (75 mL)–saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated. GC analysis (DB-5, 200–250 °C at 5 °C/min) of the crude acetal mixture shows two components: 3.4 min (91%, **34**) and 3.5 min (9%, **35**). Chromatography on silica (260–400 mesh, 80:20 Hex:EtOAc) yielded a combined 100 mg of cyclized products **34** and **35** (47%, 59% yield based on the available 80% *E*-diene in the starting material).

Characterization of 34: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.43–5.56 (m, 1 H, J = 11 Hz), 5.16 (ddd, 1 H, J = 10.6, 10.6, 0.9 Hz), 4.88 (m, 1 H), 3.76–4.00 (m, 5 H), 3.43 (ddd, 1 H, J = 3, 11, 11 Hz), 2.91–3.03 (m, 1 H), 2.20 (dddd, 1 H, J = 3, 10.6, 11, 11 Hz), 1.62–1.93 (m, 5 H), 1.58 (dd, 3 H, J = 0.9, 7 Hz), 1.10–1.39 (m, 5 H), 0.84 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 134.3, 124.1, 103.8, 80.9, 68.4, 64.8, 64.5, 41.3, 40.2, 38.7, 38.2, 37.8, 37.2, 30.5, 26.7, 13.0; FT-IR (ATR) 1447 (m), 1436 (m); combustion analysis ($C_{16}H_{26}O_3$: 72.14 C, 9.84 H) found 72.11 C, 9.86 H.

Characterization of 35: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.63 (ddd, 1 H, J = 1.5, 11, 11 Hz), 5.42 (m, 1 H), 4.91 (dd, 1 H, J = 4.7, 4.7 Hz), 3.82–3.99 (m, 5 H), 3.43 (ddd, 1 H, J = 2, 11, 11 Hz), 3.08–3.12 (m, 1 H), 2.75–2.79 (m, 1 H), 1.11–1.85 (m, 15 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 133.7, 123.7, 104.2, 78.6, 68.6, 64.8, 64.7, 37.3, 36.6, 36.3, 34.1, 32.3, 32.1, 30.7, 26.9, 12.8; FT-IR (ATR) 1451 (m), 1437 (m); HRMS analysis (EI, 75 °C, $C_{16}H_{26}O_3$ = 266.1883) found m/z 266.1871.

Preparation of *cis*-3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(2,4-pentadienyl)tetrahydropyran (31). To a stirred solution (rt) of **29** (3.70 g, 6.28 mmol) in THF (50 mL) was added concentrated H_2SO_4 (four drops). The resulting solution was refluxed (10 h) and then cooled (rt), neutralized with $NaHCO_3$ (ca. 0.2 g), and concentrated. The residue was partitioned between ether (200 mL)–saturated aqueous $NaHCO_3$ (80 mL). The organic layer was washed with brine (100 mL) and then dried ($MgSO_4$), filtered, and concentrated. The residue was taken up in hexanes (ca. 20 mL) and cooled (−10 °C) overnight, during which time triphenylsilanol crystallized. The filtrate was separated and concentrated via rotovap and the residue chromatographed on silica (260–400 mesh, 90:10 Hex:EtOAc) to yield 1.20 g (96%) of *cis*-**31** as a clear oil: HPLC analysis (SiO_2, 90:10 Hex:EtOAc at 1.5 mL/min) 4.4 (71%, *E*-diene), 4.3 min (29%, *Z*-diene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5 H), 6.57 (m, 0.3 H, *Z*-isomer), 6.30 (ddd, 0.7 H, J = 16.8, 10.3, 10.3 Hz, *E*-isomer), 6.09 (dd, 1 H, J = 10.4, 14.7), 5.49–5.78 (m, 3 H), 5.09 (dd, 1 H, J = 1.7, 16.1 Hz), 4.98 (dd, 1 H, J = 1.7, 10.1 Hz), 4.52 (s, 2 H), 4.09 (d, 2 H, J = 5.4 Hz), 3.87–3.97 (m, 1 H), 3.38–3.51 (m, 2 H), 2.02–2.45 (m, 4 H), 1.22–1.81 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.3, 137.0, 132.9, 132.2, 132.2, 132.0, 131.1, 130.7, 128.3, 127.8, 127.6, 127.35, 127.3, 117.6 (*Z*-diene), 115.4 (*E*-diene), 79.8, 72.3, 68.4, 65.9, 36.6, 35.6, 26.5, 23.6, 21.3; FTIR (ATR) 2936 (m), 1453 (m); HRMS analysis (EI, 300 °C, $C_{21}H_{28}O_2$ = 312.209) found m/z 312.209.

Iron-Catalyzed Cyclization of *cis*-3-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-(2,4-pentadienyl)tetrahydropyran (31). (a) Using No Addend. To a cooled (0–5 °C), stirred solution of $Fe(acac)_3$ (33.9 mg, 0.10 mmol), bpy (15.0 mg, 0.10 mmol), and

cis-pyran **31** (200 mg, 0.64 mmol) in dry oxygen-free benzene (7 mL) was added Et_3Al (0.26 mL, 0.30 mmol) dropwise. The resulting dark blue solution was removed from the ice bath and stirred at rt (10 h). The reaction mixture was filtered through silica (80:20 Hex:EtOAc) and concentrated to yield a mixture of *Z*- and *E* -enol ethers which were immediately acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between ether (75 mL)−saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated. GC analysis (DB-5, 200−250 °C at 5 °C/min) of the crude acetal mixture shows two components: 3.3 min (69%, **36**) and 3.8 min (31%, **37**). Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) yielded 46 mg of **36** and 25 mg of **37** (52% combined yield based on the available *E*-diene in the starting material).

(b) Using Methylfuran Addend. To a cooled (0−5 °C), stirred solution of $Fe(acac)_3$ (42.4 mg, 0.12 mmol), bpy (18.7 mg, 0.12 mmol), 2-methylfuran (0.5 mL), and *cis*-pyran **31** (250 mg, 0.80 mmol) in dry oxygen-free benzene (12 mL) was added Et_3Al (0.29 mL, 0.38 mmol) dropwise. The resulting dark blue solution was removed from the ice bath and stirred at rt (6.5 h). The mixture was filtered through silica (80:20 Hex:EtOAc) and concentrated to yield a mixture of *Z*- and *E*-enol ethers which were immediately acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between ether (75 mL)−saturated aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated. GC analysis (DB-5, 200−250 °C at 5 °C/min) of the crude acetal mixture shows two components: 3.3 min (50%, **36**) and 3.8 min (50%, **37**). Chromatography on silica (260−400 mesh, 80:20 Hex:EtOAc) yielded 54 mg of **36** and 54 mg of **37** (64% combined yield based on the available *E*-diene in the starting material).

Characterization of 36: ^1H NMR (360 MHz, $CDCl_3$) δ 5.45−5.55 (m, 1 H), 5.06 (dt, 1 H, J = 1.4, 10.1 Hz), 3.82−4.08 (m, 5 H), 3.52 (s, 1 H), 3.43 (dt, 1 H, J = 2.0, 11.5 Hz), 2.36 (m, 1 H), 1.55−1.92 (m, 10 H), 1.25−1.47 (m, 5 H); ^{13}C NMR (50.3, $CDCl_3$) δ 134.8, 124.3, 103.7, 75.1, 69.1, 64.7, 64.5, 38.6, 38.3, 38.1, 35.2, 34.7, 30.9, 29.0, 21.1, 13.3; FT-IR (ATR) 2921 (s), 2917 (s), 1442 (m), 1431 (m); combustion analysis ($C_{16}H_{26}O_3$: 72.14 C, 9.84 H) found 72.08 C, 9.89 H.

Characterization of 37: ^1H NMR (360 MHz, $CDCl_3$) δ 5.45−5.55 (m, 1 H), 5.27 (t, 1 H, J = 10.6 Hz), 4.86 (t, 1 H, J = 4.5 Hz), 3.80−3.98 (m, 5 H), 3.55−3.70 (m, 2 H), 2.11−2.20 (m, 1 H), 1.65−2.09 (m, 5 H), 1.58 (d, 3 H, J = 6.9 Hz), 1.43−1.52 (m, 4 H), 1.25−1.36 (m, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 134.5, 123.7, 103.7, 73.9, 70.0, 64.7, 64.5, 39.8, 37.8, 35.6, 34.4, 32.7, 30.4, 26.1, 24.0, 13.0; FT-IR (ATR) 2927 (s), 1442 (m); HRMS analysis (EI, 75 °C, $C_{16}H_{26}O_3$ = 266.1883) found m/z 266.1880.

Iron-Catalyzed Cyclizations of 1-[(2*Z*)-4-(Benzyloxy)-2-butenyl]-5-((2*E*)-2,4-pentadienyl)pyrrolidin-2-one (40). (a) Using the 2,2′-Bipyridine-Modified Catalyst. To stirred solution of $Fe(acac)_3$ (95.3 mg, 0.27 mmol), bpy (42.2 mg, 0.27 mmol), and pyrrolidinone **40**[39] (280 mg, 0.90 mmol) in dry oxygen-free toluene (30 mL) was added Et_3Al (0.44 mL, 0.84 mmol) dropwise. The resulting dark blue solution was warmed to 55 °C and stirred (12 h). The reaction mixture was filtered through silica (EtOAc) and concentrated to yield a mixture of *Z*- and *E*-enol ethers which were acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (5 mL). The resulting solution was stirred (8 h) and then partitioned between EtOAc (50 mL)−saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (EtOAc) yielded the indolizidinone products **45** and **46** (120 mg, 50%) as a clear liquid. ^1H NMR analysis indicates a 1.3:1 **45**:**46** mixture: TLC analysis (100% EtOAc) R_f 0.09; ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (ddd, 0.4 H, J = 10.9, 9.3 Hz), 5.57−5.51 (m, 1 H), 5.08 (ddd, 0.6 H, J = 10.9, 9.7, 1.6 Hz), 4.94 (dd, 0.4 H, J = 4.4, 3.6 Hz), 4.85 (dd, 0.6 H, J = 4.8, 4.8 Hz), 4.36 (dd, 0.6 H, J = 13.3, 4.4 Hz), 3.95−3.75 (overlapping m's, 4.4 H), 3.65−3.59 (m, 0.4 H), 3.48-3.42 (m, 0.6 H), 2.98 (d, 0.4 H, J = 13.7 Hz), 2.74−2.73 (m, 0.4 H), 2.38−2.31 (overlapping m's, 2.6 H), 2.26−2.13 (overlapping m's, 1.6 H), 1.88−1.83 (overlapping m's, 1 H), 1.76 (ddd, 0.6 H, J = 13.3, 3.6 Hz), 1.62 (dd, 1.2 H, J = 6.9, 1.6 Hz), 1.59 (dd, 1.8 H, J = 6.4, 1.6 Hz), 1.60−1.48 (overlapping m's, 1.8 H), 1.43−1.30 (overlapping m's, 1.2 H), 1.04 (dddd, 0.6 H, J = 12.9, 12.1, 11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer δ 173.1, 133.0, 125.2, 103.0, 64.9, 64.5, 56.2, 44.5, 39.9, 39.2, 36.4 , 35.4, 30.4, 24.9, 13.0; minor isomer δ 174.2, 131.1, 125.1, 103.4, 64.8, 64.6, 52.3, 39.9, 35.6, 34.4, 33.5, 33.4, 30.3, 25.7, 13.1; IR (neat, ATR) 1681 (98% absorbance, C=O).

(b) Using the Bisoxazoline-Modified Catalyst. To stirred solution of $Fe(acac)_3$ (44.5 mg, 0.13 mmol), (*R*,*R*)-**48**[45] (47.1 mg, 0.13 mmol), and pyrrolidinone **40**[39] (196 mg, 0.63 mmol) in dry oxygen-free toluene (30 mL) was added Et_3Al (0.20 mL, 0.39 mmol) dropwise. The resulting dark solution was warmed to 50 °C and stirred (12 h). The reaction mixture was filtered through silica (EtOAc) and concentrated to yield a mixture of *Z*- and *E*-enol ethers which were acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (10 mL). The resulting solution was stirred (8 h) and then partitioned between EtOAc (50 mL)−saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (EtOAc) yielded the indolizidinone **45** (72 mg, 45%) as a clear liquid: TLC analysis (EtOAc) R_f 0.09; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57−5.51 (m, 1 H), 5.11 (dd 1 H, J = 11.3, 9.3 Hz), 4.88 (t, 1 H, J = 4.8 Hz), 4.39 (dd, 1 H, J = 13.3, 4.4 Hz), 3.98−3.78 (m, 4 H), 3.50−3.44 (m, 1 H), 2.42−2.34 (m, 3 H), 2.29−2.16 (m, 2 H), 1.90 (ddd, 1 H, J = 13.3, 5.2, 2.0 Hz), 1.79 (ddd, 1 H, J = 12.9, 3.6, 3.2 Hz), 1.62 (dd, 3 H, J = 6.9, 1.6 Hz), 1.59−1.52 (m, 1 H), 1.45−1.34 (m, 2 H), 1.08 (q, 1 H, J = 11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174, 133.6, 125.9, 103.6, 65.6, 65.3, 56.9, 45.2, 40.5, 39.8, 37.0, 36.0, 31.2, 25.6, 13.9; IR (neat, ATR) 1681 (100% absorbance, C=O); combustion analysis ($C_{15}H_{23}NO_3$: 67.90 C, 8.73 H) found 67.77 C, 8.98 H.

Preparation of 1-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-((*E*)-2,4-pentadienyl)pyrrolidine (49). To a solution of 1-[(2*Z*)-4-(benzyloxy)-2-butenyl]-5-((2*E*)-2,4-pentadienyl)-2-pyrrolidinone[39] (**40**, 300 mg, 0.96 mmol) in ether (20 mL) was added $LiAlH_4$ (36 mg, 0.96 mmol). The course of the reaction was followed by TLC (EtOAc). After 10 min, the reaction was quenched by the addition of $NaSO_4(H_2O)_{10}$ and Celite (0.5 g). The resulting slurry was stirred overnight and then dried (anhydrous Na_2SO_4), filtered, and concentrated. Chromatography on silica (90:10:1 Hex:EtOAc:NEt_3) yielded the labile pyrrolidine **49** (173 mg, 0.58 mmol, 60%) as a pale yellow oil that was immediately subjected to the cyclization reaction: TLC analysis (100:1 EtOAc:NEt_3) R_f 0.50 (streak); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5 H), 6.30 (ddd, 1 H, J = 16.9, 10.3, 6.7 Hz), 6.07 (dd, 1 H, J = 15.0, 10.5 Hz) 5.80−5.60 (overlapping m's, 3 H), 5.09 (d, 1 H, J = 16.5 Hz), 4.97 (d, 1 H, J = 10.3 Hz), 4.51 (s, 2 H), 4.17−4.05 (m, 2 H), 3.42 (d, 1 H, J = 12.2 Hz), 3.14−3.06 (m, 1 H), 2.92−2.83 (m, 1 H), 2.46−2.29 (overlapping m's, 2 H), 2.17−2.01 (overlapping m's, 2 H), 1.93−1.80 (m, 1 H), 1.78−1.62 (overlapping m's, 2 H), 1.55−1.47 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 132.7, 131.9, 130.6, 128.4, 128.3, 127.8, 127.6, 115.2, 72.3, 65.8, 63.8, 54.1, 50.7, 37.24, 37.17, 30.2, 21.9; HRMS analysis ($C_{20}H_{27}ON$ (M − H) = 296.2013) found m/z 296.2008.

Iron-Catalyzed Cyclization of 1-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-((*E*)-2,4-pentadienyl)pyrrolidine (49) Using the Bisoxazoline-Modified Catalyst. To stirred solution of $Fe(acac)_3$ (42.4 mg, 0.12 mmol), (*R*,*R*)-**48**[45] (43.5 mg, 0.12 mmol), and pyrrolidine **49** (173 mg, 0.58 mmol) in dry oxygen-free toluene (30 mL) was added Et_3Al (0.20 mL, 0.39 mmol) dropwise. The resulting dark solution was stirred overnight (12 h). The reaction mixture was applied to the top of a silica gel column, and chromatography on silica ((1) hexanes; (2) 90:10:1 Hex:EtOAc:NEt_3) yielded the indolizidine **50** (113 mg, 0.38 mmol, 65%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5 H), 6.30 (d, 1 H, J = 12.6 Hz), 5.46−5.36 (m, 1 H), 5.13−5.09 (m, 1 H), 4.67 (s, 2 H), 4.61 (dd, 1 H, J = 12.6, 8.3 Hz), 3.10−

3.01 (m, 2 H), 2.19–1.96 (m, 3 H), 1.92–1.70 (m, 5 H), 1.65–1.53 (m, 1 H), 1.55 (dd, 3 H, J = 5.01, 1.67 Hz), 1.43–1.30 (m, 1 H), 1.10 (ddd, 1 H, J = 10.8, 10.8, 10.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 137.2, 134.4, 128.3, 127.6, 127.3, 123.4, 106.2, 70.8, 63.5, 59.0, 53.9, 41.2, 40.2, 37.2, 30.2, 21.0, 13.1; IR (neat, ATR) 1651 (57% absorbance, ROC=C), 1670 (40% absorbance, C=CCH_3); combustion analysis ($C_{20}H_{27}NO$: 80.76 C, 9.15 H) found 80.84 C, 9.40 H.

Iron-Catalyzed Cyclization of 1-[(*Z*)-4-(Benzyloxy)-2-butenyl]-6-((2*E*)-2,4-pentadienyl)piperidin-2-one (41) Using the Bisoxazoline-Modified Catalyst. To stirred a solution of $Fe(acac)_3$ (70.6 mg, 0.20 mmol), (*R*,*R*)-**48**[45] (72.5 mg, 0.20 mmol), and piperidinone **41**[39] (332 mg, 1.02 mmol) in dry oxygen-free toluene (30 mL) was added Et_3Al (0.32 mL, 0.62 mmol) dropwise. The resulting dark solution was warmed to 55 °C and stirred (12 h). The reaction mixture was filtered through silica (EtOAc) and concentrated to yield a mixture of enol ethers which were acetalized by treatment with ethylene glycol (1 mL) and catalytic *p*-TsOH (5 mg) in dry THF (10 mL). The resulting solution was stirred (8 h) and then partitioned between EtOAc (50 mL)–saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica (EtOAc) yielded a 5:1 mixture of quinolizidinones **55** and **56** (113 mg, 40%): TLC analysis (EtOAc) R_f 0.33; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50–5.44 (m, 1 H), 5.04 (ddd, 1 H, J = 11.3, 9.3, 1.6 Hz), 4.95 (dd, 1 H, J = 13.3, 4.0 Hz), 4.87 (dd, 1 H, J = 5.2, 4.4 Hz), 3.26–3.20 (m, 1 H), 2.36–2.24 (m, 2 H), 2.22–2.16 (m, 1 H), 2.12 (dd, 1 H, J = 12.9, 12.1 Hz), 1.94–1.89 (m, 1 H), 1.78 (dd, 1 H, J = 5.6, 2.4 Hz), 1.76 (dd, 3 H, J = 5.6, 2.4 Hz), 1.74–1.72 (m, 1 H), 1.45–1.28 (overlapping m's, 3 H), 1.14 (ddd, 1 H, J =13.3, 11.7, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 132.84, 124.9, 102.8, 64.7, 64.4, 55.5, 46.2, 40.0, 39.5, 36.8, 35.2, 32.7, 29.9, 18.9, 12.9; IR (neat, ATR) 1635 (77% absorbance, C=O); combustion analysis ($C_{16}H_{25}NO_3$: 68.79 C, 9.02 H) found 68.66 C, 8.87 H.

Preparation of 1-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-((*E*)-2,4-pentadienyl)piperidine (57). To a solution of piperidinone **41**[39] (300 mg, 0.92 mmol) in ether (20 mL) was added $LiAlH_4$ (35 mg, 0.92 mmol). The course of the reaction was followed by TLC (100% EtOAc). After 10 min, the reaction was quenched by the addition of $Na_2SO_4(H_2O)_{10}$ and Celite (0.5 g). The resulting slurry was stirred overnight (12 h) and then dried (anhydrous Na_2SO_4), filtered, and concentrated. Chromatography on silica (90:10:1 Hex:EtOAc:NEt_3) yielded the labile piperidine **57** (173 mg, 0.55 mmol, 63%) as a pale yellow oil that was immediately subjected to the cyclization reaction: TLC analysis (100:1 EtOAc:NEt_3) R_f 0.33–0.44 (streaks); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 6.30 (ddd, 1 H, J = 16.9, 10.3, 6.7 Hz), 6.05 (dd, 1 H, J = 15.0, 10.5 Hz), 5.81–5.60 (m, 3 H), 5.08 (d, 1 H, J = 16.9 Hz), 4.97 (d, 1 H, J = 10.0 Hz), 4.51 (s, 2 H), 4.14–4.03 (m, 2 H), 3.43–3.36 (m, 1 H), 3.15–3.07 (m, 1 H), 2.87–2.82 (m, 1 H), 2.41–2.16 (overlapping m's, 4 H), 1.69–1.51 (overlapping m's, 4 H), 1.42–1.18 (overlapping m's, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0 (s), 136.9 (d), 132.7 (d), 131.6 (d), 129.7 (d), 128.5 (d), 128.1 (d), 127.5 (d), 127.4 (d), 114.8 (t), 72.1 (t), 65.6 (t), 59.9 (d), 52.0 (t), 50.4 (t), 34.6 (t), 30.5 (t), 25.5 (t), 23.4 (t); IR (neat, ATR) 1650 (24% absorbance, C=C), 1602 (26% absorbance, C=C).

Iron-Catalyzed Cyclization of 1-[(*Z*)-4-(Benzyloxy)-2-butenyl]-2-((*E*)-2,4-pentadienyl)piperidine (57) Using the Bisoxazoline-Modified Catalyst. To a stirred solution of $Fe(acac)_3$ (52.2 mg, 0.15 mmol), (*R*,*R*)-**48**[45] (53.6 mg, 0.15 mmol), and piperidine **57** (231 mg, 0.74 mmol) in dry oxygen-free toluene (30 mL) was added Et_3Al (0.24 mL, 0.46 mmol) dropwise. The resulting dark blue solution was stirred overnight (12 h). The reaction mixture was applied to the top of a silica gel column, and chromatography on silica ((1) hexanes; (2) 90:10:1 Hex:EtOAc:NEt_3) yielded a 6:1 mixture of the quinolizidines **58** and **59** as a pale yellow oil that rapidly turned brown on exposure to air (163 mg, 70%): TLC analysis (100:1 EtOAc:NEt_3) R_f 0.09; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5 H), 6.29 (d, 1 H, J = 12.9 Hz), 5.42–5.34 (m, 1 H), 5.07 (dd, 1 H, J =10.9, 10.9 Hz), 4.64 (s, 2 H), 4.57 (dd, 1 H, J = 12.9, 8.9 Hz), 2.81–2.78 (m, 1 H), 2.74 (dd, 1 H, J = 11.3, 4.0 Hz), 2.16–2.07 (m, 1 H), 2.05–1.99 (m, 1 H), 1.98–1.93 (m, 1 H), 1.89 (dd, 1 H, J = 11.3, 11.3 Hz), 1.75–1.69 (m, 2 H), 1.62–1.49 (m, 7 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 137.2, 134.2, 128.3, 127.6, 127.3, 123.3, 106.2, 70.9, 62.7, 61.7, 56.1, 41.2, 39.9, 39.6, 32.9, 25.7, 24.4, 13.1; IR (neat, ATR) 1670 (63% absorbance, ROC=C), 1651 (42% absorbance, C=CCH_3); combustion analysis ($C_{21}H_{29}NO$: 80.98 C, 9.39 H) found 81.12 C, 9.46 H.

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