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Substrate control of stereoselection in the rhodium(I) catalyzed intramolecular [4 + 2] cycloaddition reaction †

Donogh J. R. O'Mahony, David B. Belanger and Tom Livinghouse *
Department of Chemistry, Montana State University, Bozeman, MT 59717, USA

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The Rh(I) catalyzed intramolecular [4 + 2] cycloaddition of representative achiral and chiral enedienes has been shown to proceed with excellent levels of stereoselectivity and in high yield under mild reaction conditions. In contrast, the corresponding noncatalyzed cycloadditions for three substrates in the latter category require higher temperatures and exhibit low levels of stereocontrol.

Cycloisomerization reactions catalyzed by electronically and sterically tunable transition metal complexes have emerged as transformations of considerable value to organic synthesis.[1] Prominent among reactions in this category are stereoselective cyclizations templated by complexes of rhodium,[2a,b] ruthenium,[2c] nickel[2d] and palladium.[2e] In contrast to conventional and "inverse electron demand" Diels–Alder reactions, [4 + 2] cycloadditions between π-components that are electronically not well differentiated typically require excessive temperatures and proceed with low levels of stereocontrol. Previous reports from these laboratories have demonstrated that electron-deficient Rh(I) complexes markedly catalyze formal [4 + 2] cycloaddition reactions of non-activated enedienes and dieneynes.[3a,b] In addition, we have shown that the enantioselective variation of this reaction is readily achieved using Rh(I) catalysts modified by *P*-chirogenic diphosphines.[3b–d] In this contribution, a number of highly diastereoselective cyclizations will be presented that will demonstrate the preparative strengths and scope of [4 + 2] cycloadditions catalyzed by achiral Rh(I) complexes.

We initiated this investigation by examining the cyclization of a series of achiral enedienes (*e.g.*, **3a**–**d**) that were connected by a *p*-toluenesulfonamide moiety. In all cases, the requisite enedienes were prepared by a Mitsunobu condensation involving the corresponding alcohol and primary *p*-toluenesulfonamide.[4] We have previously disclosed that Rh(I) complexes generated *in situ* from chlorobis(cyclooctene)rhodium(I) dimer (**1**) and two or more equivalents of tris(1,1,1,3,3,3-hexafluoroisopropyl) phosphite (**2**) possess superb activity as catalysts for intramolecular [4 + 2] cycloadditions of enedienes and dieneynes.[3a] The enedienes that were utilized in this phase of the study were selected to determine the effect that double bond geometry and substitution may have on the stereoselectivity and efficiency of cyclization. Whereas dienes **3a**–**c** all underwent efficient cycloaddition in THF at 55 °C in the presence of catalytic quantities of **1** modified by **2**, cyclization of **3d** required the use of the cationic catalyst $(Ph_3P)_3Rh^+ SbF_6^-$ (PhMe, 80 °C). This result is in complete accord with our previous study in which cationic Rh(I) complexes were shown to possess higher catalytic activities than their neutral counterparts.[3c] A summary of the results obtained for this series of cyclizations appears in Table 1.

As is evident from these results, defined alkene and diene geometries are translated to the corresponding relative product stereochemistries in a highly controlled manner. This is noteworthy as the mechanism for cyclization is doubtless a stepwise process rather than a concerted one.[5] Only in the case of **3d** was a slight loss of cycloaddition stereoselectivity observed. In this instance, the expected hexahydroindole was formed along with the corresponding 6β-phenyl epimer in a 9 : 1 ratio. *In sharp contrast to the results obtained in the presence of Rh(I) catalysts, efforts to bring about the corresponding thermal cycloadditions of enedienes* **3a**–**d** *were unsuccessful and led only to their decomposition.*

The cyclization of racemic enedienes (*e.g.*, **5a**–**c**) possessing a stereogenic center adjacent to one of the reactive π-components was subsequently examined. As before, Rh(I) complexes generated *in situ* from (**1**) and (**2**) were employed as cycloaddition catalysts in THF at 55 °C (Table 2). The stereochemical assignments for the bicyclic products were fully supported by ^{1}H NMR NOE studies and in the case of **6c** by single crystal X-ray analysis (Fig. 1).[6]

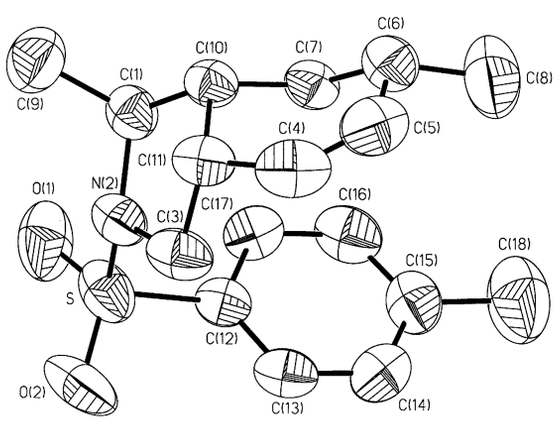
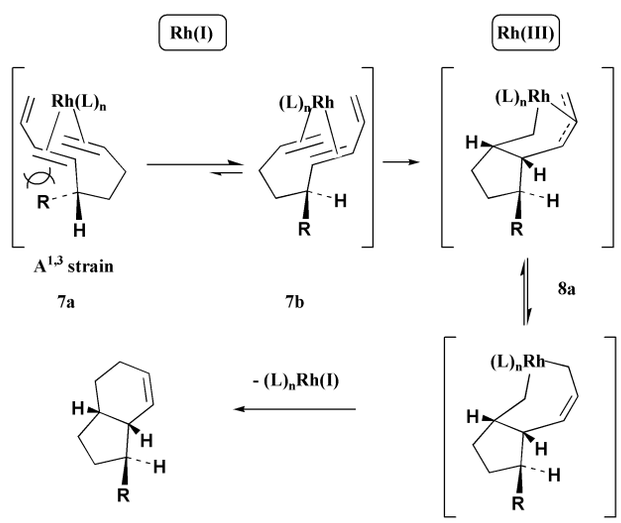


Fig. 1 ORTEP diagram of **6c**.



Scheme 1

† Electronic supplementary information (ESI) available: experimental procedures and spectroscopic data for compounds **4a**–**d** and **6a**–**c**. See http://www.rsc.org/suppdata/ob/b3/b302426c/

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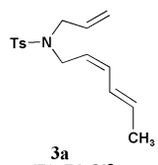
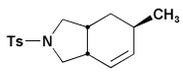
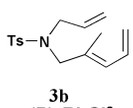
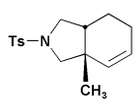
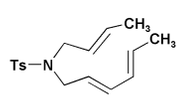
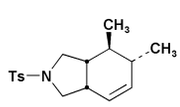
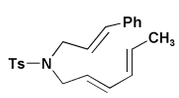
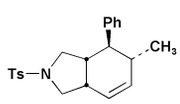
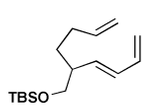
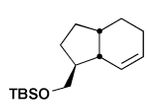
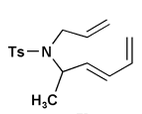
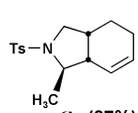
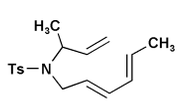
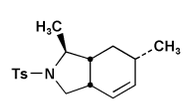
Table 1 Diastereoselective Rh(I) catalyzed cyclizations of achiral enedienes

Entry	Substrate, catalyst	Cycloadduct, yield	Conditions
1	 **3a** $(P)_nRhCl^a$ **2 mol %**	 **4a (73%) dr > 50:1**	THF, 55 °C, 36 h
2	 **3b** $(P)_nRhCl^a$ **5 mol %**	 **4b (94%) isomeric purity = 95:5**	THF, 55 °C, 24 h
3	 **3c** $(P)_nRhCl^a$ **2 mol %**	 **4c (85%) dr > 80 : 1**	THF, 55 °C, 50 h
4	 **3d**[b]	 **4d (83%) dr = 9:1**	PhMe, 80 °C, 24 h

[a] "P" = $P(O\text{-}i\text{-}C_3HF_6)_3$ (**2**). [b] Cat. = $(Ph_3P)_3Rh^+SbF_6^-$ (5 mol%).

Table 2 Diastereoselective Rh(I) catalyzed cyclizations of racemic enedienes

Entry	Substrate, catalyst	Cycloadduct, yield	Conditions
1	 **5a** $(P)_nRhCl^a$ **2 mol %**	 **6a (89%) dr = 35 : 1**	THF, 55 °C, 13 h
2	 **5b** $(P)_nRhCl^a$ **2 mol %**	 **6b (87%) dr = 35 : 1**	THF, 55 °C, 6.25 h
3	 **5c** $(P)_nRhCl^a$ **2 mol %**	 **6c (94%) dr = 19 : 1**	THF, 55 °C, 6.5 h

[a] "P" = $P(O\text{-}i\text{-}C_3HF_6)_3$ (**2**).

In all of the above cases, the Rh(I) catalyzed cyclizations proceeded with excellent levels of relative stereocontrol with the production of *cis* fused bicycles in which the substituent at the preexisting stereogenic center is oriented *exo* to the ring junction centers. The stereochemical outcome of these cycloadditions is consistent with the stepwise mechanism presented in Scheme 1 in which non-bonded interactions are minimized in the π-complexes **7a** and **7b** that are presumably in equilibrium prior to the initial bond forming event *en route* to the Rh(III) allyls **8a** and **8b**. Regeneration of the active Rh(I) complex from **8b** by reductive elimination would then complete the catalytic cycle resulting in the production of the observed cycloadduct **9**. In the instances of the enedienes **5a**–**c**, thermal control experiments at temperatures in excess of 140 °C did give rise to cycloaddition albeit with the production of *all* possible products (*e.g.*, with *exo* and *endo* substitution and *cis* and *trans* ring junctions) in modest yield.

In conclusion, we have demonstrated that representative chiral and achiral enedienes undergo highly diastereoselective [4 + 2] cycloadditions catalyzed by simple Rh(I) complexes with

excellent efficiency. The utilization of this strategy for the stereocontrolled construction of naturally occurring ring systems will be the topic of future accounts from these laboratories.

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6 Crystal data: $C_{17}H_{23}NO_2S$, FW = 305.4, monoclinic, space group *C*2/*c*, a = 26.112 (3) Å, b = 9.913 (1) Å, c = 16.461 (2) Å, $\alpha = \gamma = 90°$, β = 127.628 (6)°, V = 3374.4 (9) Å^3, T = 25 °C, Z = 8, μ = 0.196 mm^{-1}, $F(000)$ = 1312, 4913 independent reflections (5280 measured), R_{int} = 0.017, 1346 observed reflections at $F>5\sigma(F)$, 190 parameters, R_{obs} = 0.053, $_wR_{obs}$ = 0.048, $_wR_{all}$ = 0.076. CCDC reference number 206531. See http://www.rsc.org/suppdata/ob/b3/b302426c/ for crystallographic data in .cif or other electronic format.