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Palladium-catalyzed kinetic resolution of racemic cyclic and acyclic allylic carbonates with sulfur nucleophiles

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Abstract

A chiral Pd(0) complex bearing the Trost ligand in combination with S-nucleophiles effects the kinetic resolution of cyclic and acyclic allylic carbonates with excellent levels of enantioselectivity to give enantiomerically highly enriched allylic carbonates as well as allylic sulfones and sulfides. This method allows also for a new access to enantiopure cyclic allylic alcohols. © 2000 Elsevier Science Ltd. All rights reserved.

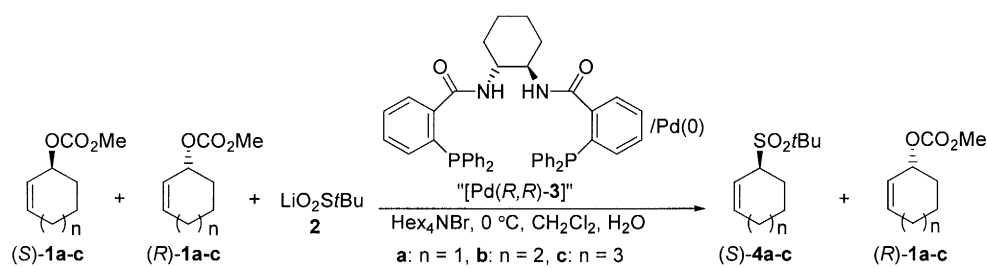
Catalytic kinetic resolution is an important method for the attainment of chiral compounds.¹ While numerous highly efficient examples using enzymes have been described,² those involving abiotic chiral catalysts are much less abundant.³ Therefore, the development of highly selective kinetic resolutions with the latter type of catalysts continues to be a topic of considerable interest.⁴ During our investigations⁵ of the Pd-catalyzed asymmetric synthesis of allylic S-derivatives by using a chiral Helmchen–Pfaltz–Williams ligand⁶ and the Trost ligand (*R,R*)-**3**⁷ we had encountered^{5a,b} a kinetic resolution of allylic acetates and carbonates.^{8,9} We now report that a highly selective kinetic resolution of cyclic and acyclic allylic carbonates is achieved through the Pd-catalyzed substitution with S-nucleophiles in the presence of (*R,R*)-**3**.

Reaction of the racemic six-ring allylic carbonate *rac*-**1a** on a 10 mmol scale with two equivalents of sulfinate **2**^{5a} at 0°C in a 1:1 mixture of water and methylene chloride in the presence of 1.5 mol% of [Pd₂dba₃·CHCl₃] (dba=dibenzylideneacetone), 4.5 mol% of (*R,R*)-**3** and tetrahexylammonium bromide as a phase transfer catalyst gave after termination of the reaction at 54% conversion and chromatography the sulfone (*S*)-**4a** with 98% ee in 49% yield and the carbonate (*R*)-**1a** with ≥99% ee in 34% yield (Table 1).¹⁰ The similar Pd-catalyzed substitution of the racemic seven-ring allylic carbonate *rac*-**1b** with sulfinate **2** furnished, at 53% conversion, the sulfone (*S*)-**4b** with 95% ee in 46% yield and the carbonate (*R*)-**1b** with 94% ee in 33% yield. The Pd-catalyzed substitution of the racemic eight-ring allylic carbonate *rac*-**1c** with sulfinate **2** proceeded under these conditions equally effective and delivered at 52% conversion the sulfone (*S*)-**4c** with 96% ee in 48% yield and the carbonate (*R*)-**1c** with ≥99% ee in 34% yield. The reaction rate decreased with increasing ring size of the allylic carbonate necessitating the reaction of *rac*-**1c** to be carried out at room temperature. According to GC and NMR spectroscopic

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analyses formation of side products was negligible, and the chemical yield of the carbonates approached in all cases the theoretical values.¹⁰ Thus, an optimization of the yields of the recovered educts should be possible. The absolute configurations of the carbonates (*R*)-**1a–c** were established by chemical correlation through hydrolysis to the corresponding cyclic allylic alcohols^{4a,b,11} and comparison of their chiroptical data with those reported in the literature. The absolute configuration of sulfone (*S*)-**4c** was confirmed by X-ray structure analysis using anomalous X-ray scattering (Fig. 1).¹² On the basis of these results and by assuming that the reactions of the intermediate allyl–Pd complexes (vide infra) derived from carbonates *rac*-**1a–c** and '[Pd(*R,R*)-**3**]' with sulfinate **2** proceed all with the same sense of asymmetric induction the absolute configurations of sulfones (*S*)-**4a** and (*S*)-**4b** were also assigned to be *S*.

Table 1
'[Pd(*R,R*)-**3**]'-catalyzed kinetic resolution of carbonates *rac*-**1a–c** with sulfinate **2**^{a,b}



<i>t</i> (h)	convn (%)	educt	ee (%)	yield (%)	$[\alpha]_D^{20}$	product	ee (%)	yield (%)	$[\alpha]_D^{20}$
0.75	54	(<i>R</i>)- 1a	≥99 ^c	34	+168.0 ^d	(<i>S</i>)- 4a	98 ^c	49	−177.1 ^f
4	53	(<i>R</i>)- 1b	94 ^c	33	+33.2 ^g	(<i>S</i>)- 4b	95 ^c	46	−94.5 ^h
24	52	(<i>R</i>)- 1c	≥99 ^c	34	−78.4 ^h	(<i>S</i>)- 4c	96 ^c	48	+135.4 ⁱ

^a Yields refer to isolated compounds. ^b Optical rotation in CH₂Cl₂. ^c GC, octakis-(2,3-di-O-pentyl-3-O-butyl-γ)-cyclodextrin. ^d *c* 1.73. ^e ¹H NMR, Eu(hfc)₃. ^f *c* 1.01. ^g *c* 1.29. ^h *c* 1.02. ⁱ *c* 1.99.

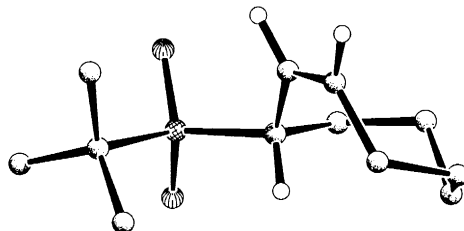


Fig. 1. Structure of sulfone (*S*)-**4c** in the crystal.

Monitoring the Pd-catalyzed reaction of carbonate *rac*-**1a** with sulfinate **2** under the above conditions by GC and NMR spectroscopy revealed that the ee value of the sulfone (*S*)-**4a** did practically not change during the course of the reaction (Fig. 2) and that the ee value of the carbonate (*R*)-**1a** increased at higher conversion. On the basis of the conversion and the ee values of carbonate (*R*)-**1a** the lower limit of the k_f/k_s value^{3a} was estimated to be 40.

The '[Pd(*R,R*)-**3**]'-catalyzed kinetic resolution could be extended to acyclic and cyclic carbonates as substrates and thiols as nucleophiles as well. Thus, reaction of carbonate *rac*-**5** on a 10 mmol scale with one equivalent of thiol **6** at 22 °C in methylene chloride in the presence of 2.5 mol% of [Pd₂dba₃·CHCl₃] and 5.5 mol% of (*R,R*)-**3** gave after termination of the reaction at 55% conversion and chromatography the sulfide (*R*)-**7**^{5b} with 93% ee in 36% yield while 36% of the carbonate (*S*)-**5** with ≥99% ee were recovered (Table 2). The similar '[Pd(*R,R*)-**3**]'-catalyzed substitution of carbonate *rac*-**1a** with thiol **6** furnished at 56% conversion the sulfide (*S*)-**8**^{5b} with 92% ee in 29% yield and the carbonate (*R*)-**1a** with ≥99% ee in 35% yield.

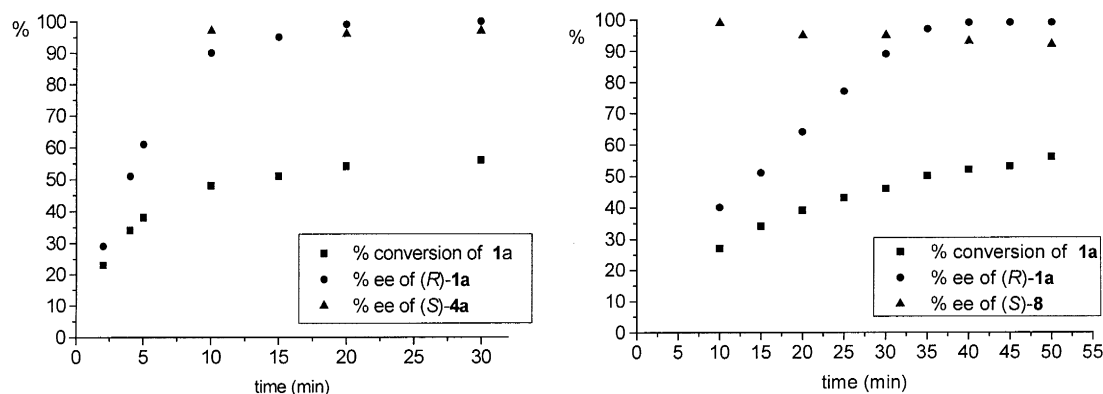


Fig. 2. '[Pd(*R,R*)-3]'-catalyzed reaction of carbonate *rac*-1a with sulfinate 2 (left) and with thiol 6 (right)

Table 2

'[Pd(*R,R*)-3]'-catalyzed kinetic resolution of carbonates *rac*-3 and *rac*-1a with thiol 6^{a,b}

t (h)	convn (%)	educt	ee (%)	yield (%)	$[\alpha]_D^{20}$	product	ee (%)	yield (%)	$[\alpha]_D^{20}$
20	55	(<i>S</i>)-5	≥99 ^c	36	-64.4 ^d	(<i>R</i>)-7	93 ^e	36	+188.1 ^f
0.9	56	(<i>R</i>)-1a	≥99 ^c	35	+168.0 ^g	(<i>S</i>)-8	92 ^e	29	-124.8 ^h

^a Yields refer to isolated compounds. ^b Optical rotation in CHCl₃. ^c GC, octakis-(2,6-di-O-pentyl-3-O-butyl)-γ-cyclodextrin. ^d *c* 1.04. ^e GC, octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin. ^f *c* 1.06. ^g *c* 1.10. ^h *c* 1.14.

The Pd-catalyzed reaction of carbonate *rac*-1a with thiol 6 was followed by GC (Fig. 2). The ee value of sulfide (*S*)-8 did practically not change during the course of the reaction, but the ee value of the carbonate (*R*)-1a increased at higher conversion. On the basis of the conversion and the ee values of carbonate (*R*)-1a the lower limit of the k_f/k_s value^{3a} was estimated to be 40.

A characteristic feature of the above Pd-catalyzed kinetic resolutions not shared by other kinetic resolutions is that the ee values of the recovered substrate and of the product are dependent on the selectivities of two different steps (Fig. 3). While the enantiomer selectivity (k_1/k_2) of the ionization determines the ee value of the recovered educt that of the product is defined by the enantioselectivity (k_3/k_4) of the substitution of the allyl-Pd complex, and the fastest reacting enantiomer of the allylic carbonate and the fastest forming enantiomer of the sulfone and sulfide have the same absolute configuration.^{5a,b} A rationalization of the selectivities is hampered at present because of the unknown structures of '[Pd(*R,R*)-3]' and the allyl-Pd complexes derived thereof.^{9c}

In summary, complex '[Pd(*R,R*)-3]' in combination with S-nucleophiles allows for a catalytic kinetic resolution of racemic cyclic and acyclic allylic carbonates with levels of enantioselectivity not observed in the previous cases^{5a,8,9} to give enantiomerically highly enriched allylic carbonates, sulfones and sulfides. Although the parent cyclic allylic alcohols of carbonates (*R*)-1a–c, which have found use as

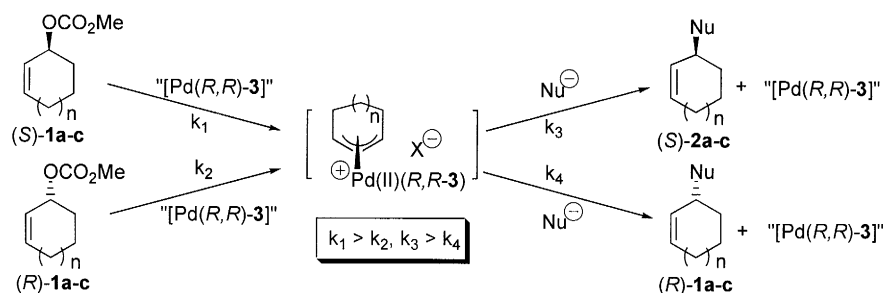


Fig. 3. '[Pd(R,R)-3]'-catalyzed kinetic resolution and asymmetric substitution

chiral synthetic intermediates, can be obtained by several methods^{4a,b,11} the kinetic resolution alluded to allows for the attainment of each alcohol in very high enantiomeric purity.¹³

Acknowledgements

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- Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, as supplementary publication no. CCDC-142405.
- All compounds were fully characterized including elemental analysis.