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# CATALYTIC IRON-MEDIATED ENE CARBOCYCLIZATIONS OF TRIENES: THE STEREOSELECTIVE PREPARATION OF N-ACYLPIPERIDINES.

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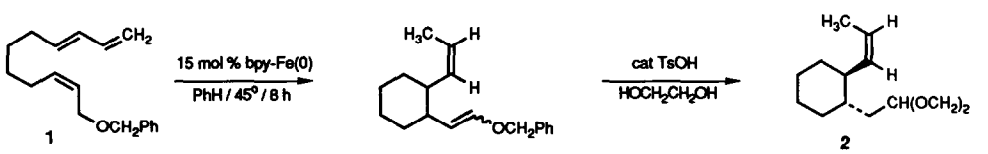
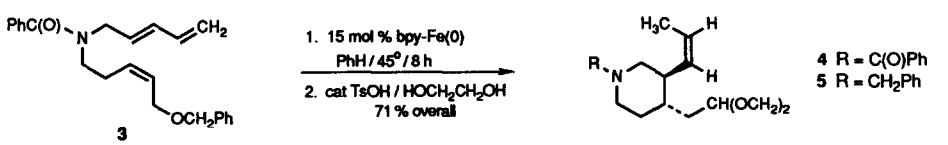
*Summary:* 5- and 6-Aza-(2Z,8E)-2,8,10-undecatriene and a 6-aza-(3Z,9E)-3,9,11-dodecatriene derivatives, substrates containing a nitrogen atom in the chain connecting the 1,3-diene and alkene functionalities, undergo efficient, stereoselective [4+4]-ene carbocyclization to yield *trans*-disubstituted N-acylpiperidines. In contrast, the corresponding (2Z,8Z)-diastereomer yields predominantly the corresponding cis isomer.

Transition-metal-mediated carbon-carbon bond construction reactions that result in the formation of a carbocyclic or heterocyclic ring are assuming an increasingly important role in the strategy of organic synthesis.[1] We have recently uncovered a facile iron-mediated cross-coupling reaction of 1,3-dienes to allylic ethers.[2] The soluble "bpy-Fe(0)$L_n$" catalyst is generated *in situ* via the reduction of iron(III) 2,4-pentanedionate by 3.1 equivalents of triethylaluminum. This novel iron-mediated carbon-carbon bond forming reaction has been applied to the construction of functionalized cyclopentyl, cyclohexyl, and tetrahydropyranyl rings from acyclic triene ether precursors.[3] For example, treatment of the 2,8,10-undecatriene ether (2Z,8E)-**1** with 10 mole percent of the iron catalyst (PhH or $PhCH_3$ / 25° / 6 h) accomplishes the efficient carbocyclization of the triene to yield a mixture of E- and Z-enol ethers, products that are formally the result of a stereoselective [4+4]-ene carbocyclization. The enol ether mixture is converted to acetal **2** by treatment of the crude reaction mixture with ethylene glycol (THF / cat *p*-TsOH / 25°) in 68% overall yield.



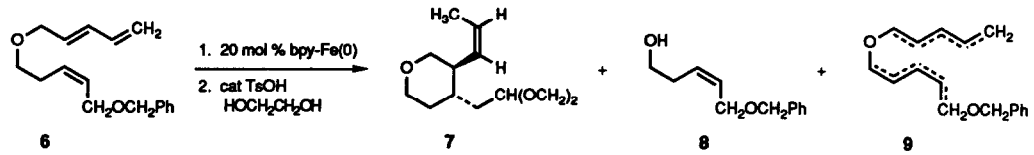

1 2

Nitrogen heterocycles are ubiquitous subunits within the ring systems of a wide variety of biologically active compounds. As part of our continuing studies on the basic characteristics of the catalytic iron-mediated ene carbocyclizations of acyclic substrates, we have investigated the applicability of the chemistry toward the preparation of certain of these ring skeletons. Treatment of the 6-aza-triene (2Z,8E)-**3**[4] with 10 mole percent iron catalyst effects efficient carbocyclization to give a crude mixture of enol ethers, which are converted to acetal **4** in an overall 71% yield. The stereochemical assignment of structure **4** is based upon an analysis of the vicinal coupling constant between the vinyl and methine hydrogens in amine **5**. The latter amine is obtained via lithium aluminum hydride reduction of amide **4**.



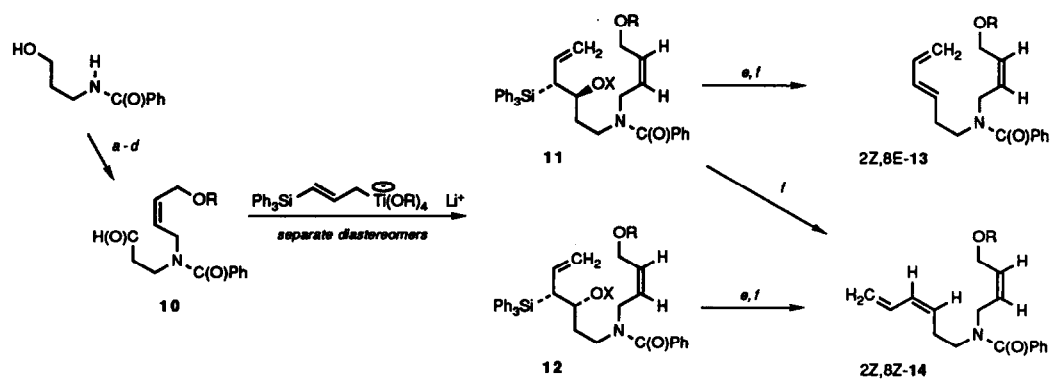

3

The efficient iron-catalyzed cyclization of **3** is in contrast to the results obtained for the reaction of the oxygen-substituted analogue **6**. While treatment of **6** with the iron catalyst also yields a single ene product after acetalization (*trans*-tetrahydropyran **7**), the chemical yield of **7** is very low (33%).[5] Accompanying **7** is the monobenzyl-protected 2-pentene-1,5-diol **8** (20%) and an inseparable mixture of di- and trienes **9** (35%). The latter compounds are apparently formed by iron-catalyzed isomerization and/or reduction of the starting triene **6**. The pentenediol derivative **8** is present in the crude reaction mixture prior to treatment with ethylene glycol/*p*-TsOH. This suggests that **8** is formed via direct cleavage of the C-O bond by the iron complex, rather than the alternative pathway via isomerization of the 1,3-diene moiety to the enol ether and liberation of **8** as a consequence of acetalization. The piperidine precursor **3** is apparently not susceptible to the analogous C-N bond cleavage.

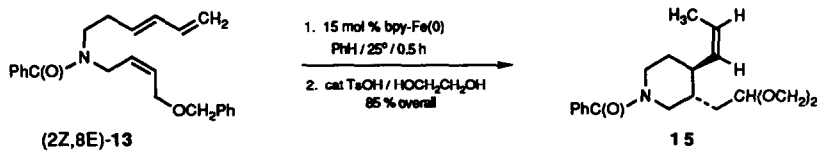



The regioisomeric 5-aza-triene ether (2Z,8E)-**13** can be prepared from (3E) 1-amino-3,5-hexadiene[6] via acylation with benzoyl chloride and dienylation of the resulting secondary amide with (2Z) 1-bromo-4-(benzyloxy)-2-butene. Alternatively, **13** is obtained in a straightforward manner from 3-amino-1-propanol via the sequence outlined in Scheme I. Condensation of aldehyde **10** with the titanium(IV) isopropoxide-modified anion of allyltriphenylsilane[7] gives a 4:1 *anti*:*syn* mixture of β-hydroxysilanes **11a** (X = H) and **12a** (X = H). The diastereomers are easily separated by flash chromatography on silica. Acid catalyzed elimination (cat $H_2SO_4$ / THF / reflux) of **11a** (X = H) proves to be inefficient. A mixture of the trienes (2Z,8E)-**13** and (2Z,8Z)-**14** is obtained. Consequently, β-hydroxysilane **11a** (X = H) is converted to the corresponding β-acetoxysilane **11b** (X = Ac). This latter derivative undergoes clean *anti*-elimination[8] upon treatment with tetrabutylammonium fluoride (TBAF) to give (2Z,8E)-**13**. The iron-catalyzed carbocyclization of **13** is extraordinarily facile. After acetalization, a single [4+4]-ene product **15** is obtained in overall 85% yield.

Scheme I. The preparation of trienes (2Z,8E)-**13** and (2Z,8Z)-**14**.

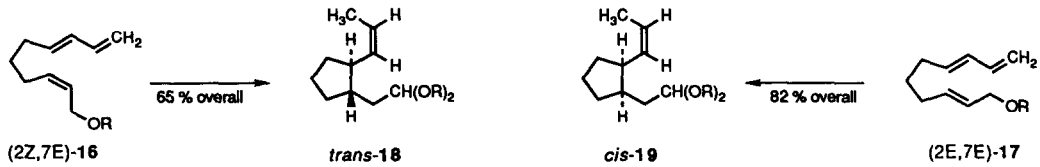



a) DHP / $H^+$ / $CH_2Cl_2$; b) 1. *n*-BuLi / THF / 0°, 2. (2Z) 1-bromo-4-benzyloxy-2-butene / 0 -> 25°; c) $CH_3OH$ / $H^+$; d) DMSO / $(COCl)_2$ / $Et_3N$ / $CH_2Cl_2$ / -78°; e) $Ac_2O$ / pyridine / 25°; f) TBAF / THF / 0°.



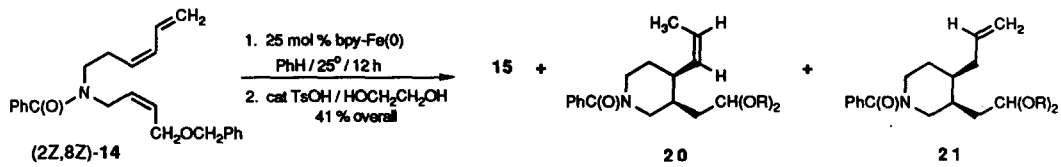

In the study of iron-catalyzed ene carbocyclizations of 2,7,9-decatriene ethers leading to substituted cyclopentanes, it was found that the E/Z-geometry of the $\Delta_{2,3}$-double bond offers a means to control the *cis*/*trans*-disposition of vicinal substituents (simple diastereoselection[9]) in the cyclopentane product. The (2Z,7E)-**16** gives rise to the *trans*-disubstituted cyclopentane **18**, while the (2E,7E)-**17** gives rise to the *cis*-disubstituted **19**. This unusual element of stereocontrol apparently arises from facial discrimination in complexation of the $\Delta_{2,3}$-double bond in the formation of an intermediate iron-triene complex.[3b] Stereospecific *syn*-oxidative cyclization of the iron-triene complex then sets the *cis*- or *trans*-relative stereochemistry observed in the final carbocycle.

Scheme II. The influence of $\Delta_{2,3}$-double bond geometry in directing simple diastereoselection the 5-membered ring ene carbocyclizations of decatriene ethers (2Z,7E)-**16** and (2E,7E)-**17**.



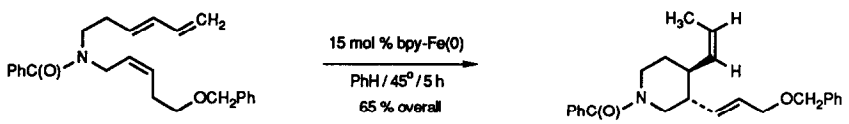

On mechanistic grounds, it seems reasonable that changing the diene geometry from E to Z should similarly have the effect of reversing the sense of simple diastereoselection observed in the cyclized product. We prepared several substrates containing Z-diene subunits in seeking an experimental confirmation of this hypothesis. In each case however, it was found that iron-catalyzed Z-to-E diene isomerization is faster than the ene carbocyclization process, and only *trans*-disubstituted carbocyclization products are isolated. Given that formation of N-acylpiperidine **15** is extremely facile, we decided to try a Z-diene substrate once again. Acylation of the minor β-hydroxysilane **12a** (X = H) with acetic anhydride in pyridine, followed by TBAF promoted *anti*-elimination of the resulting β-acetoxysilane **12b** (X = Ac) gives the desired (2Z,8Z)-triene **14**. Alternatively, (2Z,8Z)-**14** can be prepared from the major β-hydroxysilane **11a** (X = H) by potassium hydride promoted *syn*-elimination. TBAF (THF / 25° / 3 h / 80%) also cleanly effects the desired *syn*-elimination of **11a** (X = H).

Treatment of (2Z,8Z)-**14** with 25 mole percent of the iron catalyst results in the slow consumption of starting material. Triene isomerization and/or reduction products account for about half of the reaction products. In addition, a mixture of three isomeric cyclization products is isolated in 41% yield. A small amount of the *trans*-disubstituted piperidine **15** is formed accompanied by a 2:1 mixture of two *cis*-disubstituted piperidines, **20** and **21**. (The mixture of internal and terminal double bond regioisomers obtained from this cyclization is consistent



with other observations.[2,3a] While this cyclization is not synthetically useful, it is gratifying that the anticipated influence of the diene geometry as a stereochemical control element is revealed in this substrate.

All of the successful triene ether cyclizations that have been reported to date employ substrates carrying an allylic oxygen substituent.[10] Their ene carbocyclization generates a latent aldehyde in the product, functionality that is particularly useful for subsequent chemical elaboration. We now find that the iron-catalyzed ene carbocyclization is not restricted to substrates containing the allylic ether subunit. Triene **22**, the one carbon homologue of allylic ether **13**, cyclizes smoothly to compound **23**, an N-acylpiperidine containing an allylic ether subunit in place of the enol ether generated by the cyclization of **13**. The newly formed allylic ether in **23** is formed as a single double bond stereoisomer. This high *trans*-stereoselectivity is surprising in light of the observation that in carbocyclizations leading to the formation of an enol ether (e.g. **1**, **3**, **6**, and **13**), a 3:2 E:Z mixture of enol ethers is invariably obtained.




(3Z,9E)-**22** **23**

The catalytic iron-mediated triene carbocyclization reaction is proving to be a useful methodology for the stereoselective construction of five- and six-membered ring carbocycles and six-membered ring oxygen and nitrogen heterocycles. The *cis/trans*-sense of simple diastereoselectivity derives in part from the E/Z-diene and E/Z-alkene geometries. The cyclization methodology is apparently not restricted to substrates containing allylic oxygen functionality, but may be quite general with respect to the triene substrate. Further studies are in progress.

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**References and Notes.**

[1] For a few recent examples of other catalytic metal-mediated carbocyclizations methodologies under development see: a) Takacs, J.M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117-20; b) Wender, P.A.; Jenkins, T.E. *J. Am. Chem. Soc.* **1989**, *111*, 6432-4; c) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454-6; d) Trost, B. M.; Lee, D.C. *J. Org. Chem.* **1989**, *54*, 2271-4; e) Negishi, E.; Iyer, S.; Rousset, C.J. *Tetrahedron Lett.* **1989**, *30*, 291-4; f) Bapuji, S.A.; Motherwell, W.B.; Shipman; *Tetrahedron Lett.* **1989**, *30*, 7107-10; g) Larock, R.C.; Stinn, D.E. *Tetrahedron Lett.* **1989**, *30*, 2767-70; h) Taura, Y.; Tanaka, M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1989**, *30*, 6349-52.

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[4] Triene (2Z,8E)-**3** is prepared from (Z) 1-(benzyloxy)-2-penten-5-ol via the sequence: 1. phthalimide / $EtO_2CN{=}NCO_2Et$ / $Ph_3P$; 2. $NH_2NH_2$-$H_2O$ / EtOH / reflux; 3. PhC(O)Cl / pyridine; 4 a) 1.1 eq LDA / THF / 4 eq HMPA, b) 1.1 eq (E) 1-chloro-2,4-pentadiene (RN 28070-18-0).

[5] The iron-catalyzed cyclizations leading to other regioisomeric tetrahydropyrans proceed in high yield and are uncontaminated by C-O bond reductive cleavage products. See reference 3a.

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[9] Heathcock, C.H. in "Asymmetric Synthesis," J.D. Morrison, Ed., Academic Press, New York, 1983, Vol. 3.

[10] Professor A.J. Pearson (Case Western Reserve) has recently reported studies on a related ene carbocyclization using stoichiometric tricarbonyliron-diene complexes in substrates lacking an alkene-functionalized alkene. See: Pearson, A.J.; Zettler, M.W. *J. Am. Chem. Soc.* **1989**, *111*, 3908-18.

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