Inorganic Carbonates as Nucleophiles for the Asymmetric Synthesis of Vinylglycidols

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Alkali metal carbonates and bicarbonates are known for their basicity, not nucleophilicity.[1] In fact, their poor nucleophilicity makes them common bases for effecting alkylation reactions with reactive alkylating agents. In conjunction with a program directed toward the asymmetric synthesis of vinylglycidols (**1**), we considered whether carbonate or bicarbonate could function as a nucleophile and thereby serve as a water surrogate[2] in a palladium-catalyzed alkylation reaction. This strategy is attractive, given the ease of loss of carbon dioxide from monoalkyl carbonates. In this paper, we report the ability to use carbonates as nucleophiles under mild conditions and an interesting divergent reaction pathway depending upon the presence or absence of a boron cocatalyst[3] that has led to a direct practical asymmetric synthesis of vinylglycidols.

The potential utility of vinylglycidols as asymmetric building blocks,[4,5] which may be more versatile than tartaric acid derivatives, led us to envision a route from the deracemization of diene monoepoxides (**2**) using chiral palladium complexes. While protected forms are available via asymmetric palladium catalysis utilizing alcohols as nucleophiles,[3] the direct availability of vinylglycidols themselves are problematic. First, water is such a notoriously poor nucleophile in palladium-catalyzed reactions that it is an excellent solvent or cosolvent for such reactions. This fact led us to develop the use of triphenylsilanol as a water surrogate,[2] a tactic that fails here. Second, even if water would serve as a nucleophile, the greater nucleophilicity of the resulting diol would lead to it being the preferred nucleophile which in turn would produce oligomeric products. Preliminary experiments with water as nucleophile in the presence of boron cocatalysts verified this expectation.

Isoprene monoepoxide (**2a**) was chosen as the model substrate for the direct conversion (eq 1). Initial results were promising.
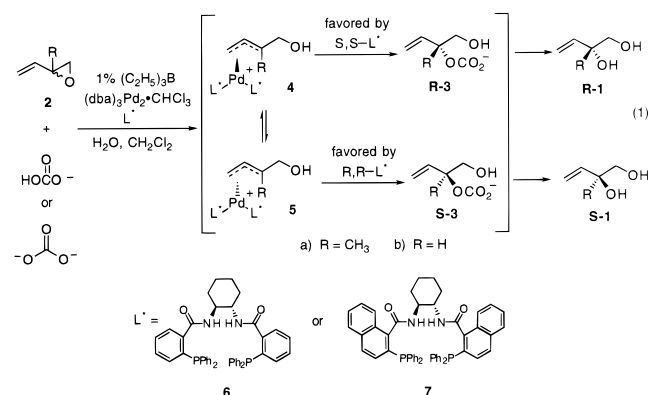
Employing 1 mol % (dba)₃Pd₂·CHCl₃, 3 mol % ligand **6**, and 1 mol % triethylborane as the standard catalyst system, sodium bicarbonate in methylene chloride−water containing tetra-*n*-butylammonium chloride gave, at room temperature, a 40% yield

of **R-1a** of 88% ee. Raising the temperature to 40 °C. increased the yield to ~80% and the ee to 97%. Replacing sodium bicarbonate with sodium carbonate or leaving out the phase-transfer catalyst gave identical results. In an optimized procedure, using the standard catalyst system, 1 equiv of sodium bicarbonate and no phase-transfer catalyst at 40 °C, a 91% isolated yield of **R-1a** of 97% ee was obtained. The absolute configuration of **1a** was assigned by comparison of its rotation, $[\alpha]_D$ +4.78° (*c* 2.50, CHCl₃), to that reported.[5]

As one of the control experiments, the reaction was performed under the above optimized conditions but at room temperature, and in the absence of triethylborane (eq 2). In this case, a quite
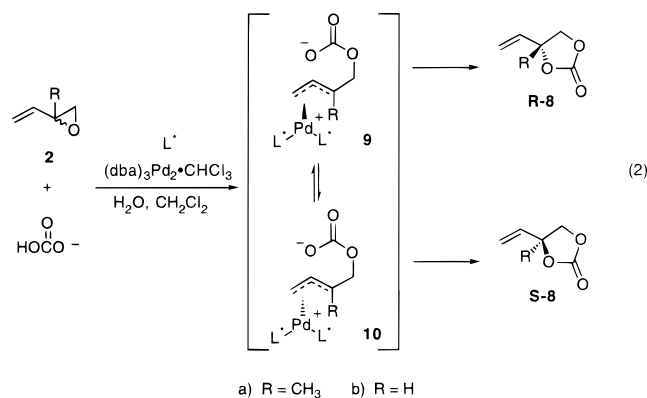
different course was observed—the formation of the cyclic carbonate **R-8a** of 93% ee in 56% yield. The change in the course of the reaction was thought to derive from the carbonate serving as a source of carbon dioxide to generate the π-allyl intermediates **9** and **10**.[6] Cyclization must be slower than their interconversion to ensure high ee. During efforts to optimize both the yield and the ee, it became clear that juggling conversion, rate of formation of **9** and **10** from **4** and **5**, and competing racemization of the product must be accomplished for satisfactory results. For example, using ammonium carbonate, at 13% conversion, the product had an ee of 92% which dropped to 1% ee at 100% conversion. With sodium bicarbonate in the presence of a 0.5 M phosphate pH 8.9 buffer, a much smaller drop occurred—from 92% ee at 12% conversion to 85% ee at 96%. These results suggest a pH-dependent product racemization. Because of the heterogeneous nature of the reaction, changing the mixing rate (which would affect the rate of conversion of intermediates **4** and **5** to **9** and **10**) also had a significant effect. More inefficient mixing lowered the yield due to increased isomerization to tiglic aldehyde[7] but maintained good ee. Too fast mixing led to improved yields but lower ee's. An appropriate balance of the

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Table 1. Dynamic Kinetic Asymmetric Transformation Cycles for Vinylglycidol Synthesis[a]

cycle	$(C_2H_5)_3B$ (%)	$(n\text{-}C_4H_9)_4$-NCl (%)	Na_2CO_3 (equiv)	H_2O (mL)	time (h)	yield (%)	ee (%)
1	0.50	5	1.2	2.0	2	60	93
2	0.25	2.5	1.2	2.0	2	68	92
3	0.25	2.5	1.2	2.0	2	73	92
4	0.25	2.5	1.2	2.0	1.8	75	91
5	0.25	2.5	1.2	2.0	1.7	75	92

[a] Initial catalyst charge consisted of 1 mol % $(dba)_3Pd_2 \cdot CHCl_3$, 3 mol % **7**, and 5 mol % DMAP. Reactions run at 0.1 M in methylene chloride.

competing effects could be achieved by adjusting the palladium loading. By lowering the $(dba)_3Pd_2 \cdot CHCl_3$ from 1% to 0.5% and the ligand to 1.5%, a 92% ee was obtained at 90% conversion in 1 day at room temperature. Lowering the Pd to 0.25% maintained the ee at 93% but saw the conversion drop to 57% in the same period of time. The optimum conditions then proved to be 0.5 mol % $(dba)_3Pd_2 \cdot CHCl_3$, 1.5 mol % **6** using 0.1 M of epoxide **2a** in the presence of sodium bicarbonate and water in methylene chloride at room temperature, whereby an 88% isolated yield of carbonate **R-8a** of 93% ee was obtained.

The higher reactivity of butadiene monoepoxide (**2b**) aggravated the oligomerization problem—a fact which made the direct extrapolation of the reaction conditions difficult. For example, utilizing the optimum conditions developed for **2a** except changing ligand to **7** which is necessary for good ee in this case, epoxide **2b** gave vinylglycidol **R-1b** of 88% ee and dimer in nearly equal amounts. Changing from triethylboron to tri-*sec*-butylboron gave **1b** of 92% ee, but the ratio of diol to oligomer fell to 1:4. In this case, it was necessary to ensure complete formation of the carbonate intermediate **R-3b** and extract it into water to minimize oligomerization. Thus, the more basic sodium carbonate was employed. Using 1 mol % $(dba)_3Pd_2 \cdot CHCl_3$, 3 mol % **7**, 1 mol % triethylborane, and 5 mol % tetra-*n*-butylammonium chloride in a methylene chloride—water two-phase system generated the monosodium salt of the carbonate **R-3b** in the water layer. Acidification of the aqueous layer with sodium bisulfate followed by extraction with ethyl acetate gave an approximately 70% yield of diol **R-1b** with 86% ee. Dropping the amount of triethylborane to 0.5 mol % to slow the rate of transfer of carbonate saw a slight increase in ee to 89%. Adding 5 mol % DMAP to this last experiment further increased the ee to 92% (74% isolated yield). The absolute configuration was established by comparison of the observed rotation $[\alpha]_D$ +35.3° (c = 1.80, i-C_3H_7OH) to the literature.[8] A dynamic kinetic asymmetric transformation "machine" was created, and the data is summarized in Table 1. Charging the reactor with the catalyst system noted above followed by 1.2 equiv of sodium carbonate and butadiene monoepoxide, separating the water layer and leaving the organic layer in the reactor, and acidifying the water layer gave a 60% yield of diol **R-1b** of 93% ee (cycle 1). For cycles 2−5, an aliquot of 0.25 mol % triethylborane and 2.5 mol % of tetra-*n*-butylammonium chloride was added in addition to the reactants and water. As shown in Table 1, the ee remained constant over all cycles. The yield increased after the first two cycles and then remained constant over all cycles. Presumably, the methylene

chloride layer must become saturated with the initial product only after the second cycle. Thus, the yield increase may derive from more effective partitioning of the initial product into the aqueous layer. It does appear that there is a slight shortening of the reaction time with later cycles which may be due to an increased concentration due to some loss of methylene chloride or slow but steady increase in the boron cocatalyst occurring. Importantly, even after 5 cycles, no loss of catalytic activity of the initial catalyst charge was noted.

The formation of the vinyl carbonate **R-8b** proceeds quite analogously to the isoprene monoepoxide case (i.e., absence of boron cocatalyst, eq 2). Using the optimized conditions as for **2a** except replacing the benzo linker ligand **6** by the naphtho version **7**, the reaction of epoxide **2b** led to an 89% isolated yield of carbonate **R-8b** of 92% ee.

The dramatic difference in the course of the reaction in the presence of the boron cocatalyst may be understood by its role as a nucleophile transfer agent (eq 3). The initial π-allylpalladium

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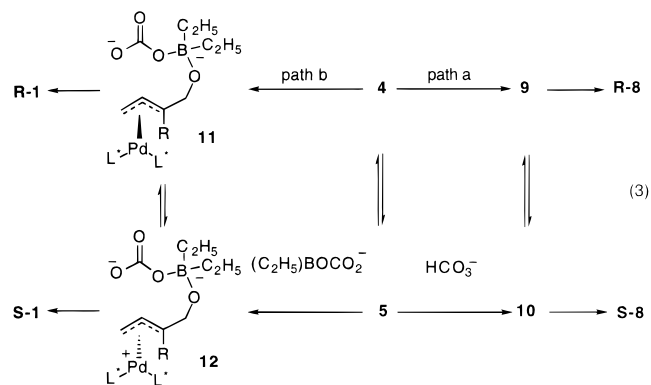
intermediates **4** and **5** may partition between direct reaction with carbon dioxide liberated from the bicarbonate or carbonate (path a) and capture by a boron—carbonate to give the "ate" complexes **11** and **12** (path b). The former leads to the cyclic carbonate, and the latter leads to diol (after acidification). The fact that as little as 0.25 mol % triethylboron completely diverts the reaction along path b shows the effectiveness of the boron cocatalysts as nucleophile delivery systems. The fact that too much boron cocatalyst lowers ee, suggesting that capture and carbonate delivery start to become faster than equilibration between **4** and **5** or **11** and **12**, also speaks to the effectiveness of the boron cocatalysts. Thus, both the diols **1** and cyclic carbonates **8** are readily available from racemic vinyl epoxides with high ee which should enhance their utility as asymmetric building blocks. This work raises the question of the general utility of carbonates as nucleophiles in metal catalyzed reactions—an uncommon role.

Supporting Information Available: Experimental procedures for preparation of **R-1a**, **R-1b**, **R-8a**, **R-8b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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