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# Nickel-Catalyzed Intramolecular [4 + 4] Cycloadditions: A New Method for the Synthesis of Polycycles Containing Eight-Membered Rings

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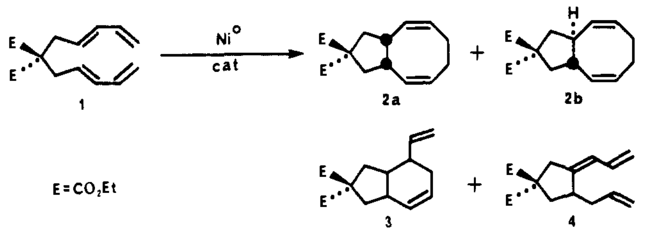
The nickel(0)-catalyzed oligomerization of 1,3-dienes holds a prominent place in the history and practice of organometallic chemistry as one of the first and most extensively studied transition-metal-catalyzed, C–C bond-forming reactions.[1] In the case of buta-1,3-diene, this process selectively affords four-, six-, eight-, or twelve-membered rings, depending on catalyst ligands and reaction conditions.[1a] Notwithstanding its enormous synthetic potential, this chemistry has not been applied to complex molecule synthesis, due in part to the low regio- and/or stereoselectivity observed in the reactions of unsymmetrical dienes,[2] the inefficiency of crossed oligomerizations,[1] and the general observation that substituted dienes are far less reactive than butadiene.[1] We now report a solution to these problems in the form of the first intramolecular nickel(0)-catalyzed cycloaddition and the initial study of stereoinduction in this reaction class. This investigation provides the basis for an efficient and direct [4 + 4] cycloaddition[3] approach to cyclooctane-containing polycycles which are generally accessible only through multistep sequences based on fragmentation and expansion reactions.[4]

Illustrative of the efficacy of this method for complex polycycle synthesis, tetraene **1**,[5] quantitatively prepared from diethyl malonate and bromopentadiene, when treated in toluene at 60 °C with 11 mol % Ni(COD)$_2$ and 33 mol % Ph$_3$P, gave cyclooctadienes **2a** and **2b**[6] (19:1, respectively) in 70% yield. The products of six-membered ring formation (**3**) and of $\beta$-hydride elimination (**4**) were also obtained in 2.6% and 12% yields, respectively. Variations in the nickel–phosphine ratio and in the ligand structure resulted in lower yields of cyclooctadiene products and preferential formation of **3** and **4**. For example, reactions conducted with Ni(COD)$_2$ and tri-*o*-tolyl phosphite (1:3, respectively) produced cyclohexenes **3** as the main products (37% yield) while the use of Ni(COD)$_2$ and tri-*o*-biphenyl phosphite (1:2, respectively) gave predominantly cyclopentanes **4** (53% yield). In all cases studied, the *cis*-cyclooctadiene **2a**, the product of a formal endo addition, was favored over the trans isomer **2b** by a factor of at least 3 to as much as 40.



The previously unexplored issue of stereoinduction in nickel-catalyzed diene oligomerizations and the effect of ring size variations on the intramolecular reactions were investigated next with tetraene **5**, readily prepared in 65% yield by alkylation of the dianion of sorbic acid[7] with 1-bromohepta-4,6-diene[8] and diazomethane esterification of the resultant product. When tetraene **5** was submitted to Ni(COD)$_2$/Ph$_3$P (1:2, respectively), cyclooctadiene **6** was produced in high yield (84%).[9] The stereoinduction in this reaction was determined by capillary GC analysis to be 99:1,[10] while the exo/endo selectivity was estimated as >95:5, favoring now the trans-fused isomer in contrast to the results obtained with **1**. The stereochemistry of **6** was unambiguously established by conversion of **6** to diol **7** which was independently prepared by a stereochemically defined sequence (Scheme I).[11]

As a further probe of stereoinduction and exo/endo selectivity, tetraene **8**, prepared from 4,6-heptadienal and pentadienyllithium,[12] was submitted to reaction with Ni(COD)$_2$/Ph$_3$P (1:2) catalyst. Cyclization again proceeded smoothly and efficiently to give only trans-fused products **9a** and **9b** (92% yield) in a ratio of 1:1.7, respectively. The epimeric relationship between these products was established by their independent conversion to a single ketone **9c**[13] while their relative stereochemistry was determined by conversion of **9b** to **10**, which was independently

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(1) For reviews and lead references, see: (a) Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, pp 613–797. (b) Keim, W.; Behr, A.; Roper, M. *Ibid.* pp 371–461. (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, 1975; Vol. 2. (d) Heimbach, P.; Jolly, P. W.; Wilke, G. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic: New York, 1970; Vol. 8, p 29.

(2) (a) Suga, K.; Watanabe, S.; Fujita, T.; Shimada, T. *J. Appl. Chem. Biotechnol.* **1973**, *23*, 131. (b) Heimbach, P.; Hey, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 528. For recent exceptions, see: Tenaglia, A.; Brun, P.; Waegell, B. *J. Organomet. Chem.* **1985**, *285*, 343 and Buch, H. M.; Schroth, G.; Mynott, R.; Binger, P. *J. Organomet. Chem.* **1983**, *247*, C63.

(3) The overall process, while formally a cycloaddition reaction, proceeds mechanistically through a series of intermediates. For further information on this point, see ref 1 and: Stephenson, L. M.; Graham, C. R. *J. Am. Chem. Soc.* **1977**, *99*, 7098.

(4) For representative, recent methods for eight-membered ring synthesis and lead references, see: (a) Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26*, 3665. (b) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541. (c) Disanayaka, B. W.; Weedon, A. C. *J. Chem. Soc., Chem. Commun.* **1985**, 1282. (d) Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323. (e) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201. (f) Paquette, L. A.; Ham, W. H.; Dime, D. S. *Tetrahedron Lett.* **1985**, *26*, 4983. (g) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869. (h) Grayson, D. H.; Wilson, J. R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1695. (i) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731. (j) Mehta, G.; Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1984**, 1058. (k) Pattenden, G.; Teague, S. J. *Tetrahedron Lett.* **1984**, *25*, 3021. (l) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (m) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190.

(5) Satisfactory NMR, IR, and low-resolution mass spectra and combustion analyses were obtained for all new compounds.

(6) Stereochemical assignments were based on $^1$H and $^{13}$C NMR analysis: **2a** exhibited two distinct ethyl esters by $^1$H NMR spectroscopy and two distinct carbonyls by $^{13}$C NMR spectroscopy, consistent with its $C_s$ symmetry; **2b** exhibited only one ethyl ester by $^1$H NMR spectroscopy (at 50 °C) and one carbonyl by $^{13}$C NMR spectroscopy, consistent with its $C_2$ symmetry.

(7) Ballester, P.; Costa, A.; Garcia-Raso, A.; Gomez-Solivellas, A.; Mestres, R. *Tetrahedron Lett.* **1985**, *26*, 3625.

(8) Prepared from hepta-4,6-dien-1-ol in 65% yield by the procedure of: Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.

(9) Ni(COD)$_2$ is a commercially available air-sensitive complex requiring some care in handling. The yellow crystalline material was used as purchased without further purification. It was transferred in a glovebag under N$_2$ or in Schlenk-type glassware. Preparation of a stock solution of Ni(COD)$_2$ approximately 0.1 M in toluene proved convenient for small-scale reactions. This yellow solution could be stored for at least 2 months in a freezer with only slight deposition of a black precipitate. In a typical preparative experiment, **5** (285 mg, 1.3 mmol) was dissolved in 1.5 mL of oxygen-free toluene inside a Schlenk-type flask with N$_2$ atmosphere. Ph$_3$P (0.13 mmol) and Ni(COD)$_2$ (0.065 mmol), from oxygen free stock solutions in toluene, were added, and the resulting red solution was warmed in a 60 °C bath for 19 h, then cooled to room temperature, allowed to air oxidize for 1 h, filtered through silica gel with Et$_2$O eluant, and concentrated in vacuo. Flash chromatography (40:1 hexanes/EtOAc) provided **6** contaminated with ca. 10% isomeric material. Chromatography on AgNO$_3$-impregnated silica gel gave analytically pure **6**.

(10) An authentic sample of the ester epimer of **6** was prepared by deprotonation of **6** (LDA, THF, room temperature, 2 h) followed by kinetic quenching with MeOH.

(11) Ester i (Brighty, K. E. Ph.D. Dissertation, Harvard University, 1985) was hydrogenated (H$_2$, 5% Pd/C, EtOH, 81%) and the resultant product reduced with LAH/THF (96%) to provide a sample of **7** identical with that derived from **6**.

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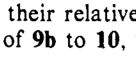

(12) Addition of pentadienyllithium (Oppolzer, W.; Burford, S. C.; Marraza, F. *Helv. Chim. Acta* **1980**, *63*, 555) to hepta-4,6-dienal (Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1982**, *47*, 337) followed by [1,3]-sigmatropic rearrangement of the crude mixture of regioisomers (Wilson, S. R.; Mao, D. T. *Tetrahedron Lett.* **1977**, 2559) and silylation provided **8** (29% overall yield).

(13) Separate samples of **9a** and **9b** were desilylated (HOAc/THF/H$_2$O, 3:1:1) and oxidized (PCC, NaOAc, CH$_2$Cl$_2$) to provide **9c** (63% and 39%, respectively).

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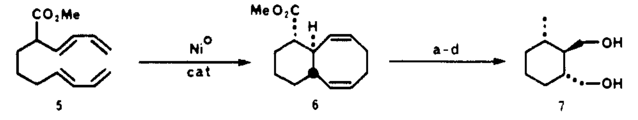
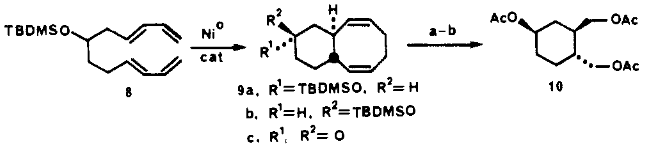
Scheme I[a]



[a](a) LAH, THF, quantitative; (b) TsCl, pyr, 0 °C, 59%; (c) $LiEt_3BH$, THF, 0 °C to room temperature, quantitative; (d) $O_3$, $CH_2Cl_2/MeOH$, -78 °C; $NaBH_4$, -78 °C to room temperature, 55%.

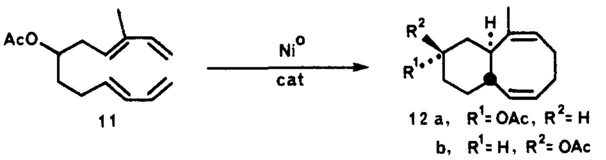
Scheme II[a]



[a](a) HOAc/THF/$H_2O$ (3:1:1), 77%, (b) $O_3$, $CH_2Cl_2/MeOH$, -78 °C; NaBH; -78 °C to room temperature; $Ac_2O$, pyr, DMAP, 18%.

prepared via a stereochemically unambiguous sequence (Scheme II).[14]

While diene substitution has been reported[3] to retard intermolecular cyclizations, the above studies involving monosubstituted dienes show that this is not a serious problem in the intramolecular reaction. Further substitution of the diene gave similar results. Thus, cyclization of **11**[15] proceeded with a rate comparable to that found for **8** and again provided trans-fused products (**12a,b**; 1:2.2)[16] in high yield (82%).



Several synthetically and mechanistically important conclusions follow from these studies. First, as with the intermolecular reactions,[1] catalyst variations influence the efficiency and product-type selectivity for these intramolecular reactions. Second, dienes connected by a three-atom tether selectively give cis-fused products whereas those connected by a four-atom chain are converted with comparably high but complementary selectivity to trans-fused products. Both results are in accord with a mechanism involving preferential formation and reaction of the more stable tetraene–nickel and bis-$\pi$-allyl complexes. Third, the remarkably high stereoinduction (99:1) observed in the reaction of tetraene **5** suggests that the ester group directs chemoselective and facial selective coordination of the catalyst to the proximate diene or that this selectivity arises through thermodynamically controlled formation of the bis-$\pi$-allyl or related complexes.[1,3] Finally, intramolecular reaction is favored over intermolecular oligomerization even in the case of the less reactive 1,2-disubstituted dienes. The above reactions serve as model studies for fundamentally new approaches to several structural classes including taxanes, ophiobolins, and fusicoccins. Further studies on the synthetic utility and origins of selectivities of this new reaction class are in progress.

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**Supplementary Material Available:** $^1H$ and $^{13}C$ NMR data for **2a,b**, **6**, **9a,b**, and **12a,b** (3 pages). Ordering information is given on any current masthead page.

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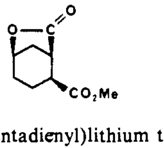
[14] Ester ii (Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 811) was epimerized (LDA, THF, -78 to -10 °C; aqueous $NH_4Cl$, 32%) and the epimer reduced to provide a triol which upon acetylation (LAH, THF; $Ac_2O$, pyr, DMAP, 64%) gave **10**, found to be identical with material derived from **9b**.



ii

[15] Addition of (3-methylpentadienyl)lithium to hepta-4,6-dienal, alkoxide-accelerated rearrangement (see ref 12), and acetylation ($Ac_2O$, pyr, DMAP) provided **11** (38% overall yield).

[16] Stereochemical assignments in **12a,b** are based on $^1H$ NMR comparison with **9a,b** and the independent conversion of **12a,b**, via saponification and oxidation, to the same ketone.

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# Synthesis of a Chiral Rhodium Alkyl via Metal Insertion into an Unstrained C–C Bond and Use of the Rate of Racemization at Carbon To Obtain a Rhodium–Carbon Bond Dissociation Energy

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We have found that directed insertion of a Rh(I) complex into an unstrained carbon–carbon bond, where one of the carbons is a chiral center, provides a new route to rhodium–chiral alkyl complexes. The substrate for C–C activation was (*S*)-8-quinolinyl $\alpha$-methoxybenzyl ketone (**1**) $[\alpha]_D$ -117°. As with all other 8-quinolinyl alkyl ketones,[1] it reacted with $[(C_2H_4)_2RhCl]_2$, in this case at 25 °C for 1 h, to give a yellow, chlorine-bridged polymer, **2** (98.6%), that was solubilized by pyridine to give the acylrhodium(III) alkyl **3**, the product of C–C cleavage (Scheme I). Ligand-promoted reductive elimination with $P(OMe)_3$ regenerated **1**.[2] Chromatographic isolation of **1** (71%) gave material with $[\alpha]_D$ -111°. The near identity between the rotation of starting and recovered **1** means either that both the C–C bond breaking and forming steps proceed with retention or both steps proceed with inversion at carbon. Since in other systems C–C bond-forming reductive eliminations proceed with retention,[3] we believe such is also the case here. Therefore, the first step in this cycle, the C–C bond breaking step, must proceed with retention as well.

If complex **3** was heated at 90 °C for 1 h, benzaldehyde formed. Several $CH_3$-derived molecules were produced, including ethane. Carrying out the thermolysis in the presence of $CCl_4$ gave $CH_3Cl$ in addition to PhCHO (>80%). Since $\alpha$-alkoxy radicals are known to fragment to carbonyl compounds and alkyl radicals,[4] these results indicate that the $Rh-CHPh(OCH_3)$ bond in **3** undergoes homolysis at 90 °C and the resulting $^{\bullet}CHPh(OCH_3)$ radical fragments to PhCHO and $^{\bullet}CH_3$. No heterolysis of the $C-OCH_3$ bond was detected when **3** was heated with excess $CD_3OD$, since the $OCD_3$ group was not incorporated into **3**.

At lower temperatures Rh–C bond homolysis also occurred, but due to the stability of the radicals formed, no new products were observed by $^1H$ NMR. However, cage escape products could be detected in a crossover experiment. When the rhodium complexes **3** and **4** were combined and heated (45 °C, 2 h) and then the ligand was regenerated with $P(OMe)_3$, the crossover ligands **6** and **7** were obtained (ca. 20% yield) in addition to the starting ligands **1** and **5**. A control experiment in which a mixture of **3** and **4** was immediately subjected to $P(OMe)_3$ gave no crossover ligands.

Heating **3** at temperature up to 60 °C cleanly racemized the carbon center, which from the above results must arise by homolysis of the Rh–C bond and recombination of the Rh and C radicals. The rate of racemization at carbon was first order in **3** and independent of the pyridine/rhodium ratio over the range

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[1] Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054.

[2] Suggs, J. W.; Wovkulich, M. J.; Cox, S. D. *Organometallics* **1985**, *4*, 1101.

[3] Flood, T. C. *Top. Stereochem.* **1981**, *12*, 37.

[4] Steenken, S.; Schushmann, H.-P.; vonSonntag, C. *J. Phys. Chem.* **1975**, 79, 763.