JOC*Note*

Cyclopentane Construction by Rh-Catalyzed Intramolecular C−H Insertion: Relative Reactivity of a Range of Catalysts

Douglass F. Taber* and Pramod V. Joshi

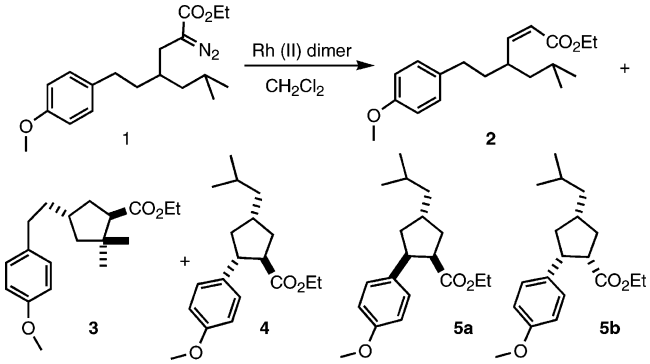
Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

Received December 4, 2003

Abstract: The preparation and Rh-mediated cyclization of the α-diazoester **1** are outlined, and its utility in determining the elements that contribute to the reactivity of the intermediate Rh-carbenoid is presented. The rate of disappearance of diazo ester **1** catalyzed by several representative Rh(II) complexes was determined. The observed relative rate constants for the reaction of the Rh(II) complexes with **1** varied over a range of $>10^7$. The reactivity of the Rh-carbenoid intermediate was explored using the ratio of the sum of (**3** + **4** + **5**) to **2** (cyclization vs elimination), the ratio of **3** to the sum of (**4** + **5**) (chemoselectivity), and the ratio of **4** to **5** (diastereoselectivity). It is striking that these four measures of reactivity were found to be independent of each other.

Cyclopentane construction by Rh-mediated C−H insertion reaction (e.g., **1** → **3** + **4** + **5**) has achieved wide popularity.[1] Several different Rh complexes have been reported to effect cyclization, with advantages of one complex over another having been reported. We thought that it would be useful to compare the several catalysts with a single substrate **1**.[2−4] As we embarked on this study, it was apparent that there were four potentially independent aspects of "reactivity": the rate of bimolecular transfer of the diazo ester to the Rh-complex,[2] the ratio of C−H insertion to β-H elimination [(**3** + **4** + **5**)/**2**],[11] the chemoselectivity (**3**/**4** + **5**),[1w] and the diastereoselectivity of the insertion (**4**/**5**).[1r]



We selected a series of Rh(II) carboxylates, Rh(II) carboxamidate[1p] (Doyle catalysts **6h**−**j**), and the bridged Rh(II) carboxylate[5b] (Lahuerta catalyst **6g**) as representative of the various Rh(II) catalysts in use today (Figure 1). Most of the carboxylate and Doyle catalysts were commercially available. They were purified by silica gel chromatography before use. The Lahuerta catalyst was prepared according to the literature procedure,[5b] and its structure was confirmed by X-ray analysis.

Observed Relative Rate Constants. Following Pirrung,[2c] we expected that the Rh catalysts would show saturation kinetics, so that disappearance of starting material would be linear with time. We monitored disappearance of the diazoester, at 27 ± 1 ° C, by following the UV absorbance at $\lambda = 265$ nm. Each of the Rh(II) complexes was purified by silica gel chromatography to ensure that no axial ligands would be present that would affect reactivity. The decrease in absorbance of the starting material was plotted versus time. The approximately linear portion of this direct plot, from 80% to 30% of the absorbance, was used to calculate, by dividing by catalyst concentrations, the relative rate constants for each of the Rh(II) complexes.

The rate constants (Table 1) varied over a range of $>10^7$. The pivalate catalyst (entry 3) stands out, being

(1) For studies of selective cyclopentane construction by Rh-mediated intramolecular C−H insertion, see: (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Taber D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (c) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (d) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 5732. (e) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (f) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605. (g) Hashimoto, S.-i.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637. (h) Corey, E J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995. (i) Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173. (j) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L. *J. Org. Chem.* **1991**, *56*, 820. (k) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1991**, *56*, 7065. (l) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436. (m) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (n) Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709. (o) Doyle, M. P.; Wetsrum, L. J.; Wolthius, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (p) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (q) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A.; Muller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (r) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757. (s) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M.; Pawda, A.; Richards, I. C. *Tetrahedron* **1996**, 52, 2489. (t) Doyle, M. P. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (u) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853. (v) Taber, D. F.; Green, J. H.; Zhang, W.; Song, R. *J. Org. Chem.* **2000**, *65*, 5436. (w) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944. (x) Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475. (y) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539. (z) Doyle, M. P.; Davies, S. B.; May, E. J. *J. Org. Chem.* **2001**, *66*, 8112.

(2) (a) Alonso, M. E.; Carmen Garcia, M.-d. *Tetrahedron* **1989**, *45*, 69. (b) Chipperfield, J. R. *J. Organomet. Chem.* **1989**, *363*, 253. (c) Pirrung, M. C.; Morehead, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (d) Pirrung, M. C.; Morehead, A. T. *J. Am. Chem. Soc.* **1996**, *118*, 8162. (e) Pirrung, M. C.; Liu, H.; Morehead, A. T. *J. Am. Chem. Soc.* **2002**, *124*, 1014.

(3) For the development of this model, see: (a) Taber, D. F.; You, K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (b) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.

(4) For a detailed theoretical treatment of Rh(II)-mediated C−H insertion, see: Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

(5) (a) Taber, D. F.; Malcolm, S. C.; Bieger, K.; Lahuerta, P.; Sanau, M.; Stiriba, S.-E.; Perez-Prieto, J.; Monge, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 860. (b) Lahuerta, P.; Periera, I.; Perez-Prieto, J.; Sarau, M.; Stiriba, S.-E.; Taber, D. F. *J. Organomet. Chem.* **2000**, *612*, 36.

10.1021/jo0303766 CCC: $27.50
Published on Web 05/15/2004

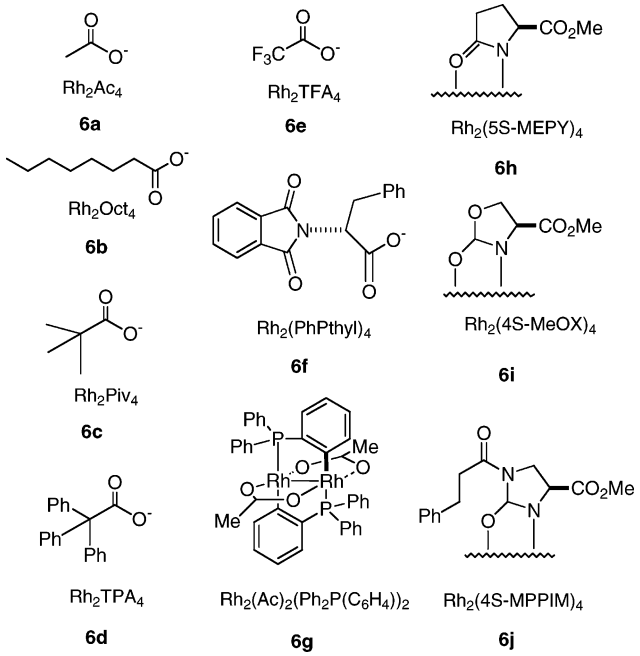


FIGURE 1. Structures of Rh(II) catalysts used in this study.

TABLE 1. Relative Rate Constants for the Rh(II) Catalysts

	catalyst	relative k_{ob}
1	Rh_2Ac_4, **6a**	2.56×10^4
2	Rh_2Oct_4, **6b**	4.28×10^4
3	Rh_2Piv_4, **6c**	2.34×10^7
4	Rh_2TPA_4, **6d**	1.06×10^5
5	Rh_2TFA_4, **6e**	1.03×10^5
6	Rh_2(*R*-PTPA)$_4$, **6f**	2.24×10^5
7	$Rh_2Ac_2(Ph_2P(C_6H_4))_2$, **6g**	5.82×10^4
8	Rh_2(5R-MEPY)$_4$, **6h**	1.0
9	Rh_2(4S-MeOX)$_4$, **6i**	3.53×10^1
10	Rh_2(4S-MPPIM)$_4$, **6j**	1.97×10^1

TABLE 2. Ratio of Insertion (3 + 4 + 5) to Alkene (2) (I/A) for the Rh(II) Catalysts

	catalysts	isolated yields (%)	I/A (HPLC)	I/A (NMR)
1	Rh_2Ac_4, **6a**	99	15.4	16.4
2	Rh_2Oct_4, **6b**	87	31.3	27.8
3	Rh_2Piv_4, **6c**	91	16.9	20.8
4	Rh_2TPA_4, **6d**	94	4.02	4.05
5	Rh_2TFA_4, **6e**	96	2.87	3.13
6	Rh_2(*R*-PTPA)$_4$, **6f**	96	43.5	52.6
7	$Rh_2Ac_2(Ph_2P(C_6H_4))_2$, **6g**	94	32.1	26.2
8	Rh_2(5*R*-MEPY)$_4$, **6h**	92	1.65	1.75
9	Rh_2(4S-MeOX)$_4$ **6i**	95	0.83	1.05
10	Rh_2(4S-MPPIM)$_4$ **6j**	96	10.3	10.3
11	*rac*- Rh_2(4*S*-MeOX)$_4$	94		1.1

almost 2 orders of magnitude faster than any of the other catalysts studied. The Rh_2(MEPY)$_4$ catalyst (entry 8) was slower than any of the carboxylates, while the bridged phosphine catalyst (entry 7) behaved like most of the other carboxylates.

Insertion to Elimination Ratios. The ratio of the insertion (Table 2) to the β-hydride elimination product (I/A) was determined for each of the catalysts. In the carboxamidate class of complexes the MeOX catalyst (entry 9) showed the most β-elimination compared to the

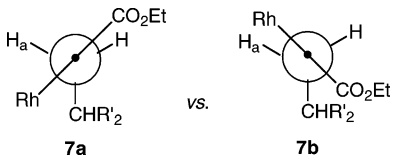
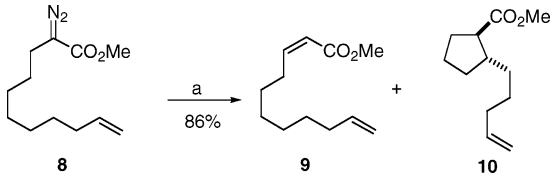


FIGURE 2. Newman projection of Rh-carbenoid.

SCHEME 1[a]



[a] Conditions: (a) Rh_2Oct_4, CH_2Cl_2, rt, I/A = 2.8/1; Rh_2(MPPIM)$_4$, CH_2Cl_2, rt, I/A = 0.

MEPY catalyst (entry 8) and MPPIM catalyst (entry 10). The amide analogue, MPPIM, showed the least β-elimination product. We were concerned that the application of an enantiomerically pure catalyst to a racemic substrate might bias the results, so we repeated one of the cyclizations using "racemic" (1:1 *R*/*S*) catalyst. The resulting product ratios (entry 11) were the same as those observed for the enantiomerically pure catalyst.

We believe that two factors govern the ratio of insertion to elimination: the "earliness" vs "lateness" of the transition state and the steric bulk of the ligand on the Rh-carbenoid. A"hot" carbenoid would have an early transition state, favoring β-H elimination over 1,5 insertion. We expect that the increased proportion of elimination observed with Rh trifluoroacetate (entry 5), for instance, is due to the electron-withdrawing nature of the ligand. This makes the carbene carbon more strongly positive and thus more reactive.

The steric effects become clear on inspecting the Newman projections of the transition states as shown in Figure 2. The conformation **7a** can lead to cyclopentane formation, while the conformation **7b** can give only β-H elimination. As the Rh carbenoid becomes larger, conformation **7b** is increasingly favored. Thus, as the steric bulk of the ligands on the Rh carbenoid increases going from acetate (entry 1) to the TPA catalyst (entry 4), there is a significant increase in the proportion of β-hydride elimination.

The α-diazo ester **1** with its γ-branching was designed to minimize β-H elimination. The reaction of α-diazo methyl undecylenate **8** with Rh_2Oct_4 (**6b**) gave an I/A ratio of 2.8, while reaction with Rh_2(MPPIM)$_4$ (**6j**) gave only the β-H elimination product **10** (Scheme 1).

Methine to Methylene Selectivity. In the carboxylate series, the TPA catalyst (Table 3, entry 4) was the most selective for methine over methylene insertion. Should this prove to be general, **6d** may add a possibility for high chemoselectivity not previously observed with Rh(II) catalysts. The other carboxylate catalysts show less preference for CH over CH_2 insertion. Our design of the α-diazo ester 1 included the *p*-methoxy group on the benzene ring, so the methylene benzylic C−H would approach the methine in reactivity. We expect that the CH/CH_2 ratios would be more pronounced with a less carefully balanced substrate.

TABLE 3. Ratio of CH/CH_2 (3/4 + 5) for the Rh(II) Catalysts

	catalyst	CH/CH_2 (HPLC)	CH/CH_2 (NMR)
1	Rh_2Ac_4, **6a**	1.09	1.03
2	Rh_2Oct_4, **6b**	1.57	1.46
3	Rh_2Piv_4, **6c**	1.77	1.67
4	Rh_2TPA_4, **6d**	10.9	CH-only
5	Rh_2TFA_4, **6e**	2.23	2.11
6	Rh_2(*R*-PTPA)$_4$, **6f**	2.73	2.66
7	$Rh_2Ac_2(Ph_2P(C_6H_4))_2$, **6g**	0.94	0.93
8	Rh_2(5*R*-MEPY)$_4$, **6h**	1.15	1.18
9	Rh_2(4*S*-MeOX)$_4$, **6i**	2.01	2.18
10	Rh_2(4*S*-MPPIM)$_4$, **6j**	2.67	2.84
11	*rac*- Rh_2(4*S*-MeOX))$_4$		2.11

TABLE 4. Ratio of CH_2 Insertion Products

	catalyst	**4/5a/5b**
1	Rh_2Ac_4, **6a**	831/1/−
2	Rh_2Oct_4, **6b**	9.1/1/−
3	Rh_2Piv_4, **6c**	5.0/1/0.4
4	Rh_2TPA_4, **6d**	20.7/1/−
5	Rh_2TFA_4, **6e**	2.1/1/0.06
6	Rh_2(*R*-PTPA)$_4$, **6f**	1.7/1/0.09
7	$Rh_2Ac_2(Ph_2P(C_6H_4))_2$, **6g**	1438/1/4.2
8	Rh_2(5*R*-MEPY)$_4$, **6h**	15.8/1/0.9
9	Rh_2(4*S*-MeOX)$_4$, **6i**	208/1/−
10	Rh_2(4*S*-MPPIM)$_4$, **6j**	1.6/1/0.07
11	*rac*-Rh_2(4*S*-MeOX)$_4$	**4** only

In the carboxamidate class, MPPIM catalyst (entry 10) was more selective than the corresponding MeOX catalyst (entry 9), with the MEPY catalyst (entry 8) being the least discriminating for CH over CH_2 insertion.

We believe that the selectivity of methine (CH) insertion over methylene (CH_2) insertion (Table 3) is a reflection of the polarizability of the Rh-carbenoid. As the carbenoid approaches the target C−H, the methine C−H is more electron rich than the methylene C−H. A more easily polarized carbenoid would respond more fully to this and give proportionally more of the methine insertion product. Statistically, for geometric reasons, only one of the two benzylic methylene C−H's is available for insertion, for cyclization leading to **4**.

Ratio of the Methylene Insertion Diastereomers. The major methylene insertion diastereomer seen with each of the Rh(II) catalysts surveyed was **4** (Table 4). For the TFA catalyst (entry 5), we observed a significant proportion of the cis diastereomers **5a** and **5b**. Among the other carboxylate catalysts, the acetate catalyst (entry 1) and the bridged catalyst (entry 7) generated Rh carbenoids that showed remarkable selectivity for the trans diastereomer **4**. In the carboxamidate (Doyle) series, the MeOX catalyst (entry 9) showed excellent selectivity for the diastereomer **4**. The MPPIM catalyst (entry 10) was the least selective.

For the cyclization of diazo ester **1** there are four[3a] competing diastereomeric chair transition states leading to CH_2 insertion products. In our model of the transition state, the Rh−C bond is aligned with the target C−H bond leading to C−C bond formation. The two most stable of these chairlike transition states, the two having the pendant alkyl group equatorial, are depicted in Figure 3. The actual product from cyclization is determined as the intermediate carbenoid commits to a particular diastereomeric transition state. If the C−C distance is short at the point of commitment (tight transition state), there will be a substantial steric interaction between the arene and the ester, and **11b** will be disfavored. If the C−C distance is longer, this interaction will not be as severe and more of **5** will be formed. Thus, it is our interpretation that the ratio of **4** to **5** is a measure of the C−C bond distance at the point of commitment of the Rh carbenoid.

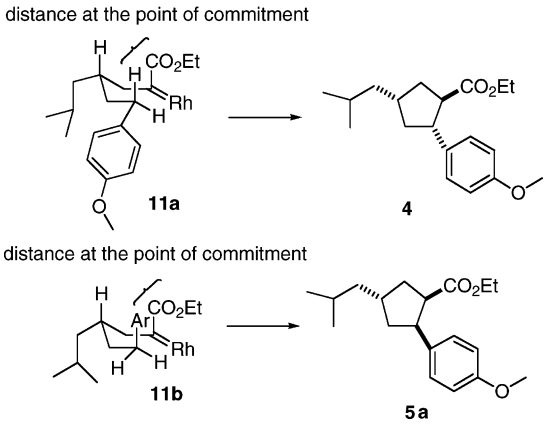


FIGURE 3. Transition states for the CH_2 insertion.

Conclusion

The α-diazo ester **1** was developed to study the several reaction parameters for Rh(II)-mediated intramolecular C−H insertion. This design incorporated an electronically biased methylene (CH_2) to compete with the methine (CH) in the insertion process. Another advantage of using diazo ester **1** was the diminution of the *β*-H elimination product. The reactivity of the Rh-carbenoid intermediate was explored using the ratio of the sum of (**3** + **4** + **5**) to **2** (insertion vs elimination), the ratio of **3** to (**4** + **5**) (chemoselectivity), and the ratio of **4**/**5** (diastereoselectivity). A fourth reactivity parameter was the observed relative rate constants for the reaction of the Rh(II) complexes with the diazo ester **1**. We had expected that we might see some correlations among these four parameters of reactivity, but in fact plots of one vs the other showed no such correlation.

It is clear that there is still much to be learned about the factors that govern selectivity in these cyclizations. Why, for instance, should there be such a difference in the turnover rate for amide vs carboxylate-derived catalysts? We hope that the results outlined here will help to establish, in time, a more detailed understanding of the mechanism of Rh-mediated intramolecular C−H insertion.

Acknowledgment. We thank the NIH (GM 60287) for financial support of this work. We express our appreciation to Profs. Charles G. Riordan, Michael P. Doyle, and Huw M. L. Davies for helpful discussions.

Supporting Information Available: Experimental procedures including the preparation of **1**, the analysis of the product mixtures from cyclization of **1,** and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0303766