Conservation of Absolute Configuration in the Acyclic Rhodium-Catalyzed Allylic Alkylation Reaction: Evidence for an *Enyl* ($\sigma + \pi$) Organorhodium Intermediate

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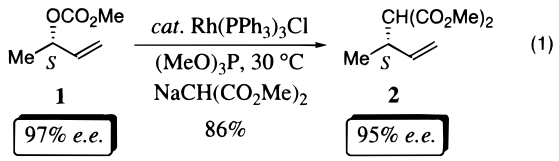
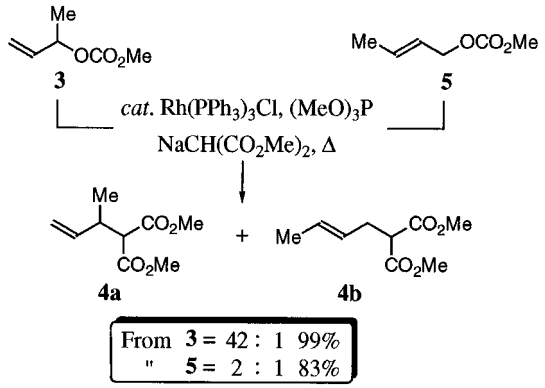
The allylic alkylation reaction represents a powerful method for carbon−carbon bond formation.[1] However, despite the wide range of substrates and organometallic complexes that have been employed, a general procedure for the retention of absolute configuration has not been forthcoming.[2,3] We recently demonstrated that Wilkinson's catalyst, [$Rh(PPh_3)_3Cl$], may be modified *in situ* to furnish a catalytically active species that facilitates the allylic alkylation of a series of racemic acyclic allylic carbonates in high yield and with excellent selectivity, favoring the *more substituted product.*[4] In this communication, we describe the first example of the asymmetric rhodium-catalyzed allylic alkylation of an enantiomerically enriched acyclic allylic carbonate **1**, with essentially complete retention of absolute configuration (eq 1). *This work also provides direct mechanistic evidence for an enyl*[5] *organorhodium species to explain the conservation of stereochemistry in the alkylation product* ***2****, and thus represents a novel method for acyclic stereocontrol.*



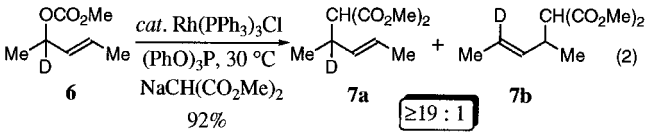
(1)

Treatment of the secondary carbonate **3** with the sodium enolate of dimethyl malonate in the presence of a catalytic amount of Wilkinson's catalyst modified with trimethyl phosphite furnished the primary and secondary substituted derivatives **4a**/**4b** in excellent yield, as a 42:1 mixture of regioisomers, in favor of **4a** (Scheme 1). However, the isomeric primary allylic carbonate **5** under analogous reaction conditions gave a substantially reduced product ratio (2:1), albeit favoring the secondary product **4a**. This result was rather intriguing, since it implied that both reactions were either not proceeding through the same π-allyl type intermediate, or the initial σ-complex was relatively slow to undergo the conventional $\sigma-\pi-\sigma$ allylic isomerization[1] relative to the rate of kinetic alkylation.

Scheme 1



To probe the origin of this rather intriguing difference, the rhodium-catalyzed allylic alkylation of the deuterated allylic carbonate **6** was examined. Treatment of **6**, in which both allylic positions are sterically equivalent, with the triphenyl phosphite modified Wilkinson's catalyst and the sodium salt of dimethyl malonate furnished the allylic alkylation product **7a** in 92% yield with ≥19:1 selectivity (eq 2). *This result strongly suggests that the rhodium allylic alkylation proceeds through a σ- rather than a π-complex in which the σ−π−σ isomerization process is slow compared to malonate displacement.*[2,7]



(2)

We reasoned that the rate of isomerization may be influenced by either the steric enviroment imposed by the alkyl substituents at either end of the allylic system and/or the degree of substitution of the organorhodium intermediate (2° vs 1°; see Scheme 2). To test this hypothesis, the unsymmetrical secondary carbonates **8a**/**b** were prepared, and treatment of **8a** under the standard reaction conditions (eq 3) furnished the allylic alkylation products **9a**/**b** in 83% yield, favoring **9a** (97:3). Treatment of the isomeric carbonate **8b**, under the analogous conditions, gave the alternative regioisomer **9b** as the major product (97:3) in 87% overall yield. Hence, these results provide additional evidence for a σ-complex rather than the more commonly observed π-complex, as the latter would be expected to furnish **9a** as the major product in both cases.[1,8] Furthermore, it appears the organorhodium intermediate is tolerant of a sterically congested enviroment and that it is the relative substitution of the organorhodium intermediate with respect to the termini of the allyl group that influences the rate of isomerization.

(1) For a recent review on the transition metal-catalyzed allylic alkylation, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and pertinent references therein.

(2) For lead references on other transition metal-catalyzed allylic alkylation reactions: see (a) Co: Bhatia, B.; Reddy, M. M.; Iqbal, J. *Tetrahedron Lett.* **1993**, *34*, 6301. (b) Fe: Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974. (c) Ir: Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263. (d) Mo: Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 897. (e) Ni: Bricout, H.; Carpentier, J.-F.; Mortreux, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1863. (f) Pt: Brown, J. M.; McIntyre, J. E. *J. Chem. Soc., Perkin Trans. 2* **1985**, 961. (g) Ru: Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945. (h) W: Lloyd-Jones, G. C.; Pfalz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462 and pertinent references therein.

(3) For the first example of a Rh-catalyzed allylic alkylation, see: Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269. We are not aware of any other reports of Rh-catalyzed allylic alkylations.

(4) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *38*, 1725.

(5) Enyl complexes are by definition those which contain discreet σ- and π-metal carbon interactions within a single ligand.[6a] Enyl complexes have been characterized by proton NMR,[6b] infrared,[6b] and *X*-ray[6c] crystallography.

(6) (a) Sharp P. R. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Chapter 2, p 272. (b) Lawson, D. N.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1733. (c) Tanaka, I.; Jin-no, N.; Kushida, T.; Tsutsui, N.; Ashida, T.; Suzuki, H.; Sakurai, H.; Moro-oka, Y.; Ikawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 657 and pertinent references therein.

(7) Iridium has also been reported to demonstrate high regioselectivity in the allylic alkylation reaction.[2c] However, treatment of the deuterium-labeled allylic carbonate **6** under the reported reaction conditions furnished the allylic alkylation products **7a**/**b** in modest yield as a 2:1 mixture of regioisomers.

(8) Treatment of *both* the isomeric allylic carbonates **8a**/**b** under analogous conditions in the presence of a catalytic amount of $Pd(PPh_3)_4$ furnished **9a** as the major product (≥19:1) in both cases. Hence, if the rhodium reaction was proceeding through a π-allyl type intermediate, **9a** would be expected *vide infra*.

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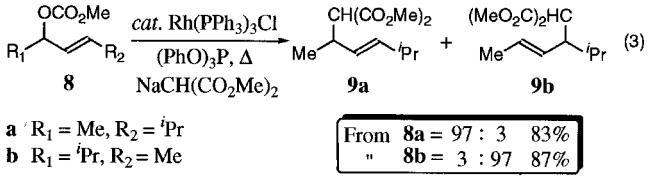
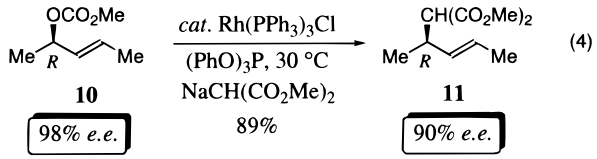
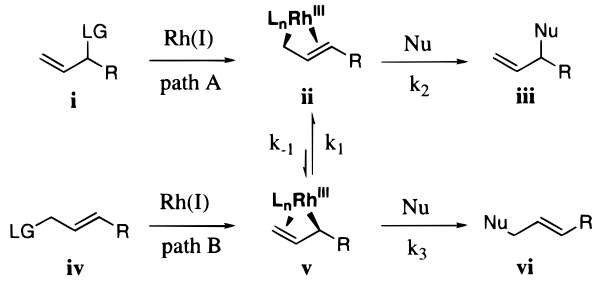


To clarify the stereochemical outcome of this reaction, and provide additional evidence in support of this hypothesis, the enantiomerically enriched allylic carbonate **10** was subjected to the reaction. Treatment of **10** under standard conditions furnished the allylic alkylation product **11** in 89% yield with 90% enantiomeric excess (eq 4). Hence, this experiment clearly demonstrates that the reaction proceeds with overall retention, suggesting a double inversion process,[9] with only 4% of the other enantiomer being formed.[10]



The enantiomerically enriched allylic carbonate **1** was expected to provide further evidence for a σ-organorhodium intermediate. Treatment of **1** under standard conditions furnished the allylic alkylation product **2** in 86% yield, with 95% enantiomeric excess (eq 1).[11] This remarkable result implies that the displacement proceeds through an *enyl*[5] intermediate, since the corresponding σ-species would have led to a significant amount of racemization, owing to rapid C−C bond rotation upon oxidative addition.

Scheme 2



Scheme 2 summarizes our current mechanistic hypothesis, which is consistent with the experimental results. In path A, treatment of the 2° allylic system **i** with rhodium presumably gives the *enyl* intermediate **ii**, which in the presence of the nucleophile undergoes a rapid S_N2' displacement, faster than isomerization to **v** ($k_2 > k_{-1}$), as exemplified by eq 1.[12] The formation of the *enyl* species explains the retention of stereochemistry. In path B, initial oxidative addition into the 1° allylic system **iv** furnishes the isomeric *enyl* **v**. The *enyl* organorhodium intermediate **v** is then influenced by its initial substitution, and undergoes isomerization to **ii** in competition with alkylation ($k_1 > k_3$), ultimately leading to a mixture of **iii** and **vi**. Hence, path A allows for net retention of the absolute configuration through the alkylation of a chiral Rh−*enyl* complex, while path B may be able to facilitate asymmetric catalysis, provided the rate of isomerization is faster than alkylation ($k_1 \gg k_3$).

In conclusion, we have delineated the mechanistic and stereochemical path for the rhodium-catalyzed allylic alkylation. We have also demonstrated the first example of the catalytic asymmetric rhodium-catalyzed allylic alkylation of enantiomerically enriched allylic carbonates, which proceeds with essentially complete retention of absolute configuration. This work provides direct mechanistic evidence for an *enyl*[5] organorhodium intermediate being responsible for the conservation of regio- and stereochemical information. This rhodium-based procedure is likely to provide a practical alternative to the more traditional transition metal-catalyzed methods, especially for transformations requiring the retention of absolute configuration.

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Supporting Information Available: Spectral data for all compounds (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(9) For an example of double inversion to give net retention of stereochemistry, see: Faller, J. W.; Linebarrier, D. *Organometallics* **1988**, *7*, 1670.

(10) The other enantiomer is presumably the result of isomerization of the organorhodium intermediate leading to alkylation from the other end of the allylic system.

(11) *Representative Experimental Procedure*: Trimethyl phosphite (12 μL, 0.1 mmol) was added directly to a red solution of Wilkinson's catalyst (23.6 mg, 0.026 mmol) in anhydrous THF (2.0 mL). The mixture was sonicated for 1−2 min, and then stirred at room temperature for ca. 10 min resulting in a light orange homogeneous solution. Dimethyl malonate (120 μL mg, 1.05 mmol) was added dropwise, via a 250 μL syringe, over ca. 5 min to a slurry of sodium hydride (60% w/w in mineral oil, 38 mg, 0.95 mmol) in anhydrous THF (2.0 mL), resulting in the evolution of H_2 gas. The optically active allylic carbonate **10** (65.8 mg, 0.51 mmol; 97% ee by capillary GC analysis) was then added dropwise, via a tared 250 μL syringe, to the preformed rhodium catalyst. The malonate solution was then added via Teflon cannula to this solution, rinsing with anhydrous THF (0.5 mL). The mixture was heated at 30 °C for ca. 2.5 h (TLC control). The reaction mixture was partitioned between diethyl ether and sequentially, 1.5 N aqueous NaOH and saturated aqueous NaCl. The organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 9:1 dichloromethane/pentane) furnished the allylic alkylation product **11** (80.9 mg, 86%) as a colorless oil, with 95% enantiomeric excess by capillary GC analysis with a Chiraldex TFA column.

(12) Oxidative addition via a direct S_N2 type process is unlikely based on the observation that increased alkene substitution in a series of primary carbonates leads to decreased reactivity, as illustrated below.