Chemically Modified β-Cyclodextrins as Supramolecular Carriers in the Biphasic Palladium-Catalyzed Cleavage of Allylic Carbonates: Activity Enhancement and Substrate-Selective Catalysis

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Catalytic amounts of chemically modified β-cyclodextrins allowed us to achieve, in high yields, the deprotection of various water-insoluble allylic carbonates in a genuine two-phase system without co-solvent. The catalytic activities were up to 300 times higher than those observed without modified cyclodextrins. The process of molecular recognition between the cyclodextrin and the substrate allowed us to perform substrate-selective catalytic reactions which cannot be achieved in homogeneous or biphasic media with conventional transition metal catalysts.

Introduction

Cyclodextrins (CyD) are cyclic oligosaccharides composed of six, seven or eight glucose units linked by an α-(1−4) glucosidic bond and have traditionally been designated as α-CyD, β-CyD or γ-CyD, respectively. These water-soluble molecules have a large intramolecular cavity which is essentially hydrophobic and which can host a large variety of organic molecules.[1] This outstanding property has been utilized for a long time in the food, cosmetic and pharmaceutical industries and still finds new potential applications.[2] For instance, the use of CyDs as inverse phase-transfer catalysts has recently been reported in reactions involving aqueous/organic two-phase systems.[3] In this particular application, the CyD forms an inclusion complex with the substrate in the organic phase or in the liquid boundary layer at the liquid/liquid interface, and then moves into the aqueous phase where it reacts with a hydrophilic molecule or salt. After reacting, the reaction product is released into the organic phase and the transfer cycle can continue.

Our continuing interest in the use of chemically modified CyDs as inverse phase-transfer catalysts in biphasic reactions involving water-soluble transition-metal catalysts led us to examine the effect of such supramolecular carriers on the palladium-catalyzed cleavage of water-insoluble allylic carbonates.[4]

The removal of an allyloxycarbonyl group from allylic carbonates in an aqueous/organic medium is a well-known process which could find interesting applications in the synthesis of peptides. The reaction is catalyzed by a water-soluble palladium/triphenylphosphane trisulfonate complex and occurs under mild conditions.[5] However, in the case of highly water-insoluble substrates, the reaction rates are low and large amounts of co-solvent are required which usually prevents the quantitative recovery of the catalytic system.

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Results and Discussion

Preliminary studies have been realized with allyl undecyl carbonate as a water-insoluble model substrate. As depicted in Figure 1, the deprotection rate of this substrate is low without a mass-transfer promoter (initial activity: 0.03 h^{-1}; conversion after 24 hours: 3%).

Interestingly, the addition of a CyD into the reaction medium improved the catalytic activity. As shown in Figure 1, best results are obtained with chemically modified β-CyDs. Indeed, whereas the initial catalytic activity was increased by a factor of about 20 in the presence of α-, β-, or γ-CyD, the most effective catalyst, dimethyl-β-cyclodextrin (DMCyD), induced a rate enhancement of 300 and the conversion was completed after 3 hours. It is worth mentioning that we have never observed such large rate increases in our previous studies. Indeed, the best catalytic enhancements in hydrocarboxylation, hydroformylation, hydrogenation and Wacker oxidation involved factors of 7, 9, 14 and 24, respectively.[4] Control experiments conducted with methyl-α-glucopyranoside and maltoheptaose (compounds which have the same subunits as the CyDs but which do not possess a lipophilic host cavity) confirm that a process of molecular recognition must operate to perform the reaction, and that enhancement of the catalytic activity cannot be attributed to a co-solvent effect of the CyDs. Moreover, the poor effect of amylose − a linear polymer of D-glucose which can adopt helical conformations with six or seven glucose units per turn − also suggests that the formation of stable inclusion complexes is crucial to achieve the deprotection. Indeed, amylose is a linear oligosaccharide which cannot strongly encapsulate the organic compounds.[6] The activity of the chemically modified CyD is strikingly dependent on the nature of the substituent group and on the degree of substitution of the CyD. Thus, 2-hydroxypropyl or 2-hydroxyethyl CyDs exhi-

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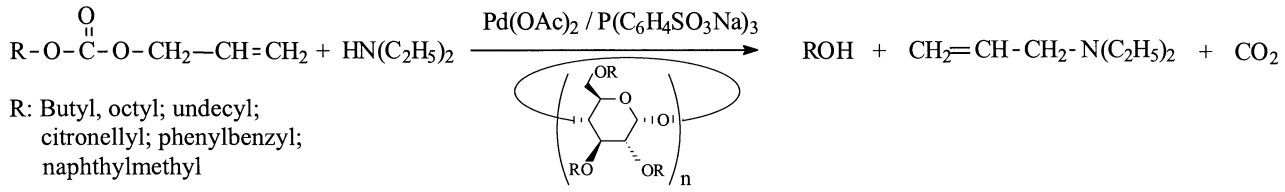

Scheme 1. Cleavage of various allylic carbonates in the presence of chemically-modified cyclodextrins

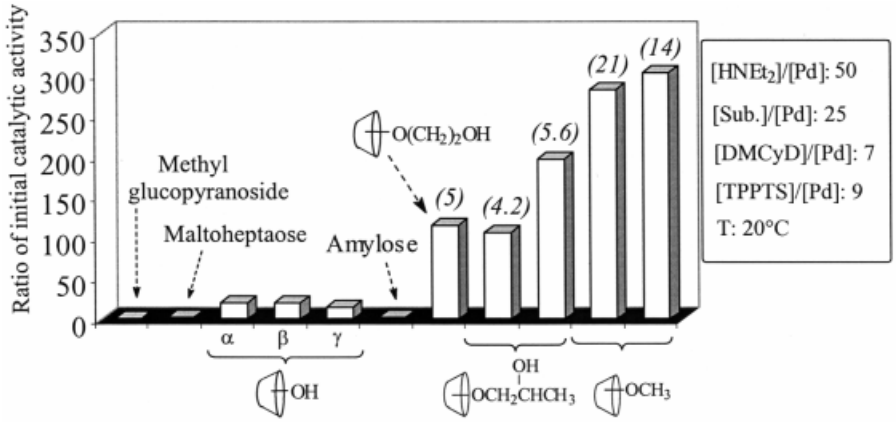

Figure 1. Effect of various acyclic oligosaccharides and cyclodextrins on the cleavage rate of allyl undecyl carbonate in a two-phase system; the chemically modified CyDs are schematically represented by a hollow truncated cone; the value in brackets corresponds to the average number of substituted hydroxyl group of the CyD; the ratio of initial catalytic activities is defined as the ratio between the initial catalytic activity in the presence of CyD and the initial catalytic activity without CyD

bited a much lower activity than the methylated derivatives of the β-CyD. With the methylated CyDs, the molecular recognition between the undecyl allyl carbonate and the host cavity is probably better. Another possible explanation could be a weaker inhibition of the CyD catalysis by the undecanol which is produced in the reaction course. Indeed, in supramolecular catalysis, product inhibition is always a potential problem. Finally, it must be pointed out that the reaction mixture is strictly biphasic, separates readily, and can be recycled four times without loss of catalytic activity.

Figure 2 shows that the nature of the substrates significantly affects the catalytic efficiency of the DMCyD. As expected, the beneficial effect of the DMCyD is less marked with substrates which do not possess a lipophilic group which fits well into the host cavity of the CyD or which are slightly soluble in water. For instance, the cleavage rate of allyl butyl carbonate, allyl octyl carbonate and allyl citronellyl carbonate is only increased by factors of 4, 40 and 160, respectively.

The difference in reactivity of phenylbenzyl allyl carbonate isomers and naphthylmethyl allyl carbonate isomers

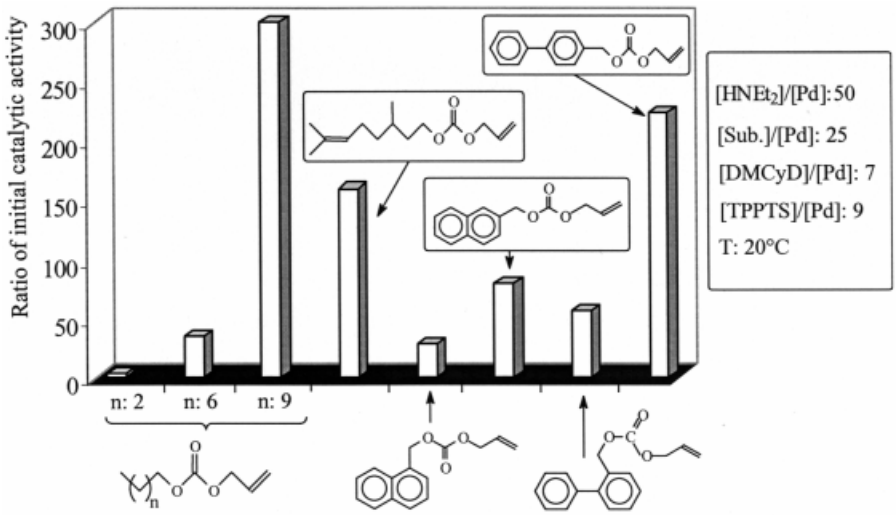

Figure 2. Ratio of initial catalytic activities as a function of the nature of the allylic carbonate; the ratio of initial catalytic activities is defined as the ratio between the initial catalytic activity in the presence of DMCyD and the initial catalytic activity without DMCyD

must also be pointed out. Indeed, the conversion of *p*-phenylbenzyl allyl carbonate is four times faster than that of *o*-phenylbenzyl allyl carbonate although these two coumpounds have the same solubility in water. Similar results have also been observed with naphthylmethyl allyl carbonates. The conversion rate of β-naphthylmethyl allyl carbonate is three times faster than that of α-naphthylmethyl allyl carbonate.

The difference in reactivity observed between the two isomers suggests that the chemically modified CyDs can be used to perform substrate-selective catalytic reactions. This possibility was established unequivocally using competitive experiments. In these experiments, the deprotection of a 50/50 mixture of *o*-phenylbenzyl allyl carbonate and *p*-phenylbenzyl allyl carbonate was carried out with a normal co-solvent (acetonitrile) or with the DMCyD.[7] The ratio of the products *p*-phenylbenzyl alcohol and *o*-phenylbenzyl alcohol, as determined by chromatography, was used as a measure of substrate selectivity. As expected, no substrate selectivity was observed in a control experiment in which acetonitrile was used as the mass-transfer promotor (50:50 product ratio). In contrast, the use of DMCyD as mass-transfer promotor led to a substantial substrate selectivity: a product ratio of 82:18 was observed in the initial stages of the reaction. These two experiments show that the substrate selectivity cannot be attributed to a different reactivity of the water-soluble palladium catalyst towards the substrate, but rather to a subtle process of molecular recognition between the DMCyD and the substrate. In fact, the β-naphthylmethyl allyl carbonate and *p*-phenylbenzyl allyl carbonate fit better in the DMCyD cavity than the α-naphthylmethyl allyl carbonate and the *o*-phenylbenzyl allyl carbonate.[1c]

Conclusion

The process of molecular recognition between the cyclodextrin and the substrate opens up new reaction possibilities which cannot easily be achieved in homogeneous or biphasic media with conventional transition metal catalysts. Further studies are currently under way in our laboratory to achieve the mono-deprotection of a doubly protected substrate by using a suitable chemically modified CyD.

Experimental Section

General: The chemically modified CyDs were supplied by Roquette Frères (Lestrem, France), Cyclolab (Budapest, Hungary) or Aldrich Chemical and were used as received without further purification. Palladium acetate and organic compounds were purchased from Strem Chemicals, Aldrich Chemical or Acros Organics in their highest purity and used without further purification. Commercially unavailable carbonates were synthesized from the corresponding alcohols by reaction with allyl chloroformate in a mixture of THF/pyridine.[5c] Trisodium tris(*m*-sulfonatophenyl)phosphane (TPPTS) was synthesized as reported by Gärtner et al.[8] All the catalytic reactions were performed under nitrogen using standard Schlenk techniques. Solvents and liquid reagents were degassed by bubbling nitrogen for 15 min, or by two freeze-pump-thaw cycles, before use.

General Procedure for the Deprotection of Carbonates: $Pd(OAc)_2$ (0.067 mmol, 15 mg), TPPTS (0.60 mmol, 0.34 g), chemically modified β-CyD (0.47 mmol) and water (3 g) were introduced under nitrogen into a Schlenk tube. After stirring for 1 h, the yellow solution was transferred into a mixture of carbonate (1.67 mmol), diethylamine (3.34 mmol, 0.24 g), heptane or toluene (3 g), and dodecane as internal standard (0.14 g). The medium was stirred at 1000 rpm at 20°C and the reaction was monitored by quantitative gas chromatographic analysis of aliquot samples of the organic layer.

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[7] The competitive experiments were conducted as described in the experimental section except that a mixture of *o*-phenylbenzyl allyl carbonate (0.835 mmol, 0.225 g) and *p*-phenylbenzyl allyl carbonate (0.835 mmol, 0.225 g) was used. In the control experiment, 0.61 g of acetonitrile was added to the reaction medium in place of DMCyD.

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