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Transition Metal-Catalyzed Intramolecular [4 + 2] Diene−Allene Cycloadditions: A Convenient Synthesis of Angularly Substituted Ring Systems with Provision for Catalyst-Controlled Chemo- and Stereocomplementarity

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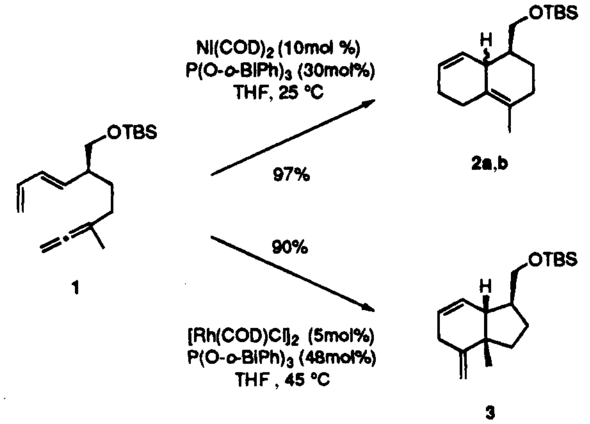
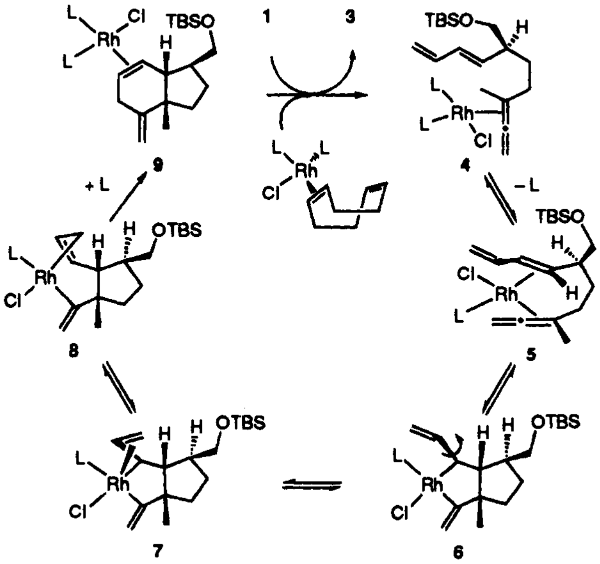
As part of our studies on transition metal-catalyzed $[m + n]$ cycloadditions,[1] we recently reported the first examples of nickel-catalyzed intramolecular [4 + 2] cycloadditions of dienes with unactivated alkynes, a process which provides convenient access to 6,6- and 6,5-fused ring systems.[2] In contrast to the elevated temperatures normally required for the Diels−Alder cycloadditions of such unactivated dienophiles, these metal-catalyzed cycloadditions proceed efficiently under mild conditions through a multistep mechanism. More recently, similar intramolecular diene−yne as well as diene−ene cycloadditions have also been extended by us and others to additional catalyst systems.[3] While servicing a number of objectives in synthesis, these catalyzed cycloadditions have not as yet been applicable to the synthesis of polycycles bearing an angular carbon substituent, a feature of numerous compounds of theoretical and medicinal significance.[4] We describe below a solution to this problem in the first examples of transition metal-catalyzed intramolecular [4 + 2] diene−allene cycloadditions.[5] These reactions provide efficient access to 6,6- and 6,5-fused rings, including notably those bearing angular carbon substituents. The first examples of catalyst-determined chemo- and stereoselectivity in these reactions are also reported.

The features of this new process are exemplified in the cycloaddition reactions of diene−allene **1** (Scheme 1).[6] Treatment of **1** in THF at 25 °C with a catalyst derived from Ni(COD)$_2$ modified with tri-*o*-biphenyl phosphite resulted in the chemospecific addition of the diene to the terminal π-system of the allene moiety, affording exclusively cycloadducts **2a,b** as a 2:1 mixture of isomers in 97% yield.[7] Remarkably, when this same diene−allene (i.e., **1**) in THF at 45 °C was treated with [Rh(COD)Cl]$_2$ modified with tri-*o*-biphenyl phosphite, the cycloaddition proceeded with a complete reversal of chemoselectivity, providing the angularly substituted hydrindane **3** as a single stereoisomer in 90% yield.[8] In striking contrast to these efficient and chemocomplementary cycloadditions, the uncatalyzed reactions of **1** occurred only at high temperatures (185 °C, $t_{1/2}$ = 16.6 h) and provided a complex mixture of products.[9]

Scheme 1



Scheme 2



A plausible mechanism for the rhodium-catalyzed reaction is presented in Scheme 2.[10] According to this sequence, coordination of the rhodium(I) catalyst to the allene followed by association with the proximate π-system of the tethered diene and oxidative addition would provide metallacyclopentane **6**. Formation of the *cis*-fused stereoisomer is in accord with our previous results for the analogous diene−diene cycloadditions[1] and the energetic preference for a *cis*-fusion between two five-membered rings.[11] The disposition of the large and small

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(1) For representative examples, see: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. Wender, P. A.; Correia, C. R. D.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089. For recent examples and lead references on other types of metal-mediated cycloadditions, see: Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831. Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579. Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 271−314.

(2) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432.

(3) Our studies have been extended to other ligands and metals, including rhodium, iron, and cobalt. For previous studies on rhodium-catalyzed intermolecular cycloadditions, see: Matsuda, I.; Shibata, M.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1987**, *28*, 3361. For recent studies on the related rhodium-catalyzed intramolecular process, see: Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145.

(4) For examples, see: Devon, T. K.; Scott, A. *Handbook of Naturally Occurring Compounds*; Academic: New York, 1972; Vol. 2, Terpenes.

(5) For surveys of nickel- and rhodium-catalyzed allene reactions, see: Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, 1975; Vol. 2, pp 117−132. Otsuka, S.; Nakamura, A. *Adv. Organomet. Chem.* **1976**, *14*, 245.

(6) Diene−allene **1** was prepared in 37% overall yield by the alkylation of sorbic acid dianion with 1-iodo-3-methyl-3,4-pentadiene followed by LAH reduction and silylation. **10** was prepared in 77% yield by the alkylation of Meldrum's acid with 1-bromo-2-methyl-2,3-butadiene and 1-bromopenta-2,4-diene. **12** was obtained in 65% yield by alkylation of 2-butyn-1,4-diol with 1-bromopenta-2,4-diene and treatment of the resultant alcohol with mesyl chloride followed by dimethyl cuprate. **16**, **18**, and **20** were prepared by the alkylation of dimethyl malonate with 1-bromopenta-2,4-diene, 1-bromo-4-methylpenta-2,4-diene, and 1-bromohexa-2,4-diene, respectively, followed by a second alkylation with 1-iodo-3-methylpenta-3,4-diene. Diene−allene **14** was prepared through the condensation of crotonaldehyde with dimethyl malonate and alkylation of the resultant diene−diester with 1-iodo-3-methylpenta-3,4-diene.

(7) The ratio of isomers was determined by ^{1}H NMR analysis of a purified mixture of **2a,b**. The stereochemistry of the major diastereomer was not determined.

(8) The stereochemistry of hydrindane **3** was determined by NOE experiments.

(9) The half-life is based on the rate of disappearance of the diene−allene substrate at the noted temperature as determined by GC analysis with dodecane as an internal standard.

(10) The mechanisms of these reactions and nature and geometry of the catalyst require further investigation. The path presented is intended only to facilitate synthetic application and guide mechanistic analysis.

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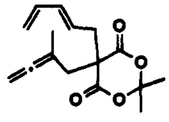
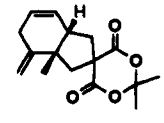
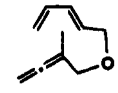
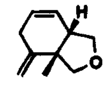
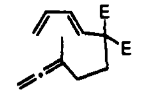
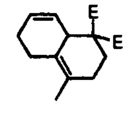
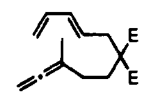
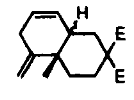
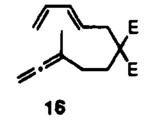
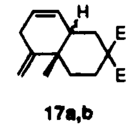
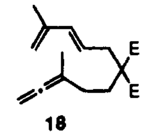
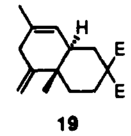
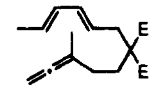
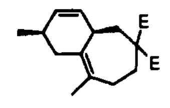
substituents (CH_2OTBS and H) relative to the ring fusion can be attributed to nonbonded interactions, which would disfavor the sterically more encumbered *endo*-orientation of the larger group during the initial C−C bond-forming event (**5** to **6**). Following rotational and positional isomerization of the σ-allyl complex **6** to **8**, reductive elimination would deliver the metal-complexed cycloadduct **9** at the end of the catalytic cycle. This path differs from the nickel-catalyzed process primarily as a result of the initial allenic site of metal coordination, which for nickel would occur preferentially at the less sterically encumbered π-bond of the allene.[12]

Comparison of the results obtained with substrates **1** and **12** (Table 1),[13,14] indicates that the efficiency and selectivity of the cycloaddition is not affected by an oxygen atom in the connecting tether. As was found for **1**, the uncatalyzed cycloaddition of diene−allene **12** proceeded only at high temperatures (140 °C, toluene, 25 h) and produced cycloadduct **13** in low yield (34% at 87% conversion) along with other products. The cycloaddition of **14** proceeded best with a modified catalyst and gave cycloadduct **15**. Further underscoring the operational advantages associated with these catalyzed reactions, the uncatalyzed cycloaddition of **14** required elevated temperatures (140 °C) and gave **15** in only 26% yield (71% conversion) along with other products.

For diene−allene **16**, various ligands with known θ and χ values were screened to determine whether the catalyst could be used to control the stereochemical course of the cycloaddition. Ligands with large θ and intermediate χ values were found to be effective in promoting the cycloaddition,[15] leading to the synthesis and testing of the novel ligands $P[OCH(CF_3)(o\text{-}CH_3\text{-}OC_6H_4)]_3$ (**22**) and $P[OCH(CF_3)(2,6\text{-}(CH_3)_2C_6H_3)]_3$ (**23**).[16] When treated with $RhCl(CH_2{=}CH_2)_2$ modified with ligand **22**, diene−allene **16** gave cycloadducts **17a,b** in 87% yield and in a ratio of 91:9 favoring the *trans* isomer. *Importantly, when this same substrate (i.e., **16**) was treated with $RhCl(CH_2{=}CH_2)_2$ modified with AgO_2CCF_3 and ligand **23**, cycloadducts **17a,b** were obtained with complementary stereoselectivity (**17a**:**17b** = 5:95).* In contrast, the uncatalyzed cycloaddition (200 °C, 19 h) of **16** gave **17a,b** in the ratio of 86:14 (*trans*:*cis* 46% yield). Finally, the cycloaddition of **20** illustrates a further advantage of these allene-based cycloadditions, as it represents an uncommon example of a metal-catalyzed intramolecular cyclization involving a five atom tether between the reactive subunits, providing in this case access to the BC ring system of molecules such as phorbol and resiniferatoxin.[17] The entropic constraints of the allenic unit presumably figure significantly in this result, suggesting that allenes could be exploited in other metal-mediated cycloadditions, which often are limited to three- and four-atom tethers.[18]

Table 1. Transition Metal-Catalyzed Intramolecular [4 + 2] Cycloadditions of Nonactivated Diene−Allenes[a,13,14]

diene−allene	cycloadduct(s), yield (*trans*:*cis*)	reaction conditions
 **10**	 **11** 98% (~0:100)	$[Rh(COD)Cl]_2$, $P(O\text{-}o\text{-}BiPh)_3$ (5 : 40 mol %) THF, 45 °C
 **12**	 **13** 94% (~0:100)	$[Rh(COD)Cl]_2$, $P(O\text{-}o\text{-}BiPh)_3$ (5 : 20 mol %) THF, 45 °C
 **14**	 **15** 77%	$Rh(H_2C{=}CH_2)_2Cl$, $P[OCH(CF_3)_2]_3$ (5 : 10 mol %) $PhCH_3$, 60 °C
 **16**	 **17a,b** 87% (~91:9=trans:cis)	$Rh(H_2C{=}CH_2)_2Cl$, $P[OCH(CF_3)\text{-}$ $(o\text{-}CH_3OPh)]_3$ (5 : 10 mol %) $PhCH_3$, 60 °C
 **16**	 **17a,b** 69% (~5:95=trans:cis)	$Rh(H_2C{=}CH_2)_2Cl$, AgO_2CCF_3, $P[OCH(CF_3)\text{-}$ $2,6\text{-}(CH_3)_2Ph)]_3$ (5 : 5 : 15 mol %) $PhCH_3$, 60 °C
 **18**	 **19** 87%	$Rh(H_2C{=}CH_2)_2Cl$, $P[OCH(CF_3)\text{-}$ $(o\text{-}CH_3OPh)]_3$ (5 : 10 mol %) $PhCH_3$, 80 °C
 **20**	 **21** 89%	$Rh(H_2C{=}CH_2)_2Cl$, $P[OCH(CF_3)_2]_3$ (5 : 10 mol %) $PhCH_3$, 80 °C

[a] E = CO_2Me.

In summary, this study provides an efficient and practical method for effecting the direct [4 + 2] cycloaddition of dienes with unactivated allenes. This process allows for the construction of 6,5-, 6,6-, and 6,7-fused ring systems in high yield under mild conditions. Access to angularly substituted bicycles is demonstrated for the former two ring systems. Modifications in the catalyst are shown to provide control over the chemoselectivity and stereoselectivity of the cycloaddition, a feature of great value in complex molecule synthesis since it can be exploited to override the intrinsic reactivity preferences of a given substrate. Further mechanistic and synthetic studies on these and related transition metal-catalyzed [*m* + *n*] cycloadditions are in progress.

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Supplementary Material Available: Spectroscopic and analytical data for compounds **1**−**3** and **10**−**21** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

(12) For pertinent data, see: Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 2780.

(13) All new compounds were characterized by IR and NMR spectroscopy and provided satisfactory elemental or exact mass analyses.

(14) A representative experimental procedure is as follows. A 250 mL Schlenk flask was flushed with nitrogen and charged with **10** (1.08 mmol) and freshly distilled anhydrous THF (100 mL). Tri-*o*-biphenyl phosphite (0.432 mmol) and $[Rh(COD)Cl]_2$ (0.054 mmol) were then added. The pale yellow solution was stirred at 45 °C for 10.5 h and then filtered through a plug of neutral alumina and concentrated in vacuo. Flash chromatography of the residue on silica afforded **11** (1.06 mmol) in 98% yield.

(15) For related work on ligand electronic χ and steric θ values, see: van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973. Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(16) The syntheses of novel phosphites **22** and **23** were accomplished according to the procedure of van Leeuwen and Roobeek: van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973.

(17) For pertinent synthetic studies and lead references, see: Wender, P. A.; Cribbs, C. M. In *Advances in Medicinal Chemistry*; Maryanoff, C. E., Maryanoff, B. E., Eds.; JAI: Greenwich, CT, 1992; Vol. 1, pp 1−53. The stereochemistry of **21** is assigned on the basis of NMR studies and by analogy with work cited in ref 2.

(18) Smith, G.; McLain, S. J.; Schrock, R. R. *J. Organomet. Chem.* **1980**, *202*, 269.