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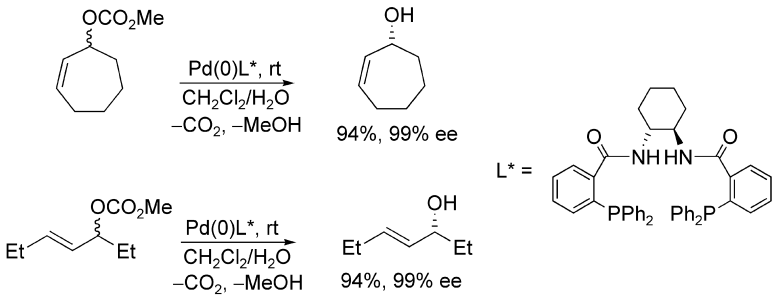


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# Palladium-Catalyzed Deracemization of Allylic Carbonates in Water with Formation of Allylic Alcohols: Hydrogen Carbonate Ion as Nucleophile in the Palladium-Catalyzed Allylic Substitution and Kinetic Resolution

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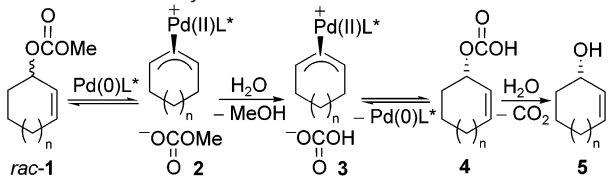
The complete conversion of a racemate to one enantiomer without intermediate separation of materials (deracemization) is one of the current challenges in asymmetric synthesis.[1] In particular, deracemization processes using abiotic chiral catalysts are much sought after. Allylic alcohols are targets of high synthetic importance because of their many applications.[2] Their deracemization[3,4] has been achieved by two methods. The first involves a dynamic kinetic resolution mediated by lipases and achiral transition metal catalysts.[5] While this method is very effective for acyclic allylic alcohols, it is less suited for cyclic substrates, and it requires the application of two catalysts. The second features a palladium(0)-catalyzed substitution of symmetrically substituted allylic esters with carboxylate ions in the presence of a chiral ligand for the palladium atom.[6] While this method gives high enantioselectivities for cyclic allylic esters, it has not yet been applied to symmetrically substituted acyclic esters. Furthermore, fine-tuning of the reaction conditions is required in order to avoid racemization of the product ester since it can also serve as a substrate for the catalyst.

It occurred to us that, by choosing a cyclic or an acyclic racemic allylic carbonate as the substrate and utilizing water as part of the reaction medium, the palladium-catalyzed allylic substitution could perhaps be turned into a facile deracemization of cyclic and acyclic allylic carbonates, leading to allylic alcohols. Racemic methyl carbonates of type *rac*-**1** are known to react with a chiral palladium catalyst with formation of the $\pi$-allyl palladium complex **2**, containing a methyl carbonate ion (Scheme 1).[7] In the presence of water, **2** should form the $\pi$-allyl palladium complex **3**, containing the hydrogen carbonate ion.[8a,b] We speculated that the hydrogen carbonate ion in turn could substitute the $\pi$-allyl palladium ion of **3**, resulting in the allylic hydrogen carbonate **4**, which should decompose in water with formation of the allylic alcohol **5** and $CO_2$.[8c,d] Moreover, the allylic carbonate-to-allylic alcohol transformation would be rendered irreversible. A prerequisite for the attainment of **5** with high ee values is that the decomposition of **4** is faster than the re-formation of **3**. The advantages of this method are that it would require only water and no external nucleophile and would give directly the allylic alcohol.

We were pleased to see that, in a test experiment, treatment of the racemic cyclohexenyl carbonate *rac*-**1b** with 2 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) and 16 mol % of $PPh_3$ in a mixture of water and $CH_2Cl_2$ furnished, after 24 h, the racemic allylic alcohol *rac*-**5b** in 96% yield (Scheme 2). Having demonstrated the feasibility of this concept, we studied reactions using **BPA**[9] as ligand for the palladium atom. To our delight, a similar treatment of *rac*-**1b** with $Pd_2(dba)_3{\cdot}CHCl_3$ and **BPA** in water/$CH_2Cl_2$ gave alcohol **5b** with 97% ee in high yield (Table 1, entry 2). Extension of the deracemization to the cycloheptenyl carbonate *rac*-**1c** under similar conditions afforded the allylic alcohol **5c** with ≥99% ee in high yield (entry 3). The deracemization of the cyclopentenyl carbonate was high yielding but less selective.

***Scheme 1.*** Proposed Mechanism of the Palladium-Catalyzed Deracemization of Allylic Carbonates in Water[a]




[a] The same scheme is proposed for racemic symmetrically substituted acyclic carbonates. L* = chiral ligand.

***Scheme 2.*** Palladium-Catalyzed Deracemization of Cyclic Allylic Carbonates in Water/$CH_2Cl_2$

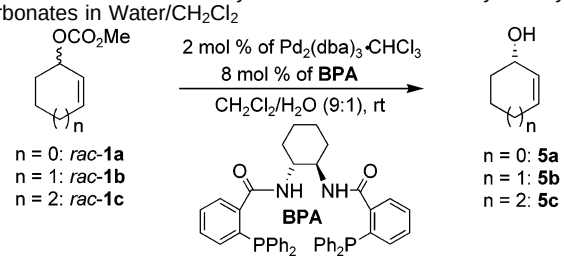
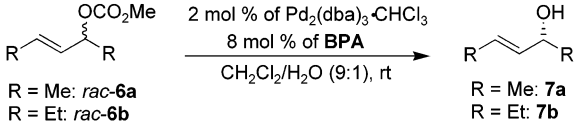



***Table 1.*** Palladium-Catalyzed Deracemization of Allylic Carbonates

| entry | substrate | time, h | alcohol | yield, %[a] | ee, %[b] |
|---|---|---|---|---|---|
| 1 | *rac*-**1a** | 16 | **5a** | 91 | 43 |
| 2 | *rac*-**1b** | 24 | **5b** | 94 | 97 |
| 3 | *rac*-**1c** | 52 | **5c** | 94 | ≥99 |
| 4 | *rac*-**6a** | 22 | **7a** | 80 | 89 |
| 5 | *rac*-**6b** | 24 | **7b** | 94 | ≥99 |

[a] Isolated yield. [b] Determined by GC on chiral stationary phase.

***Scheme 3.*** Palladium-Catalyzed Deracemization of Acyclic Allylic Carbonates in Water/$CH_2Cl_2$




Treatment of *rac*-**1a** with $Pd_2(dba)_3{\cdot}CHCl_3$ and **BPA** in water/$CH_2Cl_2$ gave the allylic alcohol **5a** with only 43% ee in high yield (entry 1). However, a more efficient deracemization of the corresponding acetate could be achieved by using the hydrogen carbonate ion as an external nucleophile (vide infra).

Fortunately, this deracemization method, which features a scission of the C−OCO bond of the allylic ester, could also be extended to acyclic carbonates (Scheme 3). Treatment of the racemic pentenyl carbonate *rac*-**6a** with $Pd_2(dba)_3{\cdot}CHCl_3$ and **BPA** in water/$CH_2Cl_2$ furnished the allylic alcohol **7a** with 89% ee in 80% yield (entry 4). Deracemization of the heptenyl carbonate *rac*-**6b** under similar conditions afforded the allylic alcohol **7b** with ≥99% ee in high yield (entry 5).



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***Scheme 4.*** Palladium-Catalyzed Kinetic Resolution and Deracemization of Cyclic Allylic Acetates with $KHCO_3$

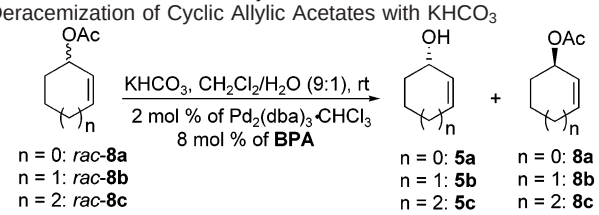


***Table 2.*** Palladium-Catalyzed Kinetic Resolution and Deracemization of Cyclic Allylic Acetates with $KHCO_3$

| | | | | acetate | | alcohol | |
|---|---|---|---|---|---|---|---|
| entry | substrate | time, h | convn, %[a] | yield, %[b] | ee, %[c] | yield, %[b] | ee, %[c] |
| 1 | *rac*-**8a** | 18 | 100 | | | 89 | 88 |
| 2 | *rac*-**8b** | 48 | 49 | 48 | 72 | 46 | 94 |
| 3 | *rac*-**8c** | 56 | 50 | 48 | 67 | 45 | ≥99 |

[a] Determined by GC. [b] Isolated yield. [c] Determined by GC on chiral stationary phase.

The results described thus far did not allow us to exclude the possibility that water or the hydroxide anion and not the hydrogen carbonate ion is the nucleophile reacting with the $\pi$-allyl palladium ion. Therefore, a number of test experiments were carried out with the cyclopentenyl acetate *rac*-**8a** (Scheme 4). Treatment of *rac*-**8a** with $Pd_2(dba)_3{\cdot}CHCl_3$ and **BPA** in water/$CH_2Cl_2$ did not lead to the formation of the allylic alcohol **5a**; the acetate was recovered in practically quantitative yield. This was not surprising, since water is known to be a very poor nucleophile in palladium-catalyzed allylic substitution.[10] Having observed no reaction of *rac*-**8a** in water, we repeated the experiment, but this time in the presence of 1.4 equiv of $KHCO_3$. This measure led to the isolation of **5a** with 88% ee in 89% yield (Table 2, entry 1). Since an aqueous solution of $KHCO_3$ (1.75 M) has a pH of 8.2, the hydroxide ion could have also acted as the nucleophile. This hypothesis was tested by submitting acetate *rac*-**8a** to catalysis in water of a similar pH but omitting $KHCO_3$. Mixtures of *rac*-**8a**, $Pd_2(dba)_3{\cdot}CHCl_3$, **BPA**, and $CH_2Cl_2$ were treated with either $H_2O/NaH_2PO_4/Na_2HPO_4$ of pH 8.2 or $H_2O$/NaOAc of pH 8.4. In both cases, formation of **5a** could not be observed, and the acetate was recovered. These results show that the hydrogen carbonate ion acts as the nucleophile and provide strong evidence for the deracemization of allylic carbonates with formation of the corresponding allylic alcohols, as proposed in Scheme 1.

The formation of **5a** with 88% ee in the palladium-catalyzed reaction of acetate *rac*-**8a** with aqueous $KHCO_3$ is remarkable. Treatment of carbonate *rac*-**1a** with water alone gave the allylic alcohol with only 43% ee. To see whether the added nucleophile is responsible for this difference in selectivity, the reaction of *rac*-**1a** in water was repeated, but this time with the addition of 1.4 equiv of $KHCO_3$. Again, alcohol **5a** was obtained with only 43% ee. The difference in enantioselectivities of the reactions of carbonate *rac*-**1a** and acetate *rac*-**8a** with the hydrogen carbonate ion may perhaps be ascribed to the operation of a nucleofuge-dependent "memory effect".[11]

The use of the hydrogen carbonate ion in the palladium-catalyzed substitution allows not only deracemization but also an interesting kinetic resolution of the racemic allylic substrate. The reactions of the cyclohexenyl acetate *rac*-**8b** and cycloheptenyl acetate *rac*-**8c** with 1.4 equiv of $KHCO_3$ in water/$CH_2Cl_2$ in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and **BPA** slowed significantly at approximately 50% conversion of the starting acetates. Chromatography afforded the enantioenriched acetates **8b** and **8c** and the highly enantioenriched alcohols **5b** and **5c** in high yields (entries 2 and 3). The stereochemical course of the kinetic resolution and the substitution with the hydrogen carbonate ion is the same as that with other nucleophiles in the presence of **BPA**.[12] We note that the palladium-catalyzed resolution of acetates *rac*-**8b** and *rac*-**8c** with the hydrogen carbonate ion in water gives the same products as a hydrolase-catalyzed resolution, which involves, however, an O−CO bond cleavage and proceeds in these cases with all enzymes studied with low enantioselectivities.[3b]

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**Supporting Information Available:** Sample experimental procedures for the deracemization of *rac*-**1b** and the resolution of *rac*-**8b**, and details of ee value determination, optical rotations, and assignment of absolute configuration for all compounds described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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