

A stereospecific intramolecular $[4\pi+4\pi]$ cycloaddition reaction between tricarbonyliron-complexed cyclohexadiene and pendant dienes

Anthony J. Pearson* and Xiaolong Wang

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA

Received 2 May 2005; accepted 4 May 2005

Available online 31 May 2005

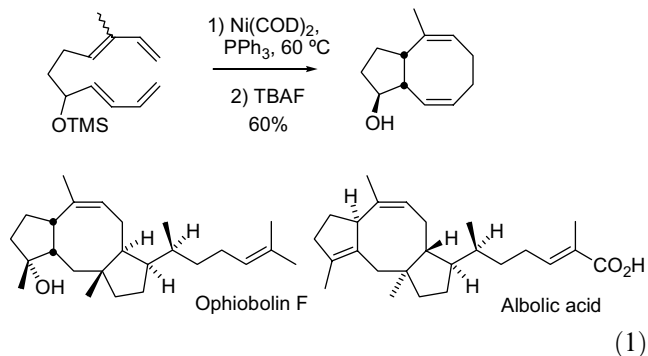
Abstract—Stereospecific intramolecular coupling of a cyclohexadiene– $\text{Fe}(\text{CO})_3$ complex with pendant dienes, to form cyclooctadienes, is described.

© 2005 Elsevier Ltd. All rights reserved.

Transition metal promoted (or catalyzed) cyclocoupling reactions of alkenes and alkynes have a rich history, and occupy an important place in organic synthesis methodology. These processes often complement their more traditional organic counterparts in terms of stereochemistry and our ability to carry out reactions that are symmetry forbidden or those that are compromised by more facile competing processes. While such transformations in the coordination sphere of a metal are often not concerted single-step processes, they are nevertheless usually stereospecific, a result of continual attachment to the metal of the reacting ligands as the key bond-forming steps proceed. A number of recent studies have focused on transition metal promoted higher order cycloaddition reactions.¹ For example, Rigby has developed methods for achieving $[6\pi+4\pi]$, as well as $[6\pi+2\pi]$ cycloadditions that utilize triene-chromium tricarbonyl complexes as the reactive 6π component.² An interesting variation that delivers ring systems with much higher levels of complexity are the multicomponent processes in which alkynes are coupled with the triene-chromium system, a reaction that has been used as a key step in a synthesis of 9-*epi*-pentalenic acid.³

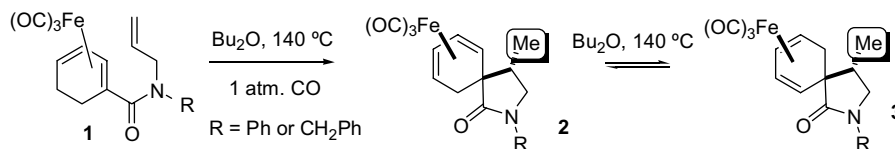
Dimerization of butadiene, catalyzed by $\text{Ni}(\text{COD})_2$, to afford 1,5-cyclooctadiene (96% yield) is one of the earliest examples of transition metals being used to effect symmetry forbidden pericyclic reactions, in this case a

$[4\pi+4\pi]$ cycloaddition (of course, *not* a concerted process).⁴ Wender has used an intramolecular variant of this reaction (Eq. 1) to afford dicyclopenta[*a,d*]cyclooctene 5-8-5 ring systems that are found in natural product structures such as ophiobolins C and F, as well as alibolic acid and ceroplastol II.⁵ In this letter, we describe a related $[4+4]$ coupling reaction that occurs using a pre-formed cyclohexadiene– $\text{Fe}(\text{CO})_3$ system as one of the 4π components.



Several years ago, we reported an intramolecular cyclocoupling reaction between a cyclohexadiene– $\text{Fe}(\text{CO})_3$ complex and a pendant alkene, which produces spirocyclic molecules.⁶ One example is shown in Scheme 1. The overall conversion corresponds to a $[6+2]$ ene reaction.⁷ While the process has been shown to be stereospecific,⁷ a subsequent rapid rearrangement of the initial product **2**, under the reaction conditions, leads to the isolation of a mixture of epimeric complexes **2** and **3**.

* Corresponding author. Tel.: +1 216 3685920; fax: +1 216 3683006; e-mail: ajp4@po.cwru.edu



Scheme 1.

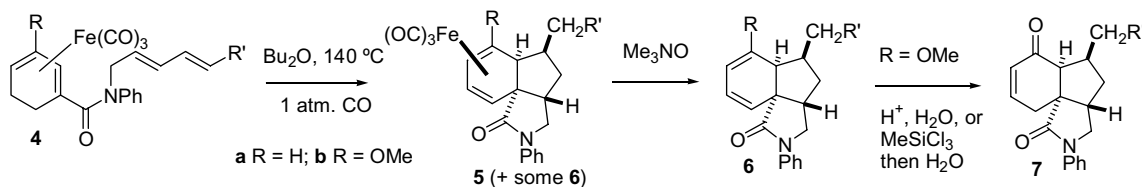
More recently, we showed that if a pendant 1,3-diene is used, the methyl group that is produced on **2** (circled on the structure) is now an allyl which can undergo a second [6+2] ene-type reaction to afford tricyclic structures.⁸ Moreover, because of the stereochemical requirements for the reaction, only the isomer related to **2** can undergo a second coupling, and the equilibrium between **2** and **3** promotes the formation of a single stereoisomer in high yield (Scheme 2). Removal of the metal using standard procedures, followed by hydrolysis of the dienol ether (for R = OMe), leads to the formation of tricyclic organic structures.

We present here a variation on this cyclocoupling reaction in which an overall (stereospecific) [4+4] cycloaddition between two dienes occurs to generate a cyclooctadiene derivative. This discovery was made when we attempted a tandem double [6+2] ene sequence on substrate **4a**, but using trimethylamine-N-oxide as the promoter of the reaction. In our early work,⁶ we had shown that this reagent could be used to effect the ene cyclocoupling between a diene-Fe(CO)₃ system and a pendant *mono* alkene, but we had not studied the procedure in any detail. However, it offers the possibility of conducting the reaction at lower temperature, and might provide an approach for improving yields for the conversion when thermally sensitive iron complexes are used. Trimethylamine-N-oxide can be used to liberate one CO ligand from a variety of metal carbonyls, a reaction that requires 2 equiv of the amine

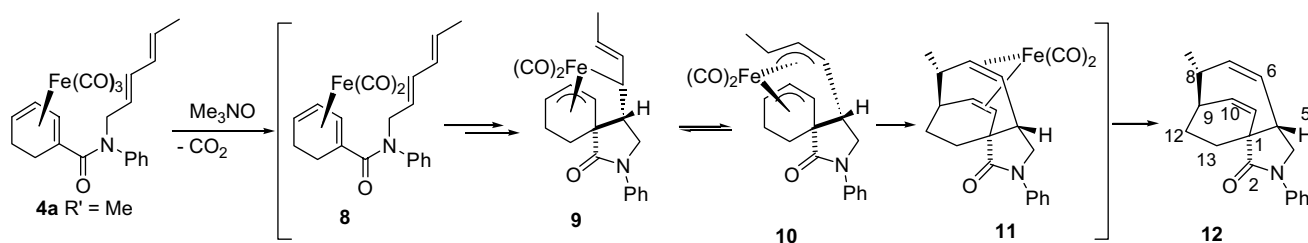
oxide.⁹ In view of the fact that our ene-type reaction requires loss of a CO ligand for its initiation, we considered the use of an amine oxide to be an alternative to thermal or photoinduced dissociation.

Treatment of substrate **4a** (R' = Me) with 2.2 equiv of Me₃NO, added in four portions over 12 h in acetonitrile at room temperature, afforded a *quantitative* yield of **12** as a *single stereoisomer*. This reaction is exceptionally clean; filtration of the reaction mixture followed by evaporation to dryness affords essentially pure **12**, with no detectable byproducts. The structure of **12** was established by NMR COSY (H9 ↔ H12 correlation), HMBC (C9 ↔ H12 correlation), and NOESY (H5 ↔ H13; H8 ↔ H12; H10 ↔ CH₃ correlations), which distinguish it from possible [4+2] cycloadducts that might result after demetallation of **4a**.¹⁰

A plausible mechanism is outlined in Scheme 3 that accounts for this conversion and its stereochemical outcome. At this stage only a tentative explanation can be offered for the divergent reaction pathways of Schemes 2 and 3, apparently depending on temperature. For a second ene cyclization to occur, complex **9**, an intermediate that is common to both the tandem double ene reaction of Scheme 2 and the [4+4] cyclocoupling shown in Scheme 3, must undergo a hydrogen transfer from the η³-cyclohexenyl ligand to the metal. This appears to be a higher energy process than the alternate conversion **9** → **10**, which at room temperature proceeds forward

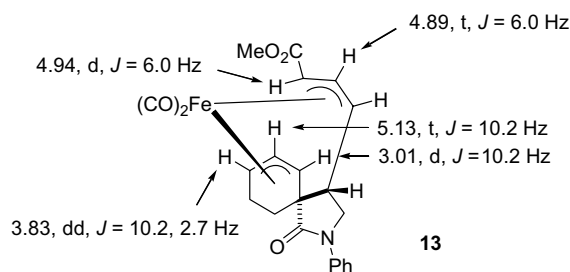


Scheme 2.



Scheme 3.

to 16e intermediate **11** that is in turn demetallated to afford **12**. At higher temperature, the reversibility of $9 \rightarrow 10$ allows eventual hydrogen shift on **9**, followed by irreversible reductive elimination to generate the ene product **5**.



This mechanism is supported by our observations on the same reaction using complex **4a** ($R' = \text{CO}_2\text{Me}$). At room temperature, essentially no cyclocoupling reaction occurred when this complex was treated with Me_3NO . When the reaction was carried out at 50°C , a complex mixture of products was obtained, from which the bis(π -allyl) complex **13** (analogous to intermediate **10**) was isolated in ca. 5% yield (diagnostic NMR data is included on the structure). The electron withdrawing ester substituent clearly has an effect on this cyclocoupling, and it is likely that the greater stability of **13** versus **10** is a result of the known stabilizing effects of electron-withdrawing groups on olefin–iron complexes.¹¹

Conclusions: Cyclohexadiene iron tricarbonyl complexes can be induced to undergo cyclocoupling with appended dienes to afford cyclooctadiene structures, an equivalent of a [4+4] cycloaddition reaction. To the best of our knowledge, this is the first example of such a reaction using cyclohexadienes, which adds a level of molecular complexity to the overall process that might be useful in constructing highly substituted cyclooctane derivatives. Future work will address the full scope of this reaction, as well as its potential applications in organic synthesis.

Acknowledgements

We are grateful to the National Science Foundation for financial support of this research.

References and notes

- Reviews: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92; Ojima, I.; Tzamariudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662; Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523–596; Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129–255; Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 477–501; Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25–31.
- Review: Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521–4538; Rigby, J. H.; Mann, L. W.; Myers, B. J. *Tetrahedron Lett.* **2001**, *42*, 8773–8775.
- Rigby, J. H.; Laxmisha, M. S.; Hudson, A. R.; Heap, C. H.; Heeg, M. J. *J. Org. Chem.* **2004**, *69*, 6751–6760.
- Jolly, P. W.; Wilke, G. In *The Organic Chemistry of Nickel*; Wiley: NY, 1975; Vol. 2, pp 213–245.
- Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrinho, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908–4909.
- Pearson, A. J.; Zettler, M.; Pinkerton, A. A. *J. Chem. Soc., Chem. Commun.* **1987**, 264–266; Pearson, A. J.; Zettler, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 3908–3918.
- Pearson, A. J.; Zettler, M. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1243–1245; Pearson, A. J.; Bennouna-Dorange, I. *J. Org. Chem.* **2001**, *66*, 3140–3145.
- Pearson, A. J.; Wang, X. *J. Am. Chem. Soc.* **2003**, *125*, 638–639.
- Shvo, Y.; Hazum, E. *Chem. Commun.* **1975**, 829–830; Birch, A. J.; Kelly, L. F. *J. Organomet. Chem.* **1985**, *286*, C5–C7; Howell, J. A. S.; Squibb, A. D.; Goldschmidt, Z.; Gottlieb, H. E.; Almadhoun, A.; Goldberg, I. *Organometallics* **1990**, *9*, 80–91.
- The procedure for this reaction, as well as spectroscopic data for **12** are as follows: To amide **4a**, $R' = \text{Me}$ (10 mg, 0.04 mmol), in 0.5 mL CH_3CN was added 3.5 mg (0.088 mmol) of Me_3NO in four portions every 3 h over 12 h at rt. The reaction mixture was then filtered through Celite and concentrated under vacuum to give 6.7 mg (100% yield) of the title compound **12** as white solid. Mp $85\text{--}87^\circ\text{C}$. $R_f = 0.38$ (1:4/EtOAc:hexanes). IR (cm^{-1} , neat): 1696, 1597. ^1H NMR (600 MHz, CDCl_3) δ : 7.70–7.10 (5H, Ph), 6.06 (dd, $J = 9.0, 6.0$ Hz, 1H, H10), 6.00 (d, $J = 9.0$ Hz, 1H, H11), 5.23 (dt, $J = 13.8, 2.4$ Hz, 1H, H6), 5.17 (dd, $J = 13.8, 1.8$ Hz, 1H, H7), 3.81 (t, $J = 8.8$ Hz, 1H, H4), 3.50 (dd, $J = 11.2, 9.2$ Hz, 1H, H4'), 3.11 (m, 1H, H5), 2.64 (m, 1H, H8), 2.55 (ddd, $J = 13.6, 6.0, 3.0$ Hz, 1H, H9), 2.18 (m, 1H, H12), 2.07 (m, 1H, H13'), 1.76–1.67 (2H, H12', H13'), 1.10 (d, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (50 MHz, CDCl_3) δ : 177.5, 139.4 (Ph-quaternary C), 132.9 (C6), 131.7 (C10), 130.0 (C11), 128.9 (Ph-m), 124.5 (Ph-p), 123.1 (C7), 119.8 (Ph-o), 52.2 (C4), 50.9 (C1), 46.7 (C5), 45.8 (C8), 35.9 (C9), 32.9 (C13), 23.9 (C12), 21.9 (Me). HRMS (m/z) for MH^+ ($\text{C}_{19}\text{H}_{22}\text{NO}$): calc: 280.1701; found: 280.1708.
- Weiss, E.; Stark, J. A.; Lancaster, J. E.; Murdoch, H. D. *Helv. Chim. Acta* **1963**, *46*, 288–297.