ORGANIC LETTERS

2004
Vol. 6, No. 8
1321−1324

Direct, Stereoselective Substitution in $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylations of Unsymmetrical Substrates

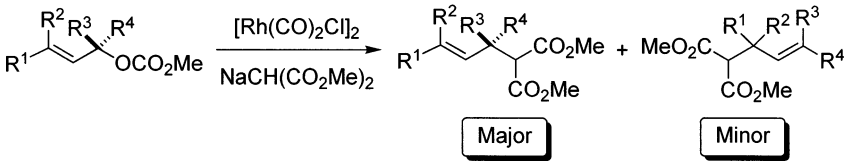
Brandon L. Ashfeld, Kenneth A. Miller, and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

sfmartin@mail.utexas.edu

Received February 26, 2004

ABSTRACT



$[Rh(CO)_2Cl]_2$ has been found to possess the unusual property of catalyzing allylic alkylations of unsymmetrical allylic carbonates with high levels of regioselectivity to provide products arising from substitution at the carbon atom bearing the leaving group, irrespective of the structure of the starting carbonate. The substitution reaction occurs with retention of stereochemistry at the reacting center, and the carbon–carbon double-bond stereochemistry of primary (*Z*)-allylic carbonates is maintained.

Transition metal-catalyzed allylic alkylations constitute one of the more widely utilized classes of reactions in modern synthetic organic chemistry.[1,2] The focus of many recent efforts in this area has been in developing catalysts that enable high regio- and stereochemical control in the substitution reaction of symmetrical and unsymmetrical substrates. Irrespective of the structure of the starting materials (e.g., **1** or **2**), palladium-catalyzed processes typically favor nucleophilic substitution at the sterically less hindered allylic terminus to give **3**,[3] whereas Ru,[4] Mo,[5] Rh,[6,7] Ir,[8] and W[9] preferentially deliver products **4** arising from attack at the more encumbered allylic terminus (Figure 1).[2,10,11] These reactions are generally believed to proceed via a transition metal-stabilized allyl intermediate that may range in structure from an unsymmetrical η^1-complex to a symmetrical η^3-allyl complex. The regioselectivity of the ensuing nucleophilic attack is then dictated by a combination of steric and electronic factors that vary with the intermediate complex and the nucleophile.[12]

Given the various catalysts capable of promoting allylic alkylations, it is generally possible to prepare either **3** or **4** through judicious selection of catalyst and allylic substrate **1** or **2**. However, that there may not be a direct correlation between the structure of **1** or **2** and the major product may sometimes be a disadvantage. Indeed, it is perhaps somewhat

(1) For reviews on transition metal-catalyzed allylic alkylations, see: (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1996. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) For leading references on other transition metal-catalyzed allylic alkylations, see: (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Heidelberg, 1980. (b) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Humphries, M. E.; Williams, J. M. J. *Chem. Eur. J.* **2000**, *6*, 353. (c) Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320. (d) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974. (e) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690. (f) Bartels, B.; Garcia-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097. (g) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563.

(3) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615

(4) (a) Ono, H.; Satake, N.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945. (b) Morisaki, Y.; Kondo T.; Mitsudo T. *Organometallics* **1999**, *18*, 4742. (c) Trost, B. M.; Fraisse, P.; Ball, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059.

(5) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S. W.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929.

(6) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. (b) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713.

(7) (a) Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, *22*, 659. (b) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *39*, 1725.

(8) Takeuchi, R. *Synlett* **2002**, 1954.

(9) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757.

(10) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647.

(11) Evans, P. A.; Nelson J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(12) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.

10.1021/ol0496529 CCC: $27.50
Published on Web 03/12/2004

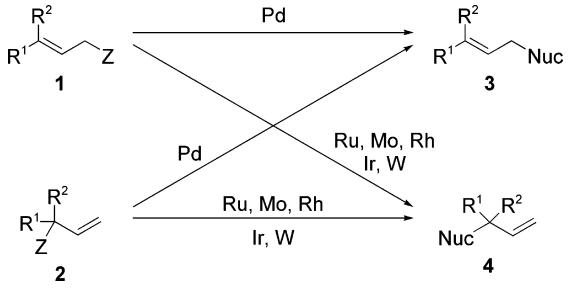


Figure 1. Regiochemical trends in transition metal-catalyzed allylic alkylations.

surprising that no *single* catalyst has yet been identified that enables direct, stereoselective allylic substitution at the carbon atom bearing the leaving group. Moreover, if such a catalyst were capable of promoting subsequent transformations, there exists the potential of developing a number of synthetically useful cascade sequences.

In the aforementioned contexts, it is noteworthy that we recently discovered that $[Rh(CO)_2Cl]_2$ catalyzed the rapid allylic alkylation of pentenyl carbonate **5a** (R^1 = Et, R^2−R^4 = H) with the sodium salt of dimethyl malonate at room temperature to provide **6a** (R^1 = Et, R^2−R^4 = H) with a high degree of regioselectivity (**6a**/**7a** = 97:3) (Figure 2).

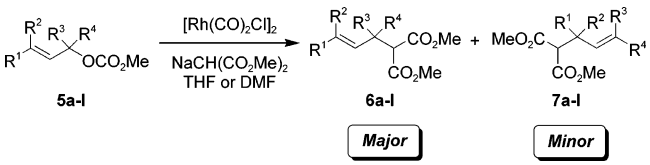
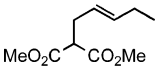
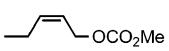
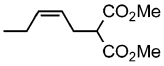
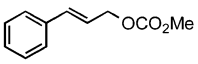
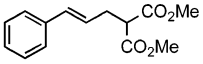
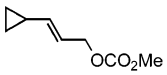
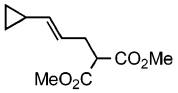
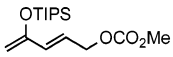
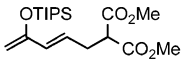
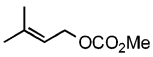
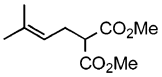
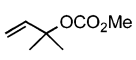
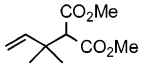
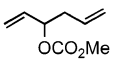
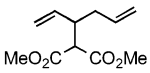
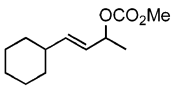
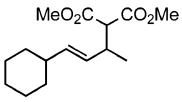
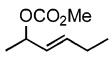
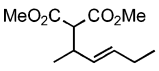
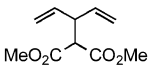
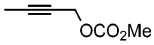
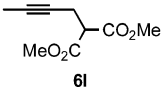


Figure 2. Direct substitution in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations.

This unexpected result immediately captured our attention because the regiochemical outcome was opposite that observed by Evans for allylic alkylations catalyzed by $RhCl(PPh_3)_3/P(OMe)_3$.[11] We therefore explored the scope of $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations, and some of our preliminary findings are summarized in Table 1.[13]

(13) **Representative Experimental Procedure.** The allylic substrate **5** (1.0 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (19 mg, 0.05 mmol) in THF (5 mL), and the solution was stirred for 30 min at room temperature. In a separate flask, dimethyl malonate (0.29 mL, 2.5 mmol) was added to a slurry of NaH (60% w/w in mineral oil, 40 mg, 2.0 mmol) in THF (5 mL) at room temperature, and the mixture was stirred for 20 min. The resulting sodium enolate was added via syringe to the solution of **5** and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then sealed in a screw cap vial under an atmosphere of argon, and stirring was continued at room temperature until the starting material was consumed (as indicated by TLC). The reaction was then filtered through a short plug of silica gel eluting with Et_2O (50 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1 or 10:1) to furnish the products **6** and **7**. All new compounds were purified (>95%) by flash chromatography and were characterized by ^1H and ^{13}C NMR, IR, and HRMS.

Table 1. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation Reactions[13]

1[c]	 **5a**	 **6a**	84	97:3
2[d]	 **5b**	 **6b**	86	99:1 (97:3)[h]
3[d]	 **5c**	 **6c**	93	90:10
4[d]	 **5d**	 **6d**	84	89:11
5[e]	 **5e**	 **6e**	94	97:3
6[f]	 **5f**	 **6f**	75	92:8
7[d]	 **5g**	 **6g**	80	94:6
8[d]	 **5h**	 **6h**	89	91:9
9[d]	 **5i**	 **6i**	94	93:7
10[g]	 **5j**	 **6j**	88	96:4
11[d,i]	 **5k**	 **6k**	74	96:4
12[d]	 **5l**	 **6l**	52	99:1

[a] Isolated yields. [b] Ratios determined by GLC. [c] THF, rt. [d] THF, 0 °C. [e] DMF, rt. [f] DMF, −20 °C. [g] DMF, 0 °C. [h] Ratio of cis/trans isomers. [i] Corresponding carbonate was unstable.

Examination of the entries in Table 1 reveals that $[Rh(CO)_2Cl]_2$ catalyzed the facile and regioselective alkylations of a variety of allylic carbonates **5a**−**l** to provide the corresponding malonates **6a**−**l** as the major products in every case. The reactions typically proceeded with excellent regiocontrol that favored substitution at the carbon atom

bearing the leaving group. A number of general trends and notable features merit additional discussion.

Primary allylic carbonates having internal disubstituted carbon−carbon double bonds selectively provided the linear alkylation products (entries 1−6). This mode of regioselectivity corresponds to that expected of palladium catalysts but is opposite to that typically observed for ruthenium, molybdenum, rhodium, and iridium catalysts.[1,14] The (*Z*)-carbonate **5b** (entry 2) underwent substitution to give the *less stable* (*Z*)-product with little isomerization to the (*E*)-isomer. This result is significant because (*Z*)-allylic substrates generally suffer extensive *Z*→E isomerization with other transition metal catalysts, although there are scattered reports of *Z*-selective allylic substititutions of (*Z*)-substrates catalyzed by iridium,[10] palladium,[15] and tungsten.[16] Alkylation of **5e** illustrates that enol ethers conjugated with the allylic subunit do not adversely affect the regiochemistry or efficiency of the reaction (entry 5). That **5f** underwent (entry 6) *any* alkylation is noteworthy because 2,3,3-trisubstituted allylic carbonates are inert to the modified Wilkinson's catalyst reported by Evans and typically require forcing conditions with other transition metal catalysts.[11,17] The isomeric tertiary allylic carbonate **5g** underwent facile alkylation to provide the product of direct substitution, even though a quaternary center was generated in the process (entry 7).

Preliminary results with secondary allylic carbonates and acetates **5h**−**k** (entries 8−11) underscore the differences between the reactivity of $[Rh(CO)_2Cl]_2$ and other catalysts capable of promoting allylic substitutions. In each of these cases, direct displacement of the leaving group is the dominant reaction pathway. This appears to be true even when the substituents at both ends of the allylic moiety are sterically and electronically similar (entry 10) or when conjugation would favor substitution at the opposite allylic terminus (entry 11). Finally, $[Rh(CO)_2Cl]_2$ may be used effectively to catalyze the alkylation of propargylic carbonates to give substituted alkynes with none of the allenic product being observed (entry 12).

That $[Rh(CO)_2Cl]_2$ catalyzes the allylic alkylations of unsymmetrical substrates to give products in which substitution occurs at the carbon atom bearing the leaving group may be regarded as a memory effect. Such phenomena have been examined in palladium-catalyzed allylic alkylations of enantioenriched and racemic secondary allylic substrates having the *same* number of substituents on the allyl moiety.[18,19] The nature of the memory effect observed in these $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations thus differs from those previously studied because the termini of the allylic moieties are unequally substituted. Mechanistic studies are underway to understand the origin of the regiochemistry in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations and why it differs from such reactions promoted by other transition metal catalysts. Of particular interest is determining whether the rhodium-stabilized allyl intermediate resembles a ($\sigma + \pi$) *enyl* complex as suggested by Evans or some other π-allyl variant.[11]

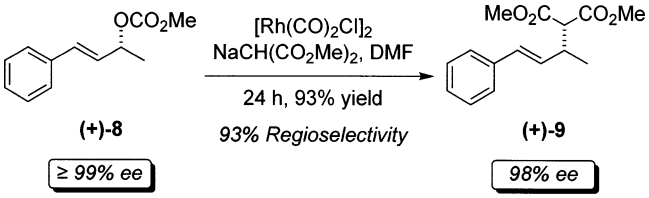


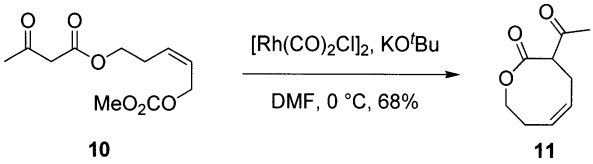
Figure 3. Retention of configuration in the $[Rh(CO)_2Cl]_2$-catalyzed allylic substitution.

To determine the stereochemical outcome of $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions, the allylic carbonate (+)-**8** was synthesized in ≥99% ee[20] in two steps from the corresponding racemic alcohol via Sharpless kinetic resolution (Figure 3). When (+)-**8** was allowed to react with the sodium salt of dimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$, (+)-**9** was obtained in 93% yield and 98% ee[20] (regioselectivity = 93:7). Like Pd,[1] Ru,[4] Mo,[21] Rh,[11] and Ir[10] catalysts, $[Rh(CO)_2Cl]_2$ thus appears to catalyze substitutions of secondary allylic carbonates with net retention of configuration.

We have thus demonstrated that $[Rh(CO)_2Cl]_2$ has the remarkable propensity to catalyze allylic substitutions at the carbon atom bearing the leaving group on substrates with a variety of substitution patterns. The following question now arises: How can this unusual reactivity be exploited in synthesis? We are currently pursuing this query on a number of fronts. For example, that allylic substitutions of (*Z*)-alkenes proceed with retention of double-bond geometry suggests that $[Rh(CO)_2Cl]_2$ might be used to catalyze cyclizations to give medium and large rings containing (*Z*)-olefins. The synthesis of rings by transition metal-catalyzed cyclizations has received considerable attention since the early 1980s.[22] Inasmuch as the synthesis of eight-membered rings is particularly demanding, we first examined whether eight-membered lactones might be formed by $[Rh(CO)_2Cl]_2$-catalyzed cyclizations. In the event, treating the β-ketoester **10** with $[Rh(CO)_2Cl]_2$ in DMF at 0 °C provided lactone **11** in 68% yield (Figure 4); none of the corresponding six-membered lactone was observed. To the best of our knowledge, this represents the first example of forming an

(14) Bhatia, B.; Reddy, M. M.; Iqbal, J. *Tetrahedron Lett.* **1993**, *34*, 6301.
(15) (a) Huntzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 2918. (b) Sjogren, M. P. T.; Hansson, S.; Akermark, B. *Organometallics* **1994**, *13*, 1963. (c) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802.
(16) Frisell, H.; Akermark, B. *Organometallics* **1995**, *14*, 561.
(17) (a) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005. (b) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636.
(18) Poli, G.; Scolastico, C. *Chemtracts: Org. Chem.* **1999**, *12*, 837.
(19) (a) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399. (b) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235. (c) Lloyd-Jones, G. C.; Stephen, S. C.; Murray, M.; Butts, C. P.; Vyskocil, S.; Kocovsky, P. *Chem. Eur. J.* **2000**, *6*, 4348. (d) Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Vyskocil, S.; Kocovsky, P. *Chem. Eur. J.* **2002**, *8*, 4443.

(20) Enantiomeric excess was determined by HPLC analysis with a chiral stationary phase column [Chiracel OD or AD].
(21) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469.
(22) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (c) Trost, B. M.; Vos, B. A.; Brzezowski, C. M.; Martina, D. P. *Tetrahedron Lett.* **1992**, *33*, 717.



10 11

Figure 4. Intramolecular $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation.

eight-membered lactone by an intramolecular, transition metal-catalyzed allylic alkylation of a β-ketoester. When this same reaction was conducted using $Pd(PPh_3)_4$ as the catalyst, a mixture (60:40) of eight- and six-membered lactones was obtained.

In summary, we have discovered that $[Rh(CO)_2Cl]_2$, a commercially available catalyst that may be easily used without special precautions to exclude oxygen, catalyzes allylic alkylations under mild and ligandless conditions. Reactions involving unsymmetrical substrates, including those with internal double bonds, proceed efficiently, rapidly, and regioselectively at the carbon atom bearing the leaving group. The substitution also proceeds stereoselectively with retention of double-bond geometry and tetrahedral chirality. The potential utility of $[Rh(CO)_2Cl]_2$ as a catalyst for promoting allylic alkylations is illustrated by the cyclization of **10** to deliver the eight-membered lactone **11**. Because $[Rh(CO)_2Cl]_2$ is known to catalyze other transformations, a number of synthetic applications may be envisaged in which allylic alkylations are combined with other transformations, resulting in cascade processes to rapidly assemble complex structures. Experiments to elucidate the mechanistic details, scope, and utility of $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions, especially in tandem reactions, are in progress and will be reported in due course.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences (GM 31077), the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research.

Supporting Information Available: Copies of ^1H NMR spectra are provided for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0496529