Tetrahedron Letters, Vol. 34, No. 39, pp. 6219-6222, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Catalytic Iron-Mediated Ene Carbocyclizations of Trienes: Investigations into the Stereoselective Formation of Some Bicyclic Lactams and Amines.

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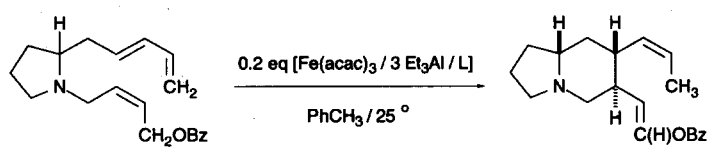
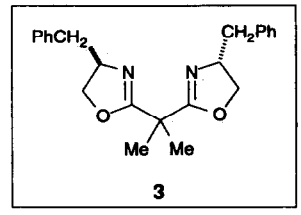
Summary: Certain bicyclic ring systems (*i.e.*, indolizidine and quinolizidine ring systems) are constructed in a stereoselective fashion using an iron-catalyzed carbocyclization. It is noteworthy that the reduced iron catalyst tolerates triene substrates containing a basic nitrogen and that the chemical efficiency and the degree of 1,3-stereoinduction are dramatically influenced by the nature of the substrate (amine versus amide) and the nature of the ligand (2,2'-bipyridine versus bisoxazoline) employed in the iron catalyst system.

Certain acyclic substrates bearing a 1,3-diene subunit and an allylic ether subunit undergo efficient, stereoselective iron-catalyzed carbocyclization to form five- and six-membered carbocycles and heterocycles.[1-5] The application of catalytic transition-metal-mediated transformations to organic synthesis constitutes an important area of current research.[6] We are interested in applying the novel iron-catalyzed bond construction to the synthesis of fused polycyclic alkaloids, but two relevant concerns are not addressed by our prior studies. First, the cyclizations we have reported involve the formation of only monocyclic ring systems from acyclic triene substrates.[7,8] Metal-alkene chelate and metallacycle structures presumably play important roles in the catalytic cycle of the iron-catalyzed carbocyclization,[1] and a priori, it is not clear whether the structural requirements of such intermediates can be accommodated in more highly constrained substrates. For example, consider a substrate in which the diene and alkene moieties are appended to a pre-existing ring, exactly the situation required for the formation of fused polycyclic ring systems. The pre-existing ring restricts the conformations accessible to the diene and alkene moieties, possibly inhibiting complexation about the iron center. A further concern relevant to alkaloid synthesis is that no substrate bearing a basic nitrogen had been previously cyclized.[3] The iron catalyst is inactivated by excess ligand,[9] so there is reason to suspect that amine-containing substrates might poison the catalyst. In spite of these concerns, the amine substrate **1** readily undergoes stereoselective iron-catalyzed cyclization. The cyclized product **2a** is obtained in 65% yield (>20:1 diastereoselectivity) as the *E*-enol ether by exposure of **1** to a catalyst system generated in situ via the reduction of iron(III) 2,4-pentanedionate ($Fe(acac)_3$) by 3.1 equivalents of triethylaluminum and modified with an equivalent of the bisoxazoline ligand **3**.



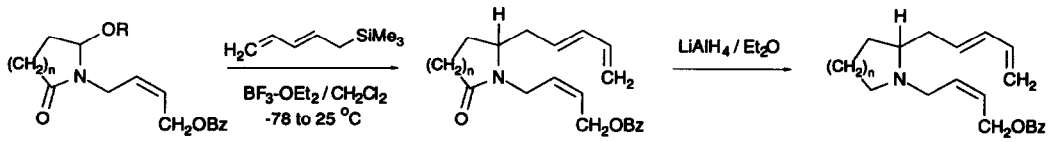
1 **2a**



3

We find that the efficacy and stereoselectivity of the iron-catalyzed cyclization to form bicyclic ring systems are dramatically influenced by the nature of the ring system to which the reacting diene and alkene moieties are appended and by the nature of the ligand coordinated to iron. Amides **6** and **7** are prepared via the addition of 1-trimethylsilyl-2,4-pentadiene[10,11] to the N-acyliminium ion[12] generated in situ by the action of BF_3-

Et_2O on **4** and **5**. Intermediates **4** and **5** are obtained via the partial reduction of the corresponding imides with $LiEt_3BH$[13,14] and used without purification. The respective imides are prepared in a straightforward manner via N-alkylation of succinimide and glutarimide with (E) 1-chloro-4-benzyloxy-2-butene.[15] The BF_3-catalyzed pentadienylsilane addition proceeds smoothly with hydroxy derivative **4** (75% overall yield from the imide), but for addition to the six-membered ring system, the partially reduced imide is best first converted to the methoxy derivative (*i.e.*, **5**, 62 % overall yield of **7** for the three steps). LAH reduction of amide **6** gives the aforementioned amine **1** (60%), and reduction of **7** affords the corresponding amine **8** (63%).

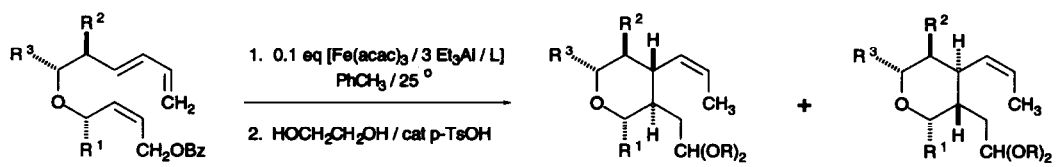


4 (n = 1, R = H)
5 (n = 2, R = Me)

6 (n = 1)
7 (n = 2)

1 (n = 1)
8 (n = 2)

Substrates **1**, **6**, **7** and **8** contain a resident stereogenic center, and as such, iron-catalyzed cyclization can potentially afford a mixture of diastereomers. Usually 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 quite high. For example, treatment of triene **9** (R^1 = Me, R^2 = R^3 = H or R^2 = Me, R^1 = R^3 = H) with a *2,2'-bipyridine-modified* reduced iron catalyst (0.1 eq [$Fe(acac)_3$ / 3 Et_3Al / bpy]) affords predominantly tetrahydropyran **10a**. The level of 1,2-stereoinduction as measured by the ratio **10a**:**10b** is greater than 30:1. In contrast, 1,3-stereoinduction in a related substrate is poor. Iron-catalyzed cyclization of **9** (R^3 = Me, R^1 = R^2 = H) affords a 1:1.3 **10a**:**10b** mixture.[2] The resident stereochemical element in the amide and amine substrates (**1**, **6**, **7** and **8**) resides in a 1,3-relationship to the newly forming bond and the choice of ligand proves crucial to the success of the cyclization.



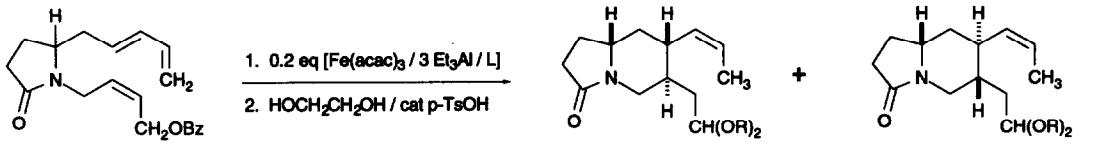
9

10a

10b

Treatment of amide **6** with the *bipyridine-modified* reduced iron catalyst (0.2 eq [$Fe(acac)_3$ / 3 Et_3Al / bpy]) under typical cyclization conditions (toluene / 50° / 12 h) affords, after acid catalyzed acetalization of the crude mixture of enol ethers with ethylene glycol, a 1.3:1 mixture of bicyclic products **11a-b** in 50% chemical yield. Within each diastereomer the relative stereochemistry between the two newly formed ring substituents is trans. This trans relative stereochemistry is consistent with previous observations for iron-catalyzed six-membered ring forming carbocyclizations of acyclic trienes (*e.g.*, the conversion of **9** to **10**). The diastereomers differ only with respect to their stereochemistry relative to the resident stereocenter,[16] and as expected from the

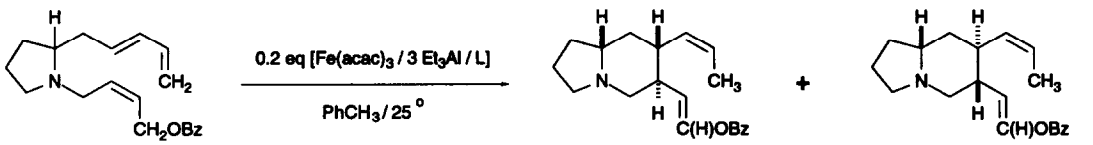
discussion above, the stereocenter residing in a 1,3-relationship to the newly forming carbon-carbon bond again fails to impose a significant stereochemical bias during cyclization.



6 **11a** (R = -CH_2-) **11b** (R = -CH_2-)

In connection with other studies, we had the bisoxazoline[17] **3** available in our labs, and examined the influence of this chiral congener of 2,2'-bipyridine[18-20] in an attempt to improve the stereoselectivity of the cyclization. Treatment of amide **6** with the *bisoxazoline-modified* iron catalyst affords cyclized product **11** in 45% yield after acetalization. ***Product 11 shows no optical rotation, indicating a racemic mixture, but the diastereomer ratio 11a:11b is greater than 20:1!*** The precise mode by which the bisoxazoline ligand exerts its influence on the stereochemistry of the cyclization is not clear, but the apparent effect is to enhance the degree of 1,3-stereoinduction from the resident stereocenter.

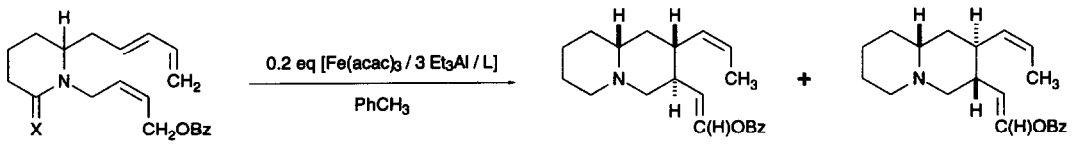
As described above, there was reason to suspect that amine substrates might poison the iron catalyst,[9] but with either the bipyridine- or bisoxazoline-modified catalyst, amine substrate **1** cyclizes more readily than amide **6** (25° versus 50° C reaction temperature). Some problems are encountered in the acetalization step however, so we isolate the labile enol ethers **2**. The bipyridine-modified iron catalyst affords cyclized product **2** in 65-70% yield as a 3:1 mixture of diastereomers **2a** and **2b**. The enol ether moieties in **2a** and **2b** are obtained as an approximate 3:2 mixture of E:Z isomers with this catalyst. Again, substituting bisoxazoline **3** for bipyridine affords a superior catalyst, giving a 65% yield of E-enol ether **2a** (>20:1 **2a**:**2b**). It is interesting to note that the bisoxazoline-modified catalyst not only exhibits higher 1,3-stereoinduction, but also affords the E-enol ether selectively, while the bipyridine-modified catalyst affords an E/Z mixture of enol ethers.



1 **2a** **2b**

The six-membered ring amine substrate **8** cyclizes with the bisoxazoline-modified catalyst in good yield (70%), under mild conditions (25° / 12 h), and with good stereoselectivity (6:1 (E)-**12a**:(E)-**12b**). Amine substrate **8** also cyclizes with the bipyridine-modified catalyst in 70% yield, however, a 3:2 mixture of diastereomers **12a** and **12b**, each as a mixture of E- and Z-enol ethers, is obtained. In contrast, amide **7** gives only a modest yield of cyclized products using the bisoxazoline-modified catalyst and does not efficiently cyclize (toluene / 50° / 12 h) using the bipyridine-modified catalyst. Apparently, the additional conformational mobility

afforded the amine relative to the amide substrate enables the former to interact with the iron catalyst whereas the latter substrate is relatively unreactive.



7 (X = O)
8 (X = H_2)

12a **12b**

The structural constraints imposed by a pre-existing ring system can markedly influence the facility of the iron-catalyzed ene carbocyclization of triene ethers. Nonetheless, we have demonstrated that certain indolizidine and quinolizidine ring systems are formed with good-to-excellent 1,3-stereoinduction and that the regioselectivity is markedly dependent on the ligand used to modify the iron catalyst. This ligand effect, if it proves to be general, should significantly extend the utility of these iron-catalyzed cyclizations. Further studies and synthetic applications of this chemistry are in progress.

Acknowledgments. Financial support of this work by the National Institutes of Health (GM34927) and the University of Nebraska Research Council is gratefully acknowledged. We thank Dr. Richard Shoemaker (UN-L) for assistance in establishing the stereochemistry in some of the structures by high field NMR spectroscopic analysis and Rajan Athalye for the preparation of **3**. The high field NMR spectrometers were purchased with funds provided by the NIH and high resolution mass spectral analyses were performed by the Midwest Center for Mass Spectrometry.

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(Received in USA 8 June 1993; accepted 30 July 1993)