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Palladium-Catalyzed Enantioselective Allylic Alkylation of Thiocarboxylate Ions: Asymmetric Synthesis of Allylic Thioesters and Memory Effect/Dynamic Kinetic Resolution of Allylic Esters

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The palladium-catalyzed allylic alkylation of KSAc and KSBz with racemic cyclic and acyclic allylic esters by using *N*,*N*′-(1*R*,2*R*)-1,2-cyclohexandiylbis[2-(diphenylphosphino)-benzamide] as ligand frequently gave the corresponding allylic thioesters with high ee values and yields. The reaction of the cyclic allylic carbonates with KSAc in the presence of H_2O was accompanied by a partial palladium-catalyzed enantioselective "hydrolysis" of the substrates with formation of the corresponding enantioenriched allylic alcohols. The degree of the "hydrolysis" was strongly dependent on the solvent and the thiocarboxylate ion. Highly selective kinetic resolutions (KRs) were observed in the palladium-catalyzed reaction of the racemic cyclohexenyl and cycloheptenyl acetates with KSAc. While the KR of the cyclohexenyl acetate is characterized by a selectivity factor $S = 72 \pm 19$, that of the cycloheptenyl acetate afforded (*R*)-cycloheptenyl acetate of ≥99% ee in 48% yield and (*S*)-cycloheptenyl thioacetate of 98% ee in 50% yield. The palladium-catalyzed reaction of the racemic cyclopentenyl acetate with KSAc showed a strong "memory effect" (ME), that is, both enantiomers reacted with different enantioselectivities. The ME was probed by studying the palladium-catalyzed reactions of both the matched acetate of ≥99% ee and the mismatched acetate of ≥99% ee with KSAc. The acetates not only reacted with different enantioselectivities and rates but also suffered an unexpected and concomitant palladium-catalyzed racemization in the presence of the chiral ligand. This led in the case of the mismatched acetate to a temporary dynamic kinetic resolution (DKR) that featured a racemization of the mismatched acetate by the chiral catalyst. Studies of the palladium-catalyzed reaction of the racemic cyclopentenyl acetate, carbonate, and naphthoate with KSAc in the presence of the chiral ligand also showed the ME to be strongly dependent on the nucleofuge. This also allowed the synthesis of (*S*)-cyclopentenyl thioacetate of 92% ee in high yield from the racemic cyclopentenyl naphthoate.

Introduction

The palladium(0)-catalyzed enantioselective allylic alkylation of sulfur nucleophiles[1−3a] and the allylic O,S-rearrangement[4−6] have been intensively studied in recent years.[7] The main incentive for these studies was the development of a catalytic asymmetric synthesis of synthetically important allylic sulfur compounds.[8] It was found that both the alkylation of sulfinate ions and 2-pyrimidinethiol (external nucleophiles) with racemic allylic esters[1a,b,d,e,2] and the mechanistically related O,S-rearrangement of racemic allylic *O*-allylic sulfinates[6c] and thiocarbamates[6a,b] (internal nucleophiles) (Scheme 1) provide excellent methods for the asymmetric synthesis of allylic sulfur compounds including sulfones, carbamates, and pyrimidyl-substituted sulfides.

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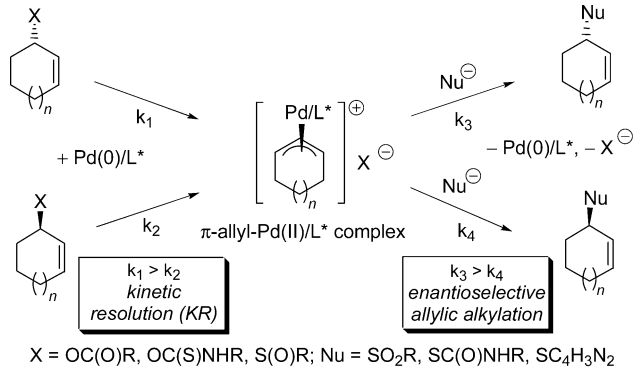
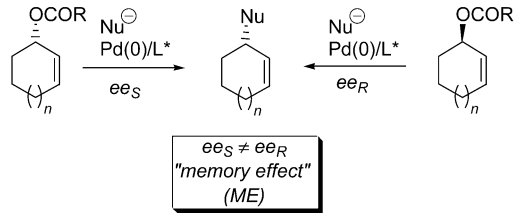
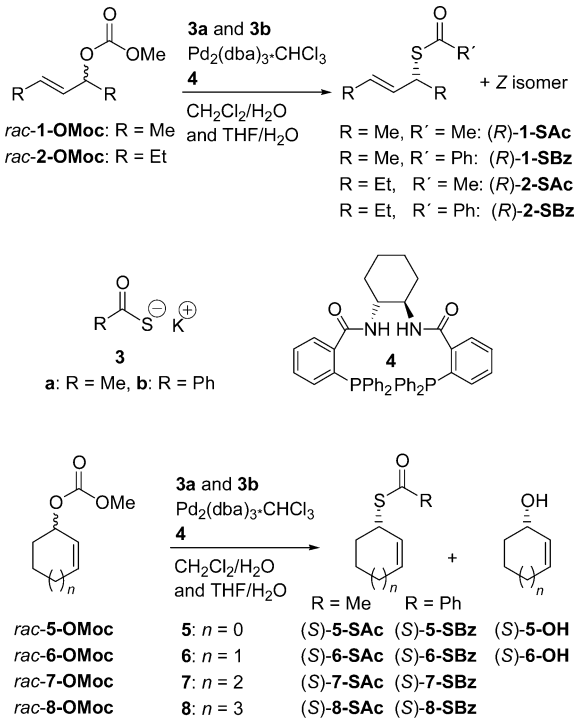
SCHEME 1. Simplified Scheme of Palladium-Catalyzed Enantioselective Allylic Alkylation, KR and ME of Racemic Substrates[a]





[a] L* = chiral ligand. This scheme also applies to acyclic substrates having a symmetrically substituted carbon skeleton.

SCHEME 2. Palladium-Catalyzed Asymmetric Synthesis of Allylic Thioesters



The use of the bisphosphane **4**[7d,h,9] (Scheme 2) as ligand for the palladium atom conveyed high enantioselectivities not only to the second step of the reaction sequence, the allylic alkylation of the sulfur nucleophile, but also to the first step, the ionization of the racemic substrate.[1b−e,10] For example, a highly efficient kinetic resolution (KR) of racemic cyclic allylic carbonates was achieved through a palladium-catalyzed reaction with lithium *tert*-butylsulfinate and ligand **4**.[1e] It was now of interest to see whether the palladium-catalyzed allylic alkylation is also applicable to the asymmetric synthesis of a further class of synthetically valuable allylic sulfur compounds, the allylic sulfides.[8,11] A greater exploitation of the potential of allylic sulfides for stereoselective synthesis including the allylic alkylation of organometallics,[11b,e] sigmatropic rearrangement[11a,c,d,f−l] and generation of chiral sulfur-stabilized carbanions[11m] has been hampered by the lack of general methods for their asymmetric synthesis.[6a,b,8] Unfortunately, the palladium-catalyzed enantioselective allylic alkylation of thiols is limited in scope because of its apparent confinement to aryl and heteroaryl thiols.[1b,c,e] We have therefore developed an interest in the palladium-catalyzed enantioselective allylic alkylation of thiocarboxylate ions as a surrogate for that of thiols. Allylic thioesters should make highly useful starting materials for the synthesis of allylic sulfides because of their ready hydrolysis to the corresponding allylic thiols[12] and the facile alkylation,[12] arylation,[6b,c,13] heteroarylation,[6b,c,12] and further derivatization of the latter at the S-atom.[14] The literature on the feasibility of a palladium-

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catalyzed enantioselective allylic alkylation of thiocarboxylate ions was, however, ambiguous. Although it had been previously described that the thioacetate ion is capable to serve as a nucleophile in palladium-catalyzed allylic alkylation in the presence of achiral ligands,[3b] its alkylation with racemic cyclohexenyl carbonate (vide infra) in the presence of various chiral phosphanes including **4** proceeded with only medium yields and enantioselectivities.[3a]

Beside the development of an asymmetric synthesis of allylic thioesters, we were also seeking with this study further information about an interesting phenomenon of the palladium-catalyzed allylic alkylation, the "memory effect" (ME) of racemic allylic substrates.[15] According to Scheme 1 both enantiomers of the allylic substrate should give the same π-allyl-palladium(II) complex or the same set of equilibrating complexes and thereby, under the influence of the chiral ligand, the alkylation product with the same ee value. It has been reported, however, that the enantiomers of certain allylic esters can give under certain conditions the substitution product with different ee values.[1e,15−19] Although the ME is mechanistically highly interesting, it is synthetically undesirable because it can diminish the efficiency of the palladium-catalyzed asymmetric synthesis. Most of the information about the ME has been gathered with ligand **4**.[1e,16−19] Several factors have been identified that influence the ME, including the structure of the carbon skeleton of the substrate, the nucleofuge, the nucleophile, the catalyst loading, and the precatalyst.[1e,15−19] However, despite several investigations, the origin of the ME is still a matter of debate.[15b,c] Recently a two catalytic cycle model, based on the formation of monomeric and oligomeric palladium(0)/**4** complexes, has been proposed in order to account for the ME with this ligand.[17] Because **4** is one of the most successful and widely used ligands in palladium-catalyzed enantioselective allylic alkylation,[7b,9] the collection of further experimental information on the ME with this ligand is desirable.

In this paper we describe the results of a study of the palladium-catalyzed enantioselective allylic alkylation of thiocarboxylate ions with racemic allylic esters in the presence of ligand **4**. This investigation not only resulted in the development of an asymmetric synthesis of allylic thioesters and widened the scope of the palladium-catalyzed KR but also gave, by using enantiopure allylic esters as substrates, new and interesting information about the ME and the dynamic kinetic resolution (DKR).

TABLE 1. Palladium-Catalyzed Asymmetric Synthesis of Allylic Thioesters in CH_2Cl_2/H_2O at 25 °C

entry	substrate	salt	convn [%][a]	*t* [h]	products[b]	yield [%]	ee [%][c,d]
1	*rac*-**1-OMoc**	KSAc	≥99	144	(*R*)-**1-SAc** (91:9)	76	84 (92)
2	*rac*-**1-OMoc**	KSBz	92	96	(*R*)-**1-SBz** (91:9)	85	87 (92)
3	*rac*-**2-OMoc**	KSBz	≥99	28[e]	(*R*)-**2-SBz** (96:4)	97	90 (49)
4	*rac*-**5-OMoc**	KSAc	≥99	24	(*S*)-**5-SAc**	62	73
					(*S*)-**5-OH**	22	57
5	*rac*-**5-OMoc**	KSBz	≥99	24	(*S*)-**5-SBz**	68	59
					(*S*)-**5-OH**	20	55
6	*rac*-**6-OMoc**	KSAc	≥99	5.25	(*S*)-**6-SAc**	51	94
					(*S*)-**6-OH**	30	82
7	*rac*-**6-OMoc**	KSBz	≥99	24	(*S*)-**6-SBz**	92	89
					(*S*)-**6-OH**	5	*f*
8	*rac*-**7-OMoc**	KSBz	73	48	(*S*)-**7-SBz**	69	86
					(*S*)-**7-OH**	*g*	

[a] Determined by GC. [b] The values in parentheses give the *E*/*Z* ratios. [c] Determined by GC (thioacetates and alcohols) and HPLC (thiobenzoates) on chiral stationary phase columns. [d] The values in parentheses give the ee values of the *Z* isomers. [e] At reflux temperature. [f] Not determined. [g] Formation of the alcohol was not detected.

Results and Discussion

I. Allylic Alkylation of Thiocarboxylate Ions. (i) Asymmetric Synthesis of Allylic Thioesters. The study of the palladium-catalyzed allylic alkylation of thiocarboxylate ions was carried out with potassium thioacetate (**3a**) (KSAc) and potassium thiobenzoate (**3b**) (KSBz) and the racemic cyclic and acyclic carbonates *rac*-**1-OMoc** (Moc = methoxycarbonyl), *rac*-**2-OMoc**, *rac*-**5-OMoc**, *rac*-**6-OMoc**, *rac*-**7-OMoc**, and *rac*-**8-OMoc**, respectively (Scheme 2). The carbonates were chosen because of their symmetrically substituted carbon skeleton, which precludes the formation of regioisomers. Furthermore, these carbonates had been previously used in palladium-catalyzed allylic alkylation of other sulfur nucleophiles in our[1b−e] and other laboratories.[2,3] Thus, a direct comparison of the reactivity of the vaious sulfur nucleophiles in palladium-catalyzed allylic alkylation with ligand **4** would be possible. Carbonates were selected instead of acetates because of their higher reactivity in palladium-catalyzed allylic alkylation.[7a] The bisphosphane **4** was used as ligand for the palladium atom because of the high enantioselectivities it provided in the allylic alkylation of a number of nucleophiles including those based on sulfur[1,2,6] with a broad range of symmetrically substituted cyclic and acyclic allylic esters.[7b,9] The carbonates *rac*-**1-OMoc**, *rac*-**2-OMoc**, *rac*-**5-OMoc**, *rac*-**6-OMoc**, and *rac*-**7-OMoc** were treated with 1.4 equiv of KSAc or 2.0 equiv of KSBz in the presence of 2 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylidene acetone) and 8 mol % of **4** in CH_2Cl_2/H_2O (9:1).

The acyclic carbonates *rac*-**1-OMoc** and *rac*-**2-OMoc** gave under these conditions (Table 1, entries 1−3) the thioesters (*R*)-**1-SAc**, (*R*)-**1-SBz**, and (*R*)-**2-SBz**, respectively, with high enantioselectivities in high yields.

Surprisingly, the formation of the (*E*)-configured allylic thioesters was accompanied by that of the corresponding

(14) Although allylic *S*-thiocarbamates make excellent starting materials for the synthesis of allylic thiols, their asymmetric synthesis through a palladium-catalyzed O,S-rearrangement of racemic allylic *O*-thiocarbamates is confined to substrates of a sufficient thermal stablity.[6a,b] For example, racemic cyclopentenyl *O*-thiocarbamates already suffer at room temperature a noncatalyzed rearrangement with formation of the corresponding racemic cyclopentenyl *S*-thiocarbamates.

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Z isomers to a degree of 4−9%. Although the *E* and *Z* isomers were not separated, an unequivocal assignment of their structures was made possible by ^{1}H and ^{13}C NMR spectroscopy of the mixture of the isomers. Instrumental was the observation of similar chemical shifts for the S-atom bearing C-atoms of the isomers, which allowed the exclusion of the structures of the isomeric *O*-allylic thioesters. Large ^{13}C NMR shift differences are normally observed for the heteroatom bearing C-atoms of *S*- and *O*-allylic esters, as exemplified by thiobenzoic acid *O*-(1-methyl-but-2-enyl) ester (δ = 72.0 ppm) and the isomeric thiobenzoic acid *S*-(1-methyl-but-2-enyl) ester (δ = 40.7 ppm).[20] We had previously observed formation of the *Z* isomer in the palladium-catalyzed reaction of *rac*-**2-OMoc** with 2-pyrimidinethiol and **4** in CH_2Cl_2 in the absence of water.[1c,e] Thus, formation of *Z* isomers in palladium-catalyzed allylic alkylation with ligand **4** seems to be more common than previously anticipated.[21] This observation may lead to a further refinement of the mechanistic picture of the palladium-catalyzed allylic alkylation with **4**. Formation of the *Z* isomers can be rationalized by proposing the existence of an equilibrium between the corresponding acyclic (*syn*,*syn*)-, (*syn*,*anti*)-, (*anti*,*syn*)-, and (*anti*,*anti*)-configured π-allyl-palladium(II)/**4** complexes, which are interconverting by an anion-promoted π-π-π-isomerization mechanism.[22] While the substitution of the (*anti*,*anti*)-configured complex should give the (*Z*,*S*)-configured thioester, that of the (*anti*,*syn*)-configured complex at the (*syn*)-configured allyl terminus should deliver the (*Z*,*R*)-configured thioester. However, the absolute configurations of the *Z* isomers were not determined, and a prediction as to the reactivity of both complexes is difficult to make. We note, however, that with the dimethylallyl substrate *rac*-**1-OMoc** the enantioselectivity of the formation of the *Z* isomer is higher than with the diethylallyl substrate *rac*-**2-OMoc** whose allyl-palladium complex carries the larger substituents at the allyl termini (cf. Table 1, entries 1−3).

Treatment of the cyclopentenyl carbonate *rac*-**5-OMoc** with KSAc (entry 4) and KSBz (entry 5) furnished thioacetate (*S*)-**5-SAc** with 73% ee and thiobenzoate (*S*)-**5-SBz** with 59% ee, respectively, in only medium yields. A similar treatment of the cyclohexenyl carbonate *rac*-**6-OMoc** with KSAc gave thioacetate (*S*)-**6-SAc** in an even lower yield of only 51% but with an higher ee value of 94% (entry 6). The somewhat low yield of (*S*)-**5-SAc**, (*S*)-**5-SBz**, and (*S*)-**6-SAc** was due to a competing palladium-catalyzed "hydrolysis" of the allylic carbonates with formation of the corresponding allylic alcohols (vide infra). However, the use of KSBz instead of KSAc in the reaction of the cyclohexenyl carbonate *rac*-**6-OMoc** helped to alleviate this problem and afforded thioester (*S*)-**6-SBz** with 89% ee in high yield (entry 7). The cycloheptenyl carbonate *rac*-**7-OMoc** showed in the reaction with KSBz, in comparison to *rac*-**5-OMoc** and *rac*-**6-OMoc**, a lower reactivity and gave thioester (*S*)-**7-SBz** with 86% ee in good yield (entry 8).

A similar study of the palladium-catalyzed allylic alkylation of KSAc and KSBz with carbonates *rac*-**1-OMoc**, *rac*-**2-OMoc**, *rac*-**5-OMoc**, *rac*-**6-OMoc**, and *rac*-**7-OMoc** in THF/H_2O (9:1) (see Supporting Information, Table S1) led to similar results in regard to yields and enantioselectivities. The enantioselectivities were, however, in the single-phase system THF/H_2O somewhat lower than in the two-phase system CH_2Cl_2/H_2O.

In summary, the palladium-catalyzed allylic alkylation of thiocarboxylate ions with racemic allylic carbonates allowes an asymmetric synthesis of highly enantioenriched acyclic and cyclic allylic thioesters in good to high yields, the only exemption being the five-membered cyclic carbonate *rac*-**5-OMoc**, which gave thioesters (*S*)-**5-SAc** and (*S*)-**5-SBz** only with medium ee values and yields. However, as will be shown later, thioacetate (*S*)-**5-SAc** can be also obtained with a high ee value in high yield by using a different racemic cyclopentenyl ester as substrate.

(ii) Competing "Hydrolysis" of Allylic Carbonates. Surprisingly, the reactions of the cyclopentenyl and cyclohexenyl carbonates *rac*-**5-OMoc** and *rac*-**6-OMoc**, respectively, with KSAc and KSBz in CH_2Cl_2/H_2O and THF/H_2O were accompanied to various degrees by a yield-diminishing formation of the allylic alcohols (*S*)-**5-OH** and (*S*)-**6-OH**, respectively (cf. Scheme 2, Table 1, entries 4−7). The alcohols were nonracemic and possessed the same absolute configuration as the corresponding thioesters. The degree of the alcohol formation was strongly dependent on the solvent system. Whereas in the two-phase system CH_2Cl_2/H_2O the alcohols were formed to a degree of 20−30% (cf. Table 1, entries 4−6), alcohol formation in the single-phase system THF/H_2O was only negligible (see Supporting Information, Table S1). Alcohol formation was also dependent on the thiocarboxylate ion. Although in the reaction of the carbonate *rac*-**6-OMe** with KSBz in CH_2Cl_2/H_2O formation of the alcohol (*S*)-**6-OH** was hardly noticeable, 30% of the alcohol was formed in the reaction with the less reactive KSAc. It had been previously found that the treatment of the carbonates *rac*-**1-OMoc**, *rac*-**2-OMoc**, *rac*-**5-OMoc**, *rac*-**6-OMoc**, *rac*-**7-OMoc**, and *rac*-**8-OMoc** with $Pd_2(dba)_3$·$CHCl_3$ and **4** in the presence of H_2O and in the absence of an external nucleophile leads to a highly enantioselective and almost quantitative formation of the corresponding allylic alcohols.[19] We have presented evidence showing that the palladium-catalyzed "hydrolysis" of allylic carbonates is most likely caused by the series of events depicted in Scheme 3 for *rac*-**5-OMoc** and *rac*-**6-OMoc**. Ionization of the racemic allylic carbonates upon reaction with the palladium(0)/**4** catalyst generated the corresponding π-allyl-palladium(II)/**4** complexes and the methyl carbonate ion. Because of the presence of water the methyl carbonate ion was hydrolyzed to the hydrogen carbonate ion and MeOH. The hydrogen carbonate ion acted as an oxygen nucleophile and substituted the π-allyl-palladium(II)/**4** complexes with formation of the hydrogen carbonates (*S*)-**5-OHyc** (Hyc = hydrogen carbonate) and (*S*)-**6-OHyc**, the hydrolysis of which with water gave the allylic alcohols (*S*)-**5-OH** and (*S*)-**6-OH**, respectively, and CO_2. The formation of the corresponding allylic alcohols in the reactions of *rac*-**5-OMoc** and *rac*-**6-OMoc** with thiocarboxylate ions in the presence of H_2O shows that the hydrogen carbonate ion can effectively compete with the sulfur nucleophile in the substitution of the π-allyl-palladium(II)/**4** complexes.

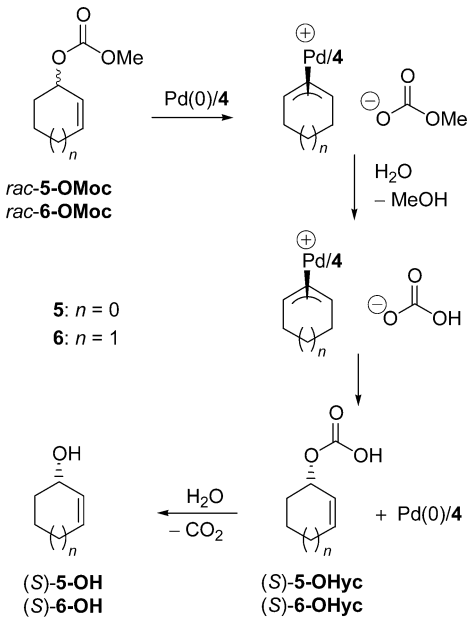
(20) Lüssem, B. J. Master's Thesis, RWTH Aachen, 1999.
(21) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(22) (a) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (b) Sjogren, M. P. T.; Hansson, S.; Åkermark, B.; Vitagliano, A. *Organometallics* **1994**, *13*, 1963.

TABLE 2. Palladium-Catalyzed KR of Allylic Carbonates and Acetates with Thiocarboxylate Ions at 25 °C

entry	substrate	*t* [h]	salt	solvent	convn [%][a]	products[b]	yield [%]	ee [%][c,d]
1	*rac*-**8-OMoc**	48[c]	KSAc	THF/H_2O	53	(*R*)-**8-OMoc**	48[e]	72
						(*S*)-**8-SAc**	42[e]	84
2	*rac*-**8-OMoc**	48[f]	KSBz	THF/H_2O	67	(*R*)-**8-OMoc**	28	94
						(*S*)-**8-SBz**	56	73
3	*rac*-**2-OMoc**	3.5[g]	KSBz	CH_2Cl_2/H_2O	48	(*R*)-**2-SBz** (97:3)	44	93 (63)
						(*S*)-**2-OMoc**	47	57
4	*rac*-**1-OAc**	72	KSAc	CH_2Cl_2/H_2O	35	(*R*)-**1-SAc** (91:9)	32	86 (99)
						(*S*)-**1-OAc**	44	60
5	*rac*-**1-OAc**	23	KSBz	CH_2Cl_2/H_2O	56	(*R*)-**1-SBz** (85:15)	53	83 (95)
						(*S*)-**1-OAc**	22	99
6	*rac*-**5-OAc**	1.7	KSAc	CH_2Cl_2/H_2O	62	(*S*)-**5-SAc**	52	92
						(*R*)-**5-OAc**	40	62
7	*rac*-**5-OAc**	22	KSAc	CH_2Cl_2/H_2O	≥99	(*S*)-**5-SAc**	99	58
8	*rac*-**6-OAc**	12	KSAc	CH_2Cl_2/H_2O	51	(*S*)-**6-SAc**	48	97
						(*R*)-**6-OAc**	43	≥99
9	*rac*-**7-OAc**	43	KSAc	CH_2Cl_2/H_2O	51	(*S*)-**7-SAc**	50	98
						(*R*)-**7-OAc**	48	≥99

[a] Determined by GC. [b] The values in parentheses give the *E*/*Z* ratios. [c] Determined by GC on chiral stationary phase containing column. [d] The values in parentheses give the ee values of the *Z* isomers. [e] Chemical yield. [f] At 45 °C. [g] At reflux temperature.

SCHEME 3. Mechanistic Scheme for Competing Palladium-Catalyzed "Hydrolysis" of Allylic Carbonates in Their Reactions with Thiocarboxylate Ions in the Presence of Water



The significantly higher degree of alcohol formation in CH_2Cl_2/H_2O as compared to THF/H_2O can perhaps be rationalized as follows. In the two-phase system CH_2Cl_2/H_2O the reactions will predominately take place in the organic phase and the solubilities of KSAc and KSBz in the organic phase are most likely only low. The allylpalladium complex and its hydrogen carbonate counterion are contained as a contact ion pair in the organic phase and the thiocarboxylate ion can enter the organic phase via an anion exchange of the ion pair. Thus, the concentration of the thiocarboxylate ion in the organic phase is low and perhaps comparable to that of the hydrogen carbonate ion. Therefore the latter can effectively compete in the substitution of the π-allylpalladium(II)/**4** complex. In the single-phase system THF/H_2O, however, the concentration of the thiocarboxylate ion is much higher than that of the hydrogen carbonate ion and the reaction of the allyl-palladium complex with the sulfur nucleophile dominates.

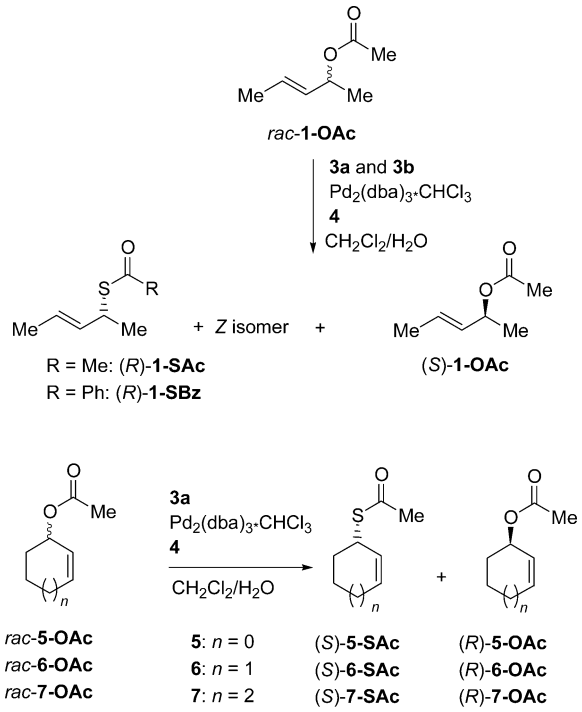
(iii) Kinetic Resolution of Allylic Esters. In the reaction of the cyclooctenyl carbonate *rac*-**8-OMoc**[1e] with KSAc in THF/H_2O (cf. Scheme 2) the conversion of the substrate even at 45 °C did not exceed 53% and a mixture of thioacetate (*S*)-**8-SAc** and carbonate (*R*)-**8-OAc** in a ratio of 53:47 was isolated. Formation of thioacetate (*S*)-**8-SAc** of 84% ee and of carbonate (*R*)-**8-OMoc** of 72% ee in a ratio of approximately 1:1 (Table 2, entry 1) showed that an efficient KR had occurred (cf. Scheme 1). Similar results were recorded in the reaction of carbonate *rac*-**8-OMoc** with KSBz (entry 2). The results recorded after the termination of the reaction of the acyclic carbonate *rac*-2-**OMoc** with KSBz in CH_2Cl_2/H_2O at 48% conversion also revealed the operation of a KR in this case (entry 3). Because of the strong current interest in both the catalytic KR[23,24] and the palladium-catalyzed KR in particular,[1b−e,10,19,25] the KRs of the racemic allylic acetates *rac*-**1-OAc**, *rac*-**5-OAc**, *rac*-**6-OAc**, and *rac*-**7-OAc** with thiocarboxylate ions and **4** were investigated in more detail (Scheme 4). The acetates were selected instead of the corresponding carbonates in order to avoid the competing formation of the corresponding allylic alcohols (vide supra). All reactions were carried out in CH_2Cl_2/H_2O (9:1) by using 2 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ and 8 mol % of **4**.

Termination of the reaction of the pentenyl acetate *rac*-**1-OAc** with KSAc at 35% conversion showed the operation of a highly selective KR (entry 4). However, a 50% conversion of the substrate could be achieved neither at 25 °C nor at reflux temperature. This is in contrast to the reactivity of carbonate *rac*-**1-OMoc** (cf. Table 1, entry

(23) For reviews, see: (a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475. (b) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489. (c) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (e) Huerta, F. F.; Mindis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (f) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578. (g) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407.

(24) For reviews, see: (a) Gais, H.-J.; Theil, F. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. II, p 335. (b) Williams, J. M. J.; Parker, R. J.; Neri, C. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K.; Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. I, p 287.

SCHEME 4. Palladium-Catalyzed KR of Allylic Acetates with KSAc (3a) and KSBz (3b)



1) and perhaps reflects the lower reactivity of allylic acetates in palladium-catalyzed alkylation.[7a] This problem could be overcome, however, by the use of the more reactive KSBz instead of KSAc. Here, at 56% conversion of *rac*-**1-OAc** the thiobenzoate (*R*)-**1-SBz** of 83% ee was isolated in 53% yield (entry 5) and the acetate (*S*)-**1-OAc**[26a] of 99% ee was recovered in 22% yield. The low yield of (*S*)-**1-OAc** was due to considerable losses encountered during isolation of the acetate because of its volatility.

Surprising results were obtained in the case of the KR of the cyclic acetates *rac*-**5-OAc**, *rac*-**6-OAc**, and *rac*-**7-OAc**. The cyclopentenyl acetate exhibited by far the highest reactivity of all three acetates. Thioacetate (*S*)-**5-SAc** of 92% ee was obtained in 52% yield at 62% conversion of the substrate (entry 6). Strangely, however, the ee value of the recovered acetate (*R*)-**5-OAc**[26b] was only 62% (vide infra). Furthermore, the thioacetate (*S*)-**5-SAc**, which was isolated in 99% yield, had an ee value of only 58% ee at the full conversion of the substrate (entry 7) (vide infra).

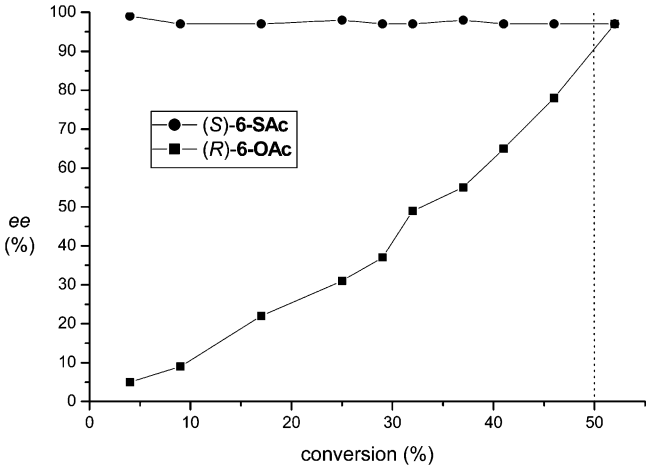


FIGURE 1. Dependencies of the ee values of thioacetate (*S*)-**6-SAc** and acetate (*R*)-**6-OAc** on the conversion of the substrate in the reaction of *rac*-**6-OAc** with KSAc.

A very high enantiomeric selectivity was exhibited by the catalyst in the reaction of the cyclohexenyl acetate *rac*-**6-OAc** with KSAc on a 2.5 mmol scale. This led to the isolation of the thioacetate (*S*)-**6-SAc** of 97% ee in 48% yield and the acetate (*R*)-**6-OAc**[26c] of ≥99% ee in 43% yield (entry 7). The reaction came practically to a complete halt after 51% conversion of the substrate. A further conversion of 2% took place only within a period of 24 h, and even an increase of the amount of the precatalyst $Pd_2(dba)_3{\cdot}CHCl_3$ from 2 to 5 mol % and that of ligand **4** from 8 to 20 mol % saw no conversion of the remaining acetate (*R*)-**6-OAc**. To determine the selectivity factor *S*,[27] the KR of *rac*-**6-OAc** was repeated and the ee values of the acetate and thioacetate were monitored over the whole course of the reaction.

Figure 1[28] shows the dependencies of the ee values of thioacetate (*S*)-**6-SAc** and acetate (*R*)-**6-OAc** on the conversion of the substrate. In accordance with the mechanistic scheme depicted in Scheme 1, the ee value of the thioacetate (*S*)-**6-SAc** was high and remained practically constant over the whole course of the reaction, whereas that of the acetate (*R*)-**6-OAc** increased steadily. Nonlinear regression of the selectivity factor *S*[29a] for 10 pairs of ee values and conversions gave $S = 72 \pm 19$.[29b] This value corresponds well with $S = 74 \pm 7$ for the palladium(0)/**4**-catalyzed KR of *rac*-**6-OMoc** with lithium *tert*-butylsulfinate in CH_2Cl_2/H_2O and with $S = 77 \pm 11$ for that of *rac*-**6-OMoc** with 2-pyrimidinethiol in CH_2Cl_2.[1e] These results demonstrate that the efficiency of the palladium-catalyzed KR with **4** is independent of the nucleofuge and the nucleophile. Almost the same results in terms of selectivities and yields were obtained when the KR of *rac*-**6-OAc** with KSAc was carried out on a 10 mmol scale.

A similar efficient KR took place in the reaction of the cycloheptenyl acetate *rac*-**7-OAc** with KSAc. The reaction came practically to a complete halt at 51% conversion of

(25) (a) Hayashi, T.; Yamamoto, A.; Yoshihiko, I. *J. Chem. Soc. Chem. Commun.* **1986**, 1090. (b) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073. (c) Brunner, H.; Deml, I.; Dirnberger, W.; Ittner, K.-P.; Reisser, W.; Zimmermann, M. *Eur. J. Inorg. Chem.* **1999**, 51. (d) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem.* **1998**, *110*, 3302; *Angew. Chem., Int. Ed.* **1998**, *37*, 3118. (e) Nishimata, T.; Yamaguchi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5713. (f) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105. (g) Longmire, J. M.; Wang, B.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 5435. (h) Okauchi, T.; Fujita, K.; Ohtagura, T.; Ohshima, S.; Minami, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1397. (i) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237.

(26) (a) McKew, J. C.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 4589. (b) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721. (c) Hashimoto, T.; Fukazawa, T.; Shimoji, Y. *Tetrahedron: Asymmetry* **1996**, *6*, 1649. (d) Ito, S.; Kasai, M.; Ziffer, H.; Silverton, J. V. *Can. J. Chem.* **1987**, *65*, 574. (e) Wahab, A.; Tavares, D. F.; Rauk, A. *Can. J. Chem.* **1990**, *68*, 1559.

(27) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(28) The lines connecting the points of measurement (●, ■, ▲) are only meant to show their togetherness and do not represent further points of measurement.

(29) (a) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem.* **2001**, *113*, 4419; *Angew. Chem., Int. Ed.* **2001**, *40*, 4289. (b) The program Origin 6.1 was used.

the substrate. The acetate (*R*)-**7-OAc**[26d] of ≥99% ee was obtained in 48% yield and the thioacetate (*S*)-**7-SAc** of 98% ee was isolated in 50% yield (entry 9). Even an increase of the amount of $Pd_2(dba)_3$·$CHCl_3$ from 2 to 4 mol % and that of **4** from 8 to 16 mol % did not lead to a conversion of the remaining acetate (*R*)-**7-OAc**.

The results of the KRs described above show, in agreement with previous results,[1e,10,19] that with ligand **4** the fast-reacting (matched) enantiomer of the acyclic acetates has the (*R*)- and that of the slow-reacting (mismatched) enantiomer the (*S*)-configuration. In the case of the cyclic acetates the enantiomer preference is the opposite.

II. "Memory Effect" and Dynamic Kinetic Resolution of Cyclopentenyl Acetate. (i) Reaction of the Racemic Substrate. A comparison of the enantioselectivities of the KRs and substitutions of the acetates *rac*-**5-OAc**, *rac*-**6-OAc**, and *rac*-**7-OAc** with KSAc (cf. Table 2, entries 6−9; Scheme 1) reveals, beside common features, interesting differences. While in all three cases the enantioselectivities of the allylic alkylation of the nucleophile with the matched acetates are apparently high, the selectivities of the KRs of the three racemates differ significantly. The selectivity of the KR is high for the six- and seven-membered cyclic acetates but is apparently low for the five-membered cyclic acetate. Furthermore, the enantioselectivity of the allylic alkylation of KSAc with the five-membered acetate *rac*-**5-OAc** under complete turnover conditions is much lower than under incomplete turnover conditions, for example at 62% conversion. A similar low enantioselectivity was observed in the case of the alkylation of thiocarboxylate ions with the carbonate *rac*-**5-OMoc** under complete turnover conditions (cf. Table 1, entry 5). This stands in contrast to the reactivity of the six- and seven-membered carbonates *rac*-**6-OMoc** and *rac*-**7-OMoc**, respectively, which delivered under high turnover conditions the corresponding thioesters with high ee values (cf. Table 1, entries 7 and 8). Although the six- and seven-membered acetates *rac*-**6-OAc** and *rac*-**7-OAc** were not studied under high turnover conditions, they are expected to show a reactivity similar to that of the carbonates. These differences in reactivity of *rac*-**5-OAc**, *rac*-**6-OAc**, and *rac*-**7-OAc** point to (1) the operation of a strong Me in the case of *rac*-**5-OAc**,[1e,16−19] the alkylation with the matched acetate (*S*)-**5-OAc** proceeding with a high enantioselectivity and that with the mismatched acetate (*R*)-**5-OAc** with a low enantioselectivity and (2) a racemization of the mismatched acetate (*S*)-**5-OAc** during the course of the substitution reaction. To verify these assumptions, the reaction of the racemic acetate *rac*-**5-OAc** with KSAc was repeated and the ee values of (*S*)-**5-SAc** and (*R*)-**5-OAc** were monitored over almost the whole course of the reaction (Figure 2 and Supporting Information, Table S2). Figure 2[28] shows the dependencies of the ee values of (*S*)-**5-SAc** and (*R*)-**5-OAc** on the conversion of the substrate. The ee value of (*S*)-**5-SAc** remained high at 96% until approximately 50% conversion. An increase of the conversion from 50% up to ≥99% led to a strong decrease of the ee value of the thioacetate. These results support the assumption of the operation of a strong ME. A control experiment demonstrated that a possible partial racemization of (*S*)-**5-SAc** under high turnover conditions cannot be held responsible for the decrease of the ee value of the thioacetate.

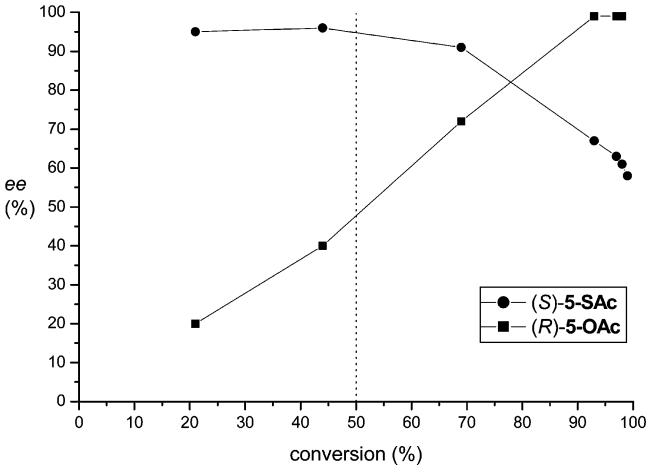
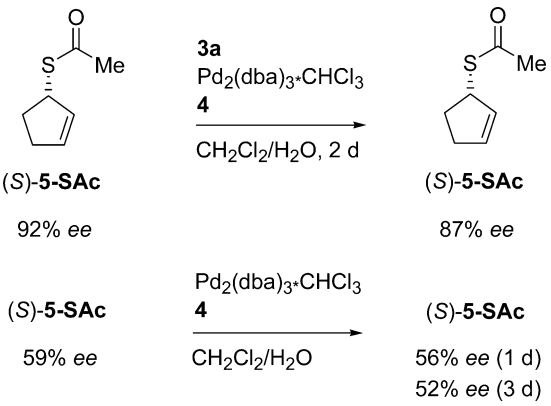


FIGURE 2. Dependencies of the ee values of the thioacetate (*S*)-**5-SAc** and the mismatched acetate (*R*)-**5-OAc** on the conversion of the substrate in the reaction of *rac*-**5-OAc** with KSAc.

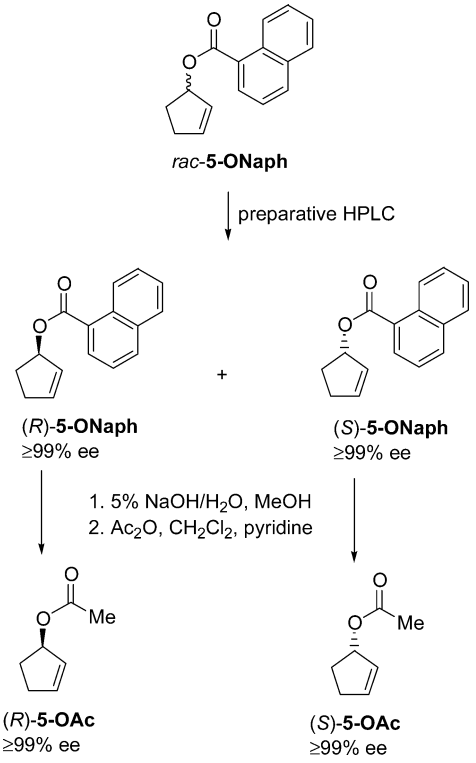
SCHEME 5. Configurational Stability of Thioacetate (*S*)-5-SAc during Palladium-Catalyzed Allylic Alkylation



Treatment of thioacetate (*S*)-**5-SAc** of 92% ee with KSAc in CH_2Cl_2/H_2O (9:1) in the presence of 2 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 8 mol % of **4** for 2 d and a subsequent workup led to an almost quantitative recovery of (*S*)-**5-SAc** that still had an ee value of 87% (Scheme 5). Thus, only a minor racemization of the thioacetate occurred within this period of time. Interestingly, the omission of the nucleophile KSAc (condition of no turnover) in the above experiment did also not lead to a significant racemization of (*S*)-**5-SAc**. Treatment of (*S*)-**5-SAc** of 59% ee with 2 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 8 mol % of **4** in CH_2Cl_2 for 1 d (3 d) and a subsequent workup afforded (*S*)-**5-SAc** with 56% ee (52% ee).

(ii) Reactions of the Enantiopure Substrates. To gain more insight into the ME and the origin of the apparently low selectivity of the KR of *rac*-**5-OAc**, a determination of the stereochemical course of the reactions of both the matched acetate (*S*)-**5-OAc** and the mismatched acetate (*R*)-**5-OAc**, in separate experiments, by using the enantiopure acetates was desirable. Although the ME of the cyclopentenyl acetate with **4** had been previously studied with $NaCH(CO_2R)_2$ by employing (*S*)-**5-OAc** of 55% ee,[17a] the low enantiomeric enrichment

SCHEME 6. Synthesis of Enantiopure Cyclopentenyl Acetates (*R*)-5-OAc and (*S*)-5-OAc



of the acetate precluded the observation of more subtle effects including a possible racemization of the remaining substrate.[30]

Preparative HPLC of the racemic cyclopentenyl naphthoate *rac*-**5-ONaph** on a Chiralcel-OD column on a 6-g scale readily afforded the naphthoates (*S*)-**5-ONaph**[31] and (*R*)-**5-ONaph** each of ≥99% ee and in 46% yield (Scheme 6). Hydrolysis of (*R*)-**5-ONaph** and (*S*)-**5-ONaph** furnished the enantiopure alcohols (*R*)-**5-OH**[26e] and (*S*)-**5-OH**, respectively. Their acylation gave the corresponding enantiopure acetates (*R*)-**5-OAc**[26b] and (*S*)-**5-OAc**.

Both acetates (*S*)-**5-OAc** and (*R*)-**5-OAc** were separately submitted to a palladium-catalyzed reaction with 1.4 equiv of KSAc in the presence of 2 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 8 mol % of **4** in CH_2Cl_2/H_2O (9:1) (Scheme 7). The ee values of the thioacetate and the remaining acetate were monitored over the whole range of the reactions. The reaction of the matched acetate (*S*)-**5-OAc** was faster than that of the mismatched acetate (*R*)-**5-OAc**.

Figure 3[28] shows the dependencies of the ee values of the matched acetate (*S*)-**5-OAc** and the thioacetate (*S*)-**5-SAc** on the conversion of the substrate (Supporting Information, Table S3).

The ee value of acetate (*S*)-**5-OAc**, which was ≥98% at the beginning, decreased with increasing conversion; in other words the mismatched acetate (*R*)-**5-OAc** was formed. At approximately 50% conversion only the presence of the racemic acetate *rac*-**5-OAc** was detected. From that point on the mismatched acetate (*R*)-**5-OAc**

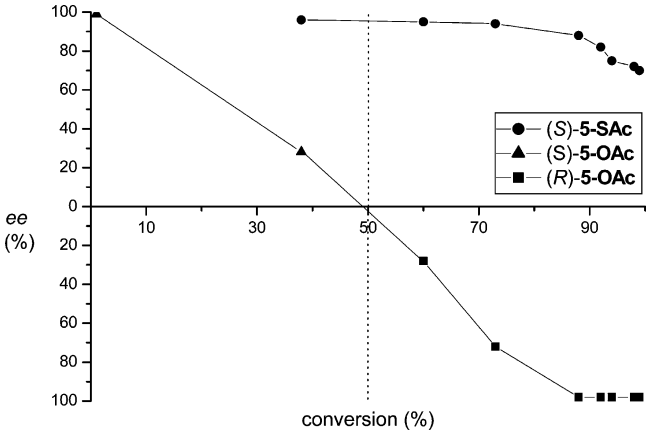
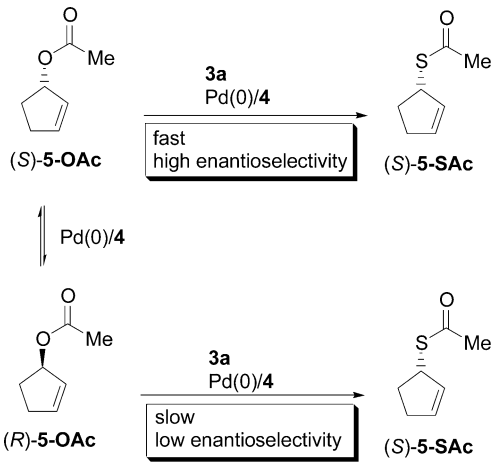


FIGURE 3. Dependencies of the ee values of the thioacetate (*S*)-**5-SAc** and the matched acetate (*S*)-**5-OAc** on the conversion of the substrate in the reaction of (*S*)-**5-OAc** with KSAc.

SCHEME 7. ME, Racemization, and DKR of Acetates (*S*)-5-OAc and (*R*)-5-OAc in Their Palladium-Catalyzed Reactions with KSAc



was in excess and its ee value increased with increasing conversion of the substrate to reach ≥99% at 88% conversion. The ee value of the thioacetate (*S*)-**5-SAc** remained high up to approximately 75% conversion but decreased at higher conversion. These results show that at the beginning of the reaction of (*S*)-**5-OAc** with KSAc a partial racemization of the matched acetate occurred. The matched acetate (*S*)-**5-OAc** reacted preferentially and delivered the thioacetate (*S*)-**5-SAc** with high enantioselectivity up to 80% conversion. At the same time the concentration of the mismatched acetate (*R*)-**5-OAc** gradually increased. After the consumption of most of the matched acetate (*S*)-**5-OAc**, the ee value of the thioacetate (*S*)-**5-SAc** decreased presumably because of the onset of a substitution of the mismatched acetate (*R*)-**5-OAc**, which proceeded with a lower enantioselectivity. Whether at high conversion, where GC analysis only showed the presence of the mismatched acetate (*R*)-**5-OAc**, also a partial racemization of (*R*)-**5-OAc** occurred is difficult to decide because of the possibility of a fast consumption of the matched acetate (*S*)-**5-OAc**.

Having recorded these unexpected results in the reaction of the matched acetate (*S*)-**5-OAc** with KSAc, it was of interest to see whether the mismatched acetate (*R*)-**5-OAc** would exhibit a behavior similar to that of the

(30) For an in-depth study of the ME of cyclopentenyl esters by using isotopically labeled racemic substrates, see ref 16.
(31) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.

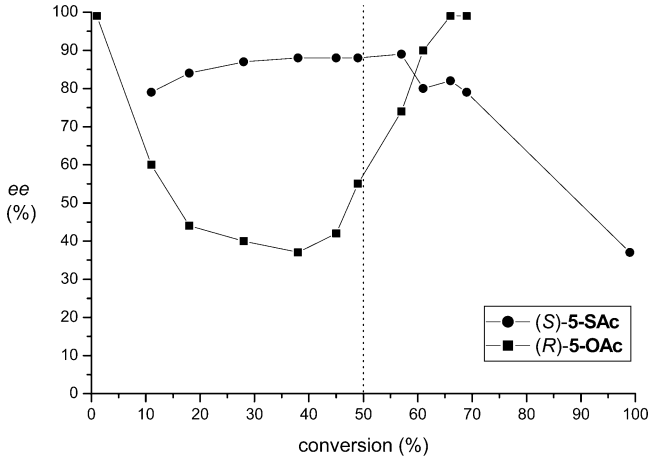
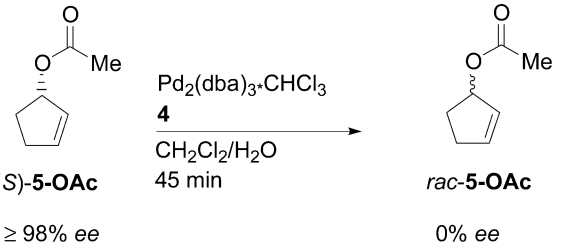


FIGURE 4. Dependencies of the ee values of the thioacetate (*S*)-**5-SAc** and the mismatched acetate (*R*)-**5-OAc** on the conversion of the substrate in the reaction of (*R*)-**5-OAc** with KSAc.

matched acetate or, according to Figure 2, show a ME and react with low enantioselectivity.

Figure 4[28] shows for the reaction of the mismatched acetate (*R*)-**5-OAc** with KSAc complex similar dependencies of the ee values of the components on the conversion of the substrate as in the case of the matched acetate. From the onset of the reaction the ee value of the mismatched acetate (*R*)-**5-OAc**, which was ≥99%, decreased; in other words, the matched acetate (*S*)-**5-OAc** was formed. The ee value of (*R*)-**5-OAc** remained almost constant between approximately 18% and 45% conversion and increased again strongly at higher conversion. Surprisingly, the ee value of the thioacetate (*S*)-**5-SAc** was much higher than anticipated and even increased with increasing conversion. Finally, the ee value of the thioacetate decreased at higher conversion where only the presence of (*R*)-**5-OAc** was detected by GC analysis. These results suggest that at the beginning of the reaction a partial racemization of the mismatched acetate (*R*)-**5-OAc** occurred with formation of the matched acetate (*S*)-**5-OAc**, which reacted with high enantioselectivity. The observation of almost constant ee values of the acetate (*R*)-**5-OAc** and the thioacetate (*S*)-**5-SAc** between 18% and 45% conversion of the substrate strongly indicates that at this point of the reaction a dynamic kinetic resolution (DKR)[23e−g] was established, which involved a racemization of the mismatched acetate and a preferentially substitution of the matched acetate, both in the presence of the chiral catalyst. Surprisingly, however, the DKR apparently ceased at a conversion higher than 45%. From that point on the ee value of (*R*)-**5-OAc** increased, and as a consequence of the lower enantioselectivity of the reaction of the mismatched acetate (*R*)-**5-OAc**, the ee value of the thioacetate (*S*)-**5-OAc** strongly decreased. Examples of this type of DKR that involves a racemization of the substrate under full turnover condition are scarce in a palladium-catalyzed allylic alkylation.[7] The DKR is different from the dynamic kinetic asymmetric transformation of an racemic allylic ester in palladium-catalyzed allylic alkylation, which features an equilibration of diastereomeric π-allyl-palladium(II) complexes.[32]

SCHEME 8. Palladium-Catalyzed Racemization of Acetate (*S*)-5-OAc

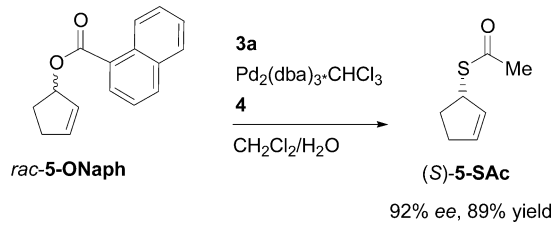


It was now of interest to see whether a palladium-catalyzed racemization of the cyclopentenyl acetate would also occur in the absence of the nucleophile, the condition of no turnover.[10a] Thus, the enantiopure acetate (*S*)-**5-OAc** was treated with 2 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 8 mol % of **4** in CH_2Cl_2/H_2O under the same conditions used above but by omitting KSAc (Scheme 8). After a short reaction time the acetate (*S*)-**5-OAc** had been completely racemized and *rac*-**5-OAc** was isolated in almost quantitative yield. The racemization of (*S*)-**5-OAc** and (*R*)-**5-OAc** without nucleophile perhaps proceeds through a Pd(0)/**4**-catalyzed ionization depicted in Scheme 1 followed by an addition of the acetate ion to the palladium atom and a subsequent reductive elimination.[10a,33] The racemization of the acetates in the presence of KSAc, the condition of complete turnover, is perhaps more complex, as hinted by the dependencies of the ee values of the substrates on their conversion (cf. Figures 3 and 4).

In summary, the results of the reactions of the matched acetate (*S*)-**5-OAc** and the mismatched acetate (*R*)-**5-OAc** with KSAc confirm the operation of a ME. The matched acetate reacts with an enantioselectivity significantly higher than that of the mismatched acetate. This effect is, however, superimposed by a temporary concomitant racemization and DRK of the acetates. As a consequence of these effects both acetates deliver the thioacetate (*S*)-**5-SAc** up to a relatively high conversion with high enantioselectivities. However, the DKR of the mismatched acetate (*R*)-**5-OAc** is only a temporary one, and thus the ee value of the thioacetate decreases strongly at a high conversion of the substrate because of the preferential reaction of the mismatched acetate. In the case of the matched acetate (*S*)-**5-OAc** this effect also operates, although to a much lesser degree. A rationalization of the various aspects of the palladium(0)/**4**-catalyzed reactions of the cyclopentenyl esters including the ME, which have been described previously[1e,16−19] and in this Article, is difficult at present. A major obstacle to the development of a mechanistic scheme is the formation of not one but several monomeric, oligomeric, and diastereomeric Pd(0)/**4** as well as π-allyl-Pd(II)/**4** complexes upon reaction of the racemic allylic ester with the precatalyst and the bisphosphane **4**.[17,34] These complexes, which are in rapid equilibrium, are most likely endowed with not only a different reactivity but also selectivity. Recently a two catalytic cycle working model has been proposed in order to rationalize the ME. It features a

(32) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.
(33) Grennber, H.; Langer, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190.
(34) (a) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707. (b) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **2000**, 2447.

SCHEME 9. Asymmetric Synthesis of Cyclopentenyl Thioacetate (*S*)-5-SAc



highly selective monomeric cyclic for the matched enantiomer and a less enantioselective oligomeric cycle for the mismatched enantiomer.[17] In accordance with this model would be the previous observation that the ME increases with increasing catalyst loading.[34b,18b] This effect is particularly expressed in the case of cyclopentenyl esters.[18b] For example, although at a catalyst loading of 2 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 8 mol % of **4** the six- and seven-membered cyclic allylic esters showed no ME in the reactions with thiocarboxylate ions, the five-membered cyclic esters exhibited a strong ME (cf. Tables 1 and 2). We have now also observed a strong ME in the reaction of the cyclohexenyl carbonate *rac*-**6-OMoc** with KSAc in THF/H_2O. An increase of the catalyst loading from 2 to 5 mol % of $Pd_2(dba)_3$·$CHCl_3$ and that of ligand **4** from 8 to 20 mol % saw under the condition of complete turnover a decrease of the ee value of the thioacetate (*S*)-**6-SAc** from 73% to 33% (see Supporting Information, Table S1, entries 6 and 7).

(iii) Asymmetric Synthesis of Cyclopentenyl Thioacetate. An efficient asymmetric synthesis of the cyclopentenyl thioacetate (*S*)-**5-SAc** from acetate *rac*-**5-OAc** or carbonate *rac*-**5-OMoc** was precluded because of the operation of a strong ME and other effects. Therefore the palladium-catalyzed reaction of the naphthoate *rac*-**5-ONaph** with 1.4 equiv of KSAc in the presence of 2 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 8 mol % of **4** in CH_2Cl_2/H_2O was studied. It was hoped that the ME would be suppressed in this case because of the other nucleofuge.[16,19]

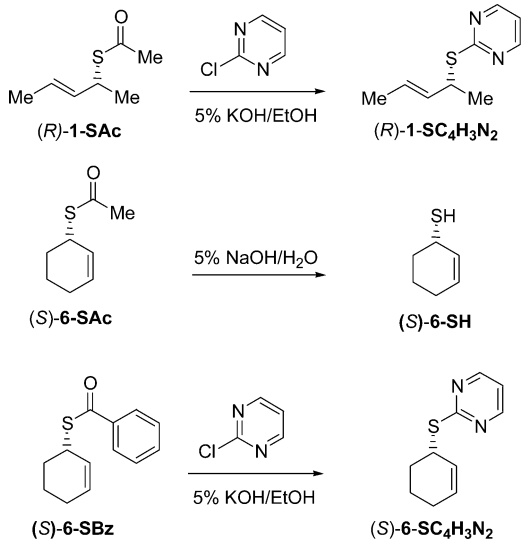
Indeed, by using the naphthoate *rac*-**5-ONaph** as starting material the thioacetate (*S*)-**5-SAc** was isolated with 92% ee in high yield (Scheme 9). Although this result is synthetically welcome, it also gives testimony to the complexity of the palladium-catalyzed allylic alkylation with ligand **4** since a similar reaction of *rac*-**5-ONaph** with 2-pyrimidinethiol as nucleophile in CH_2Cl_2 still showed a strong ME.[1e]

III. Configurational Assignments

The absolute configuration of thioacetate (*R*)-**1-SAc** was assigned through chemical correlation with sulfide (*R*)-**1-$SC_4H_3N_2$**[1e] as outlined in Scheme 10.

The acyclic thioesters (*R*)-**1-SAc**, (*R*)-**1-SBz,** and (*R*)-**2-SBz** were also assigned the *R* configuration since all of them possess the same sign of optical rotation. The absolute configuration of the cyclic thioacetate (*S*)-**6-SAc** was assigned through chemical correlation with thiol (*S*)-**6-SH**.[10d] The cyclic thioesters (*S*)-**5-SAc**, (*S*)-**6-SAc**, (*S*)-**7-SAc**, (*S*)-**5-SBz**, (*S*)-**6-SBz,** and (S)-**7-SBz** were also assigned the *S* configuration because of the same sign of optical rotation. In addition the absolute configuration of the cyclic thiobenzoate (*S*)-**6-SBz** was assigned by

SCHEME 10. Assignments of Absolute Configurations of Thioesters (*R*)-1-SAc, (*S*)-6-SAc, and (*S*)-6-SBz



chemical correlation with sulfide (*S*)-**6- $SC_4H_3N_2$**.[1e] Although the eight-membered thiobenzoate (*S*)-**8-SBz** exhibits the opposite sign of optical rotation as the seven-membered thiobenzoate (*S*)-**7-SBz**, it was also assigned the *S* configuration. We had previously noted a similar change of the sign of optical rotation in the case of the corresponding seven- and eight-membered cyclic *tert*-butyl sulfones, which both had the same absolute configuration.[1e] The absolute configurations of acetates (*S*)-**2-OMoc**,[1e] (*S*)-**1-OAc**,[26a] (*R*)-**6-OAc**,[26c] and (*R*)-**7-OAc**,[26d] carbonate (*R*)-**8-OMoc**,[1e] and alcohols (*S*)-**5-OH**[26e] and (*S*)-**6-OH**[26b] were assigned on the basis of their chiroptical data.

Conclusion

The palladium-catalyzed allylic alkylation of thiocarboxylate ions with racemic allylic esters in the presence of ligand **4** allows the asymmetric synthesis of cyclic and acyclic allylic thioesters. The necessary use of water in the allylic alkylations of the thiocarboxylate ions led with some allylic carbonates to a competing palladium-catalyzed "hydrolysis" with formation of the corresponding enantioenriched allylic alcohols. Formation of allylic alcohols in palladium-catalyzed allylic alkylation of external nucleophiles with allylic carbonates in the presence of water has not been previously reported. It may limit in certain cases the application of allylic carbonates in palladium-catalyzed allylic alkylation in water, a topic that has found much interest recently.[7d] In the present cases the unwanted side reaction could be avoided by choosing the more reactive thiobenzoate ion as nucleophile.

The reaction of the racemic allylic acetates with thiocarboxylate ions was accompanied by a KR of the substrates. The KRs were highly efficient for the six- and seven-membered cyclic acetates in terms of both the selectivities of enantiomer differentiation and of the allylic alkylation. The similar *S* values of the KRs of cyclohexenyl acetate with KSAc, lithium *tert*-butylsulfinate, and 2-pyrimidinethiol show that the selectivity is nearly independent of the nucleophile and the solvent.

The racemic cyclopentenyl acetates showed a strong ME in the palladium-catalyzed reaction with the thiocarboxylate ions. The matched acetate reacted with an enantioselectivity higher than that of the mismatched acetate. Most interestingly, this effect was superimposed by a concomitant racemization of both acetates. This led to the establishment of a DKR in the case of the mismatched acetate, and as a result both acetates deliver the thioacetate with high enantiomeric excess up to approximately 70% conversion. However, because of yet unknown reasons, a lasting DKR was not established over the whole range of the reaction, and thus the enantioselectivity of the allylic alkylation decreased substantially at higher conversion. Rationalization of the ME with ligand **4** is hampered because of the most likely involvement of not only one but several monomeric, oligomeric, and diastereomeric Pd(0)/**4** and π-allyl-Pd(II)/**4** complexes in several catalytic cycles. The recently proposed two catalytic cycle model for the equilibrating monomeric and oligomeric complexes and their diastereomers[17] may perhaps represent a good starting point for the development of a mechanistic scheme for the various aspects of the palladium-catalyzed allylic alkylation with this ligand, including the influence of the catalyst loading on the ME.

Experimental Section

General Procedure for Palladium-catalyzed Reactions of Carbonates with KSAc and KSBz (GP1). A Schlenk flask was successively charged with $Pd_2dba_3{\cdot}CHCl_3$, ligand **4**, and CH_2Cl_2 or THF, and the resulting orange solution was stirred at room temperature for 15 min. In the meantime a second Schlenk flask was charged with KSAc or KSBz and degassed water. The content of the first flask was added via a syringe to that of the second flask followed by the addition of the neat racemic allylic carbonate. Subsequently, the reaction mixture was stirred at room temperature if not stated otherwise, and the progress of the reaction was monitored by GC. For workup the reaction mixture was diluted with hexane/EtOAc, 20:1 (200 mL) and filtered through a layer (3 cm × 2 cm) of flash silica gel. The filtrate was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography and/or Kugelrohr distillation gave the allylic thioester.

General Procedure for Palladium-Catalyzed KR of Allylic Acetates with KSAc and KSBz (GP2). A Schlenk flask was successively charged with $Pd_2dba_3{\cdot}CHCl_3$, ligand **4**, and CH_2Cl_2, and the resulting orange solution was stirred at room temperature for 15 min. In the meantime a second Schlenk flask was charged with KSAc or KSBz and degassed water. The content of the first flask was added via a syringe to that of the second flask followed by the addition of the neat racemic allylic acetate. Subsequently, the reaction mixture was stirred at room temperature if not stated otherwise, and the progress of the reaction was monitored by GC. After the stated conversion of the substrate, the reaction mixture was diluted with hexane/EtOAc (20:1) (200 mL) and filtered through a layer of flash silica gel (3 cm × 2 cm). The filtrate was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography and/or kugelrohr distillation gave the allylic thioester and the allylic acetate.

Reaction of Carbonate *rac*-6-OMoc with KSAc. Thioacetic Acid (*S*)-*S*-Cyclohex-2-enyl Ester ((*S*)-6-SAc). Following GP1, to a solution of $Pd_2dba_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSAc (400 mg, 3.5 mmol) in degassed water (2 mL) and carbonate *rac*-**6-OMoc** (390 mg, 2.5 mmol). After the mixture stirred for 5.25 h at room temperature, a complete conversion of the carbonate was observed. For workup the mixture was diluted with hexane/EtOAc (10:1) (200 mL) and filtered through a layer of flash silica gel (3 cm × 2 cm). The filtrate was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (hexane/EtOAc, 20:1) afforded thioacetate (*S*)-**6-SAc** (199 mg, 51%) of 94% ee [GC, Lipodex γ, t_R ((*S*)-**6-SAc**) = 16.95 min, t_R ((*R*)-**6-SAc**) = 16.79 min] and alcohol (*S*)-**6-OH** (73 mg, 30%) of 82% ee [GC, CP-Chirasil-Dex-CB, t_R ((*S*)-**6-OH** = 27.05 min, t_R ((*R*)-**6-OH**) = 28.70 min)]; $[\alpha]_D$ −92.9 (*c* 0.98, CH_2Cl_2). Data for (*S*)-**6-SAc**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62−1.81 (m, 3 H), 1.96−2.10 (m, 3 H), 2.31 (s, 3 H), 4.16−4.20 (m, 1 H), 5.58−5.66 (m, 1 H), 5.83 (dtd, J = 10.0, J = 3.7, J = 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (u), 24.7 (u), 29.5 (u), 30.5 (d), 39.8 (d), 126.2 (d), 130.8 (d), 195.7 (u); IR (neat) $\tilde{\nu}$ 3028 (m), 2925 (s), 2860 (m), 2836 (m), 1690 (s), 1444 (m), 1431 (m), 1353 (m), 1256 (w), 1212 (w), 1136 (s), 1110 (s), 1039 (m), 1000 (w), 988 (w), 955 (m), 918 (w) cm^{-1}; MS (EI) *m*/*z* 156 (8) [M$^+$], 113 (10), 81 (100), 80 (46), 79 (48), 77 (12). Anal. Calcd for $C_8H_{12}OS$ (156.25): C 61.50, H 7.74. Found: C 61.25; H 7.76. Data for (*S*)-**6-OH**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54−1.77 (m, 4 H), 1.83−2.10 (m, 3 H), 4.17−4.23 (m, 1 H), 5.72−5.78 (m, 1 H), 5.81−5.87 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9 (u), 25.0 (u), 32.0 (u), 65.4 (d), 129.6 (d), 130.4 (d).

Reaction of Carbonate *rac*-6-OMoc with KSBz. Thiobenzoic Acid (*S*)-*S*-Cyclohex-2-enyl Ester ((*S*)-6-SBz). Following GP1, to a solution of $Pd_2dba_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSBz (881 mg, 5 mmol) in degassed water (2 mL) and carbonate *rac*-**6-OMoc** (390 mg, 2.5 mmol). After the mixture stirred for 24 h at room temperature, a complete conversion of the carbonate was observed and a mixture of **(*S*)-6-SBz** and (*S*)-**6-OH** in a ratio of 88:12 (GC) was formed. Workup and chromatography (hexane/EtOAc, 20:1) afforded thiobenzoate (*S*)-**6-SBz** (504 mg, 92%) as a colorless oil: 89% ee [HPLC, Chiralcel-OD-H, heptane/2-propanol, 100:1, 1.00 mL/min t_R ((*S*)-**6-SBz**) = 17.09 min, t_R ((*R*)-**6-SBz**) = 18.92 min]; $[\alpha]_D$ −243.9 (*c* 1.02, CH_2Cl_2). A similar reaction of *rac*-**6-OMoc** with KSBz in THF/water (9:1) for 15 h at room temperature furnished after workup thiobenzoate (*S*)-**6-SBz** (487 mg, 89%) of 72% ee: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70−1.92 (m, 3 H), 2.04−2.15 (m, 3 H), 4.38−4.46 (m, 1 H), 5.70−5.76 (m, 1 H), 5.86−5.92 (m, 1 H), 7.40−7.45 (m, 2 H), 7.52−7.57 (m, 1 H), 7.94−7.98 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.38 (u), 25.1 (u), 23.0 (u), 40.2 (d), 126.4 (d), 127.4 (d), 128.8 (d), 131.3 (d), 133.5 (d), 137.3 (u), 191.9 (u); IR (neat) $\tilde{\nu}$ 3028 (w), 2926 (m), 2859 (w), 2834 (w), 1660 (s), 1597 (w), 1581 (w), 1448 (m), 1430 (w), 1201 (s), 1175 (s), 1000 (w), 910 (s) cm^{-1}; MS (EI) *m*/*z* 218 (37) [M$^+$], 139 (12), 105 (100), 81 (57), 80 (31), 79 (18), 77 (33). Anal. Calcd for $C_{13}H_{14}OS$ (218.32): C 71.52, H 6.46. Found: C 71.54, H 6.54.

Resolution of Acetate *rac*-6-OAc with KSAc. Following GP2, to a solution of $Pd_2dba_3{\cdot}CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSAc (400 mg, 3.5 mmol) in degassed water (2 mL) and acetate *rac*-**6-OAc** (350 mg, 2.5 mmol). After the mixture stirred for 12 h at room temperature, a 51% conversion of the acetate was observed. Workup and chromatography (hexane/EtOAc, 20:1) afforded thioacetate (*S*)-**6-SAc** (187 mg, 48%) of 97% ee [GC, Lipodex γ, t_R ((*S*)-**6-SAc**) = 16.95 min, t_R ((*R*)-**6-SAc**) = 16.79 min]; $[\alpha]_D$ −265.9 (*c* 1.00, CH_2Cl_2) and acetate (*R*)-**6-OAc** (150 mg, 43%) of ≥ 99% ee [GC, Lipodex γ, t_R ((*R*)-**6-OAc** = 10.35 min, t_R ((*S*)-**6-OAc**) = 10.73 min (co-injection)]; $[\alpha]_D$ +216.9 (*c* 0.99, CH_2Cl_2) as colorless oils. Data for (*R*)-**6-OAc**: ^{1}H NMR (400 MHz) δ 1.53−2.06 (m, 9 H), 5.15−5.21 (m, 1 H), 5.60−5.66 (m, 1 H), 5.85−5.91 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (u), 21.7 (d), 25.2 (u), 28.6 (u), 68.3 (d), 125.9 (d), 132.8 (d), 170.8 (u).

A similar resolution of *rac*-**6-OAc** with KSAc in CH_2Cl_2/water (9:1) was carried out on a 10 mmol scale. Following GP2, to a solution of $Pd_2dba_3{\cdot}CHCl_3$ (204 mg, 0.20 mmol) and ligand

4 (552 mg, 0.80 mmol) in CH_2Cl_2 (72 mL) were successively added a solution of KSAc (1.60 g, 14 mmol) in degassed water (8 mL) and acetate *rac*-**6-OAc** (1.4 g, 10 mmol). After the mixture stirred for 12 h at room temperature, a 51% conversion was observed. Workup furnished thioacetate (*S*)-**6-SAc** (750 mg, 48%) of 97% ee and acetate (*R*)-**6-OAc** (616 mg, 44%) of ≥99% ee.

Reaction of Acetate *rac*-5-OAc with KSAc. To a solution of Pd_2dba_3·$CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSAc (400 mg, 3.5 mmol) in degassed water (2 mL) and acetate *rac*-**5-OAc** (320 mg, 2.5 mmol). After the mixture stirred at room temperature for 22 h, a complete conversion of the acetate was observed. Workup and chromatography (hexane/EtOAc, 20:1) afforded thioacetate (*S*)-**5-SAc** (352 mg, 99%) of 58% ee [GC, Lipodex γ, t_R ((*S*)-**5-SAc**) = 16.36 min, t_R ((*R*)-**5-SAc**) = 16.07 min] as a colorless oil.

Resolution of Naphthoate *rac*-5-ONaph by HPLC on Chiral Stationary Phase Containing Column. Naphthoic Acid (*R*)- and (*S*)-Cyclopent-2-enyl Ester (*R*)-5-ONaph and (*S*)-5-ONaph. Resolution of *rac*-**5-ONaph** (6.00 g) on a Chiralcel-OD column (250 mm × 50 mm) (hexane/ethanol, 99.5:0.5, 40 flow/min, 16 bar, 50 mg racemate/1 mL solvent, (t_R ((*S*)-**5-ONaph**) = 49.0 min, t_R ((*R*)-**5-ONaph**) = 61 min, 75 mg per injection) gave (*S*)-**5-ONaph** (2.76 g, 46%) and (*R*)-**5-ONaph** (2.76 g, 46%). Data for (*R*)-**5-ONaph**: ≥99% ee [HPLC, Chiralcel-OD-H, heptane/2-propanol, 99:1, 0.6 mL/min, t_R ((*S*)-**5-ONaph**) = 13.73 min, t_R ((*R*)-**5-ONaph**) = 14.57 min]; $[\alpha]_D$ +190.0 (*c* 0.99, CH_2Cl_2). Data for (*S*)-**5-ONaph**: ≥99% ee; $[\alpha]_D$ −189.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01−2.09 (m, 1 H), 2.32−2.50 (m, 2 H), 2.54−2.66 (m, 1 H), 6.00−6.08 (m, 2 H), 6.16−6.19 (m, 1 H), 7.42−7.52 (m, 2 H), 7.56−7.62 (m, 1 H), 7.82−7.86 (m, 1 H), 7.94−7.98 (m, 1 H), 8.13−8.16 (m, 1 H), 8.88−8.94 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9 (u), 31.1 (u), 81.1 (d), 124.3 (d), 125.6 (d), 125.9 (d), 127.4 (u), 127.5 (d), 128.3 (d), 129.2 (d), 129.8 (d), 131.1 (u), 132.9 (d), 133.6 (u), 137.6 (d), 167.3 (u). IR (neat) $\tilde{\nu}$ 3054 (w), 2971 (w), 2943 (w), 2853 (w), 1709 (s), 1593 (w), 1576 (w), 1510 (m), 1453 (w), 1364 (w), 1337 (m), 1277 (t), 1244 (t), 1197 (t), 1135 (t), 1073 (w), 1030 (s), 1009 (m), 947 (w) cm^{-1}; MS (EI) *m*/*z* 238 (23) [M^+], 173 (10), 172 (10), 155 (30), 127 (27), 67 (19). Anal. Calcd for $C_{16}H_{14}O_2$: C 80.65, H 5.92. Found: C 80.62, H 5.92.

Reaction of Acetates (*S*)-5-OAc and (*R*)-5-OAc with KSAc. Following GP1, to a solution of Pd_2dba_3·$CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSAc (400 mg, 3.5 mmol) in degassed water (2 mL) and acetate (*S*)-**5-OAc** (315 mg, 2.5 mmol) of ≥99% ee. During the reaction samples were withdrawn, and the conversion and the ee values of the acetate (*R*)-**5-OAc** and the thioacetate (*S*)-**5-SAc** were determined by GC (Lipodex γ). The reaction of enantiomerically pure acetate (*R*)-**5-OAc** of ≥99% ee with KSAc was carried out in a similar way.

Racemization of (*S*)-5-OAc. To a solution of Pd_2dba_3·$CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) was added degassed water (2 mL) and acetate (*S*)-**5-OAc** (315 mg, 2.5 mmol, ≥99% ee). GC analysis after 45 min showed the acetate to be racemic. Workup afforded *rac*-**5-OAc** (305 mg, 96%).

Reaction of Naphthoate *rac*-5-ONaph with KSAc. To a solution of Pd_2dba_3·$CHCl_3$ (52 mg, 0.05 mmol) and ligand **4** (138 mg, 0.20 mmol) in CH_2Cl_2 (18 mL) were successively added a solution of KSAc (400 mg, 3.5 mmol) in degassed water (2 mL) and naphthoate *rac*-**5-ONaph** (596 mg, 2.5 mmol). After the mixture stirred at room temperature for 3 h, a complete conversion of the naphthoate was observed. Workup and chromatography (hexane/EtOAc, 20:1) afforded thioacetate (*S*)-**5-SAc** (317 mg, 89%) as a colorless oil of 92% ee [GC, Lipodex γ, t_R ((*S*)-**5-SAc**) = 16.36 min, t_R ((*R*)-**5-SAc**) = 16.07 min]; $[\alpha]_D$ −202.3 (*c* 1.00, CH_2Cl_2).

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Supporting Information Available: General experimental procedures, spectral, analytical and mass spectrometric data for all new compounds not described in the Experimental Section, and Tables S1−S4. This material is available free of charge via the Internet at http://pubs.acs.org.

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