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Recognition and Catalysis in Allylic Alkylations

Christoph Gibson and Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and The Department of Chemistry, The Scripps Research Institute, MB-26, 10550 North Torrey Pines Rd., La Jolla, California 92037

jrebek@scripps.edu

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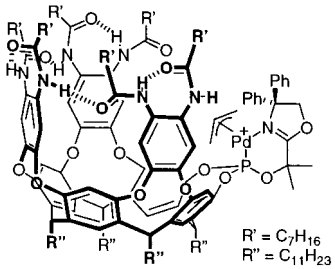
ABSTRACT



A cavitand outfitted with a chelated palladium atom catalyzes allylic alkylation reactions. Molecular recognition by the cavitand distinguishes between closely related structures and results in subtle substrate specificities.

One goal of modern physical organic chemistry is to merge molecular recognition with chemical catalysis. To that end, synthetic receptors have been furnished with appropriate functional groups,[1] with the idea of placing the functionality of the host near the resident guest. Placing functional groups on concave surfaces is challenging, but progress has been made with inwardly directed carboxyl groups[2] and porphyrin-containing macrocycles.[3] These show high affinities for complementary guests[4] and accelerate reactions not catalyzed by enzymes.[5] The synthesis and evaluation of a cavitand bearing a palladium catalyst near the guest site is reported here. The system expresses molecular recognition in its catalytic action.

The specific arrangement draws on the work of Pfaltz et al., who recently described the chiral palladium ligand **5** (Figure 1).[6] Palladium-catalyzed reactions of monosubstituted allylic substrates such as **1** or **2** with nucleophiles typically result in linear products (**3**).[7] In contrast, aryl-substituted allyl acetates (R = Ar) yield predominantly the branched isomer **4** ($Nu^- = HC(CO_2Me)_2^-$) with good regio- and enantioselectivities when compound **5** is employed as the palladium ligand.

Catalyst precursor *exo*-**7** features a diphenyl-substituted oxazoline attached to a cavitand. Such cavitands are capable of binding size- and shape-complementary molecules such as adamantanes.[8] The geminal phenyl groups of the oxazoline were expected to destabilize η^3-complex **B** as well as the transition states leading to this isomer (Figure 2). The pathway involving the η^3-complex **A** should dominate, as the residue R of the substrate is forced into the cavitand. Nucleophilic attack takes place preferentially at the allyl terminus trans to the Pd−P bond in such complexes,[9] and reaction at the unsubstituted allyl end should be favored.

(1) For recent reviews, see: (a) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (b) Motherwell, W. B.; Bingham, M. J.; Six, Y. *Tetrahedron* **2001**, *57*, 4663.

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(3) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2247.

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(8) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 12216.

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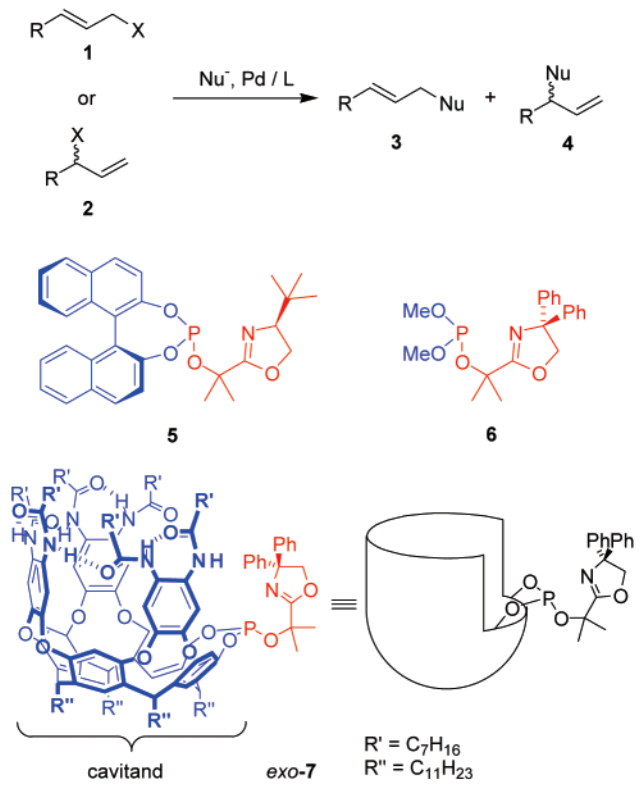


Figure 1. Palladium-catalyzed allylic alkylation. The design of supramolecular palladium ligand *exo*-**7** based on ligand **5**. Ligand **6** was used for control experiments.

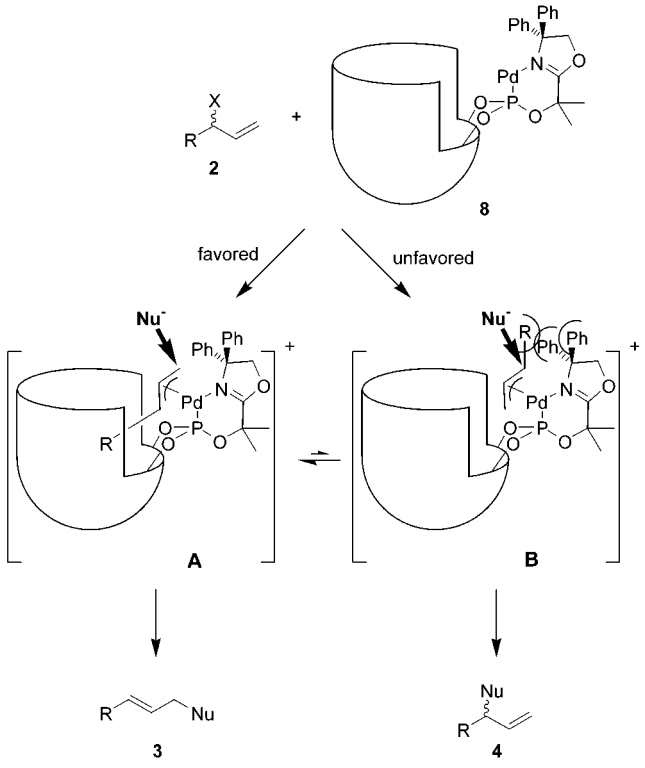


Figure 2. Predicted nucleophilic attack on the η^3-copmlexes **A** and **B**. The steric hindrance caused by the geminal phenyl groups of the oxazoline favors a reaction pathway involving η^3-complex **A** that results in the formation of the linear product **3**.

The synthesis of ligand *exo*-**7** is shown in Scheme 1. First, chlorophosphite **10** was generated in situ by treating diol **9**[10] with PCl_3 using pyridine as the base. The reaction of **10** with alcohol **11** in the presence of triethylamine yielded a 7:3 mixture of *exo*-**7** and *endo*-**7**, which could be separated by chromatography.[11] The presence of Et_3N proved essential for the selective formation of *exo*-**7** and implies that Et_3-NHCl occupies the interior of intermediate **10**[12] and the formation of the undesired isomer *endo*-**7** is suppressed. Both phosphites are configurationally stable up to 100 °C; at higher temperatures they decompose.

The reactions of substrates **2a**−**e** with dimethyl malonate were tested with cavitand *exo*-**7** and ligand **6** (Table 1). In all cases, the linear products **3a**−**e** were exclusively formed. Contrary to ligand **6**, the reaction rate varies significantly with different substrates when *exo*-**7** is employed as the palladium ligand. The conversion of substrates **2b** and **2c** was complete after 2 days, whereas the reaction of the bulkier substrates **2d** and **2e** were approximately four times slower. Remarkably, the smaller substrate **2a** exhibited the lowest reaction rate.

Competiton experiments interrogated the substrate specificity of *exo*-**7** (Table 2). The η^3-complexes of *exo*-**7** and **6** bear a single positive charge and are suited for study by electrospray mass spectrometry. The structural differences of the η^3-complexes are minor, so the relative abundances of their signals in the mass spectra were assumed to accurately reflect the solution concentrations of the allyl palladium species present in the reaction mixture. Surprisingly, after one turnover, the mass spectrum of a 1:1 mixture of substrates **2a** and **2b** in the presence of *exo*-**7** revealed a 91:9 distribution in favor of the **2a**-derived η^3-complex. After 4 days, the mixture of **2a** and **2b** yielded predominantly product **3a**, although substrate **2b** showed an overall reaction rate substantially higher than that of **2a** (compare Table 1). These data suggest that palladium(0) species **8** forms the η^3-complex more quickly with substrate **2a**, but this complex is practically inert to nucleophilic attack by the malonate. Substrate **2a** is an *inhibitor* of catalyst **8**. Model ligand **6** showed the same preference for substrate **2a** without inhibitory effects. Substrate **2b** also adds more rapidly to the

(9) (a) Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523. (b) Brown, J. M.; Hulmes, D. J.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (c) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031.

(10) Renslo, A. R.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 7459.

(11) The structural assignment is mainly based on the capability of binding guest molecules, which was determined by means of ^{1}H NMR in $C_6D_5CD_3$. Cavitand *exo*-**7** showed with an association constant K_{ass} of approximately 100 M^{-1} a distinct affinity to *N*-adamant-1-yl-3-*p*-tolyl-acrylamide. In the case of *endo*-**7**, however, no encapsulation could be detected, which indicates that the cavity of this stereoisomer is blocked by the introversive oxazoline.

(12) Ma, S.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 2600.

Scheme 1

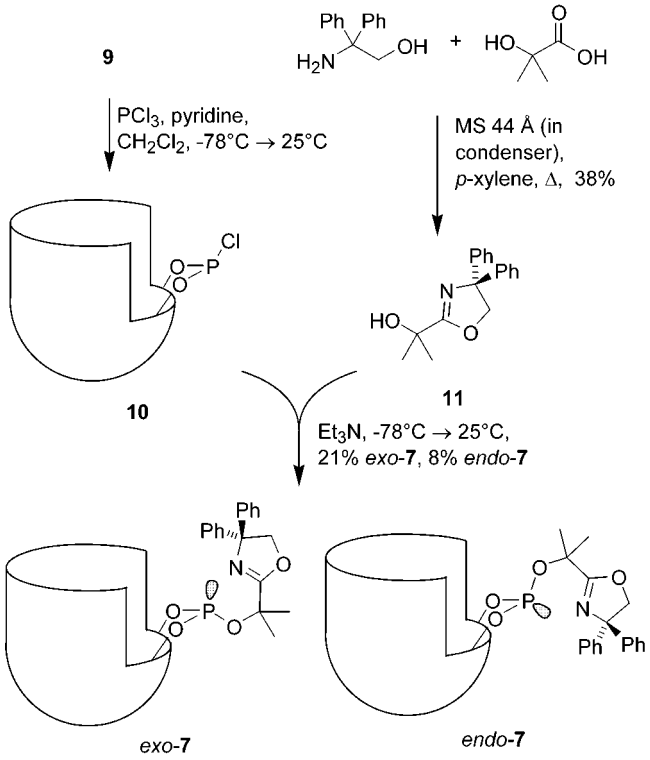
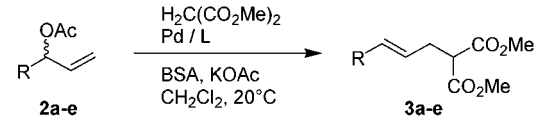
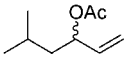
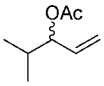
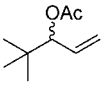
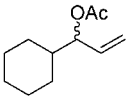
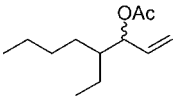


Table 1. Allylic Alkylation of Various Substrates **2a**−**e** Using Ligands *exo*-**7** or **6**[a]



substrate		ligand *exo*-**7** (L) reaction time	ligand *exo*-**7** (L) yield	ligand **6** (L) reaction time	ligand **6** (L) yield
	**2a**	6 d[b]	38%	2 h	85%
	**2b**	2 d	76%	2 h	91%
	**2c**	2 d	96%	2 h	81%
	**2d**	6 d[b]	74%	2 h	78%
	**2e**	6 d[b]	60%	2 h	82%

[a] Using 1.4 mol % $[Pd(C_3H_5)Cl]_2$, 3.2 mol % L, 3 equiv of $CH_2(CO_2Me)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA). [b] Substrate was not completely converted.

palladium(0) species than the allyl acetate **2c**. The rate of the oxidative addition depends on the connectivity of the homoallylic carbon atom; it decreases in the order **2a** (secondary) > **2b** (tertiary) > **2c** (quaternary).

To address this connectivity effect, we examined substrates **2b**, **2d**, and **2e**, all of which represent a tertiary carbon atom in the homoallylic position (Table 2 and Figure 3). Pairwise comparison of these substrates with palladium ligand **6** showed no significant difference in reaction rates for either the oxidative addition or the overall reaction. Competition experiments of **2b** and **2d** with *exo*-**7** showed, after ap-

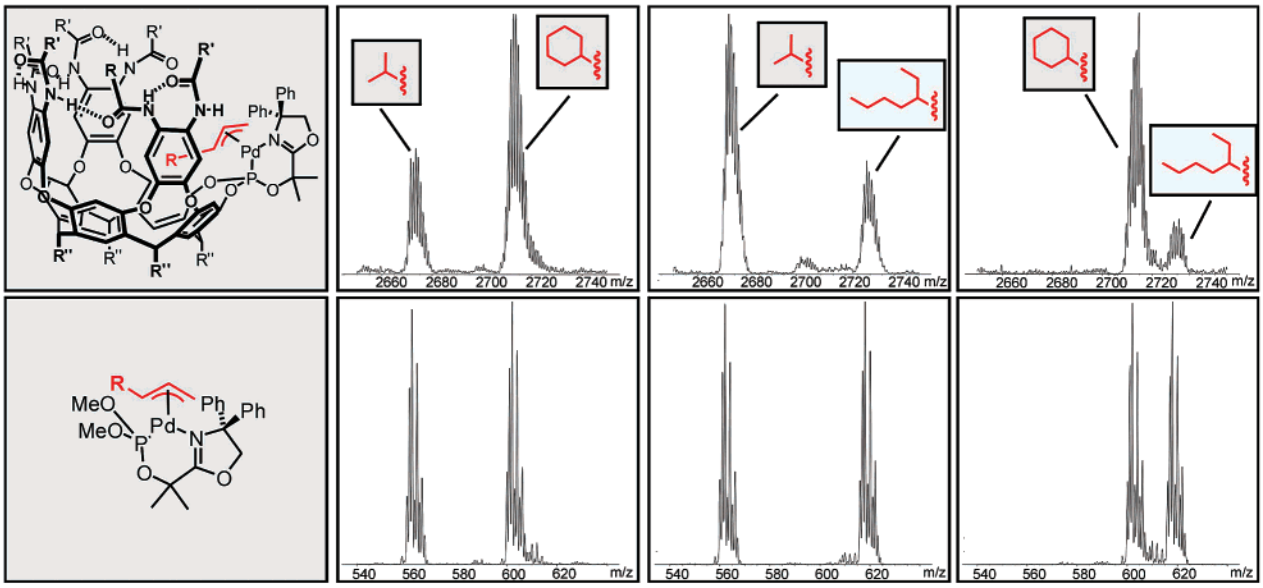


Figure 3. Mass spectrometric analysis of reaction mixtures containing an equimolar amount of two substrates after one turnover using palladium ligands *exo*-**7** (upper row) or **6** (lower row).

Table 2. Allylic Alkylation of Various Substrates **2a**−**e** Using Ligands *exo*-**7** or **6**[a]

	ligand *exo*-**7** (L)			ligand **6** (L)		
substrates	ratio of η^3-complexes[b]	yield[c] (time)	product distribution[d]	ratio of η^3-complexes[e]	yield (time)	product distribution[d]
2a and **2b**	**2a**:**2b** 91:9	20% (4 d)	**3a**:**3b** 85:15	**2a**:**2b** 96:4	36% (80 min)	**3a**:**3b** 87:13
2b and **2c**	**2b**:**2c** 95:5	35% (2 d)	**3b**:**3c** 91:9	**2b**:**2c** 99:1	61% (80 min)	**3b**:**3c** 98:2
2b and **2d**	**2b**:**2d** 32:68	32% (2 d)	**3b**:**3d** 29:71	**2b**:**2d** 48:52	46% (80 min)	**3b**:**3d** 42:58
2b and **2e**	**2b**:**2e** 70:30	35% (2 d)	**3b**:**3e** 67:33	**2b**:**2e** 49:51	58% (80 min)	**3b**:**3e** 52:48
2d and **2e**	**2d**:**2e** 87:13	29% (2 d)	**3d**:**3e** 86:14	**2d**:**2e** 50:50	64% (80 min)	**3d**:**3e** 47:53

[a] For experimental conditions, see Table 1. [b] Determined by mass spectrometry after 2 h. [c] Calculated by halving the sum of the individual yields of both products. [d] Determined by ^{1}H NMR after workup. [e] Determined by mass spectrometry after 20 min.

proximately one turnover, a 32:68 distribution in favor of the substrate **2d**-derived η^3-complex. The mass spectrum of substrates **2b** and **2e** showed nearly the same ratio, but the allyl acetate **2b** was favored. The mass spectrum of a mixture of **2d** and **2e** revealed a considerable substrate specificity of 87:13 in favor of **2d**. The ability of catalyst **8** to stabilize the transition state of the oxidative addition decreases in the order cyclohexyl (**2d**) > *iso*-propyl (**2b**) > 1-ethyl pentyl (**2e**). The selectivity in product formation of **3b**, **3d**, and **3e** correlates strongly with the substrate specificity, associated with the oxidative addition. This result underscores the potential of cavitand-containing catalysts in organic synthesis.

In summary, the palladium complex of a cavitand receptor catalyzes allylic alkylations and exhibits a subtle substrate specificity that distinguishes between closely related structures. These properties encourage further development of cavitands as regio- and enantioselective catalysts.

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Supporting Information Available: Representative experimental procedures and selected spectral characterization for the compounds reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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