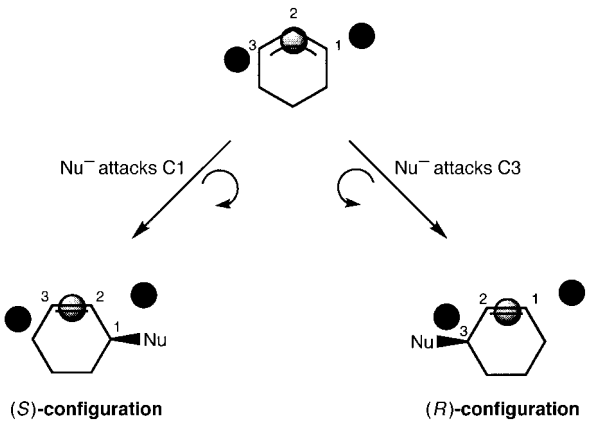

Scheme 2. Preferential formation of the product with *S* configuration. The methyl groups at C11 and C32 are represented by black circles, and the Pd atom by a gray circle.

nated between C1 and C3, which otherwise differ little in their steric and electronic properties.

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[4] a) M. Kranenburg, J. G. P. Delis, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Vrieze, N. Veldman, A. L. Spek, K. Goubitz, J. Fraanje, *J. Chem. Soc. Dalton Trans.* **1997**, 1839 – 1849; b) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081 – 3089; c) M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 25 – 27.

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[8] BSA = *N*,*O*-bis(trimethylsilyl)acetamide.

[9] a) Crystal data for $C_{32}H_{43}OP_2SPd \cdot BF_4$: $M_r = 730.92$, orthorhombic, space group $P2_12_12_1$, $a = 14.521(4)$, $b = 16.047(5)$, $c = 13.971(4)$ Å, $V = 3255(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.49$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 6.65$ mm^{-1}. Data were collected on a Philips PW1100/16 diffractometer with graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda = 1.5418$ Å) at $-100\,^{\circ}$C. A yellow crystal of dimensions $0.02 \times 0.30 \times 0.30$ mm was used, and a total of 2270 reflections were collected ($3 < \theta < 54^{\circ}$); 1931 reflections with $I > 3\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct methods and refined against $|F|$. Hydrogen atoms were introduced as fixed contributors. Empirical absorption corrections, transmission factors: 0.53/1.00. For all computations the Nonius OpenMoleN package[9b] was used. The absolute structure was determined by refining the Flack *x* parameter: $x = 0.02(2)$. Final results: $R(F) = 0.032$, $Rw(F) = 0.045$, GOF = 1.051, maximum residual electron density 0.69 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101072. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). b) C. K. Fair in MoleN. "An Interactive Intelligent System for Crystal Structure Analysis". Nonius, Delft, The Netherlands, 1990.

[10] A SPARTAN computer graphic programme was used, but in view of the approximate nature of these calculations, more detailed studies are in progress.

[11] The involvement of a rotational motion to explain, in part, the enantioselectivity of catalytic reactions with a P – N ligand was proposed by Brown et al.[3f] See also ref. [3d].

Mechanistic Implications of the Observation of Kinetic Resolution in a Palladium-Catalyzed Enantioselective Allylic Alkylation**

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The mechanism of Pd-catalyzed enantioselective allylic alkylation involves two steps which are of major importance in the catalytic cycle.[1] First, the allylic substrate, usually in the

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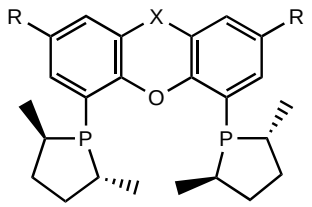
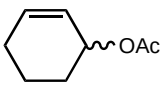
form of the acetate or carbonate, is activated by a Pd^0 complex with the probable formation of a (η^2-olefin)Pd^0 intermediate, which loses the anion to give a stable (η^3-allyl)Pd^{II} cationic intermediate. The second step involves the attack of the nucleophile on this cation to form the olefin product, which is bound η^2 to the Pd^0 center. The product is released in a subsequent step. Although the nature of the transition state in the second step and its role in determining the enantioselectivity of the overall process[2] have been extensively investigated, studies on the activation of the allylic substrate by Pd^0 are limited, since only one observation of enantioselective discrimination of the substrate (i.e., kinetic chiral resolution) by a Pd catalyst has been reported.[3] In most cases, rapid equilibration of the enantiomers apparently takes place and obscures any kinetic resolution process. It has even been proposed that this step is completely nonselective, which would be very surprising, since the reactions involved in the first step can be regarded as the reverse of those in the product-formation step, which can be highly enantioselective. We previously found that Pd catalysts containing the (*R*,*R*)-duxantphospholane ligands **A** and **B** give excellent product enantioselectivities[4] in the allylic alkylation reaction. We now report that kinetic resolution also occurs in the substrate-activation step and propose a mechanism that involves a favored rotational isomer.[4]

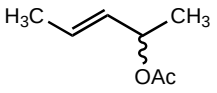


A: R = Me, X = S

B: R = H, X = $C(CH_3)_2$



rac-**1**



rac-**2**

We used *rac*-cyclohexenyl acetate (*rac*-**1**) and the *rac*-dimethylpropenyl acetate *rac*-**2** as substrates. In the reaction of dimethyl malonate with 0.5 equivalents of [{Pd(η^3-C_3H_5)Cl}$_2$], one equivalent of **A**, and 100 equivalents of *rac*-**1** in THF, (*S*)-**1** reacted much faster than (*R*)-**1** (Table 1). With BSA as base in THF, after 66% conversion to the (*S*)-malonate product with about 90% *ee*, the remaining acetate **1** had an *R*:*S* enantiomer ratio of 94:6 (88% *ee* (*R*), entry 1). We found that k_S/k_R had a constant value of 7 and was independent of the degree of conversion. The value of k_S/k_R does not change on increasing the quantity of **1** (400 equiv, entry 2), although the discrimination is somewhat temperature-dependent ($k_S/k_R \approx 8$ at 0 °C, entry 3). With NaH as base in THF (500 equiv **1**, entry 4) a slightly lower ratio ($k_S/k_R \approx 5$) is observed. However, for all reactions at 20 °C, the *ee* value of the malonate product remained almost unchanged at 82–87% (*S*). Furthermore, the *ee* of the product is the same at 50 and 100% conversion. Since (*S*)-**1** and (*R*)-**1** do not readily interconvert, the product enantioselectivity is not derived from the chirality of the substrate,[6] that is, no memory effect occurs.[5] Thus, the same *anti-anti*-(η^3-cyclohexenyl)Pd cation is formed from both (*S*)-**1** and (*R*)-**1**, and preferential attack[4] of the malonate on one of the allylic carbon atoms results in the observed enantioselectivity. Similar results were obtained with **B** as ligand. In CH_2Cl_2 with BSA/KOAc, both the reaction rate and k_S/k_R ratio of 2.4 (entry 5) were considerably lower, but the enantiomeric excess of the product remained unchanged.

High enantiodiscrimination and product enantioselectivity were also obtained with *rac*-**2**, for which in principle several (η^3-allyl)Pd cationic intermediates are possible. Figure 1 shows the composition of the reaction mixture as a function of time for the reaction of dimethyl malonate with *rac*-**2** (100 equiv), BSA/KOAc, and 1% **B** in THF at 20 °C. After 3 min 80% conversion to the malonate product has occurred, and the residual **2** has an *ee* of 92% (R), which corresponds to a k_S/k_R ratio of about 5. The decrease in concentraion of both (*S*)-**2** and (*R*)-**2** is first order with respect to substrate concentration. The half-lives of (*S*)-**2** and (*R*)-**2** in the first two to three half-lives of the reaction at 20 °C are approximately 30 s and 2 min, respectively. Similar values were obtained at 0 °C ($t_{1/2}$((*S*)-**2**) ≈ 7 min, $t_{1/2}$((*R*)-**2**) ≈ 1 h, $k_S/k_R \approx$ 6). As in the reaction of *rac*-**1**, the *ee* value of the malonate product from *rac*-**2** is the same at 50 and 100% conversion (*ee* = 82%). Therefore, the *S* and the *R* substrates must yield the same intermediate (η^3-allyl)Pd species, or if several

Table 1. Results of the kinetic chiral resolution.

Entry	Ligand	Substrate	Substrate/cat.	Solvent	Base	*T* [°C]	*t*	Conversion[b] [%]	*ee*[b] [%]	k_S/k_R[c]
1	A	*rac*-**1**	100	THF	BSA[a]	20	15 min	66	88	7.2
2	A	*rac*-**1**	400	THF	BSA	20	24 h	65	87	7.2
3	A	*rac*-**1**	100	THF	BSA	0	30 min	54	70	8.1
4	A	*rac*-**1**	500	THF	NaH	20	5 min	53	55	4.9
5	A	*rac*-**1**	100	CH_2Cl_2	BSA	20	35 min	87	77	2.4
6	B	*rac*-**2**	100	THF	BSA	20	3 min	80	92	4.3
7	B	*rac*-**2**	100	THF	BSA	0	45 min	66	82	5.8
8	A	*rac*-**2**	100	CH_2Cl_2	BSA	0	2 h	72	0	1.0

[a] BSA = *N*,*O*-bis(trimethylsily)acetamide. [b] Conversion and enantiomeric excess were determined by gas chromatography on a chiral stationary phase (β-cyclodextrin capillary column, 30 m × 0.25 mm, SGE 25QC2). For both substrates, the *R* enantiomer reacts more slowly, as was determined by comparing the optical rotations with literature values.[13, 14] [c] $k_S/k_R = \ln[(1 - C/100)(1 - ee/100)]/\ln[(1 - C/100)(1+ee/100)]$ (C = conversion; ee = enantiomeric excess of the recovered substrate).[3]

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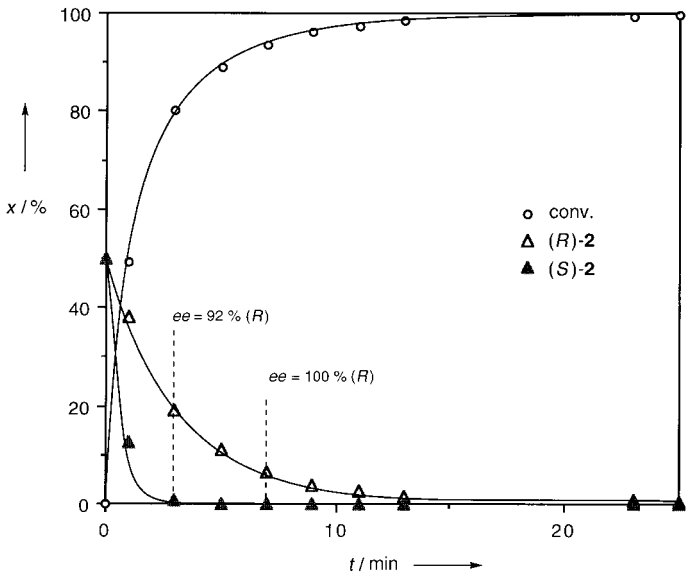


Figure 1. Fraction x of (R) and (S)-**2** in the Pd-catalyzed allylic alkylation (determined by gas chromatography on a β-cyclodextrin capillary column, 30 m × 0.25 mm, SGE 25QC2).

intermediates are involved, they must be equilibrated by fast exchange.

The cationic (η^3-dimethylpropenyl)Pd complex was isolated as the SbF_6^- salt after the reaction of **2** with the Pd catalyst with **B** as ligand. The ^1H, ^{13}C, and ^{31}P NOESY NMR data at 243 K in CD_2Cl_2 show the presence of an equilibrium mixture predominantly of the *exo* and *endo* forms of the *syn*,*anti*-(η^3-allyl)Pd diastereomers[7] in a ratio of about 6:1.

Our conclusions are illustrated in Scheme 1 for **2** as substrate.[7] The interacting methyl groups on the phospholane[8] ligand are depicted as "barriers **a** and **b**.

1) The initial complexation of **2** (R = Me) leads to four possible (η^2-olefin)Pd complexes.

2) The selective conversion of these complexes into the (η^3-allyl)Pd cations by oxidative addition results in the kinetic chiral resolution of **2**. Since interconversion of the (η^3-allyl)Pd cations is rapid under catalytic conditions, the reverse of this step must be sufficiently slow[6] in THF to allow kinetic resolution to occur.

3) If an antiperiplanar configuration[9] is assumed for oxidative addition and the preferential rotation (PR) model[4] with an early transition state is applied, we see that formation of two of the (η^3-allyl Pd) cations is disallowed, since clockwise rotation in the intermediates $\mathbf{O}_{S2}$ and $\mathbf{O}_{R2}$ is impeded by the the methyl group **a**.[8]

4) The kinetic resolution data show that the conversion of $\mathbf{O}_{S1}$ into the *syn*,*anti*-(η^3-dimethylpropenyl)Pd cation is more rapid than that of $\mathbf{O}_{R1}$ into the *syn*,*syn* form.

5) Since the *syn*,*anti*-(η^3-dimethylpropenyl)Pd cations are the most stable isomers and undergo rapid exchange under catalytic conditions the *syn*,*syn* form originating from $\mathbf{O}_{R1}$ would be expected to isomerize rapidly into these isomers.[10]

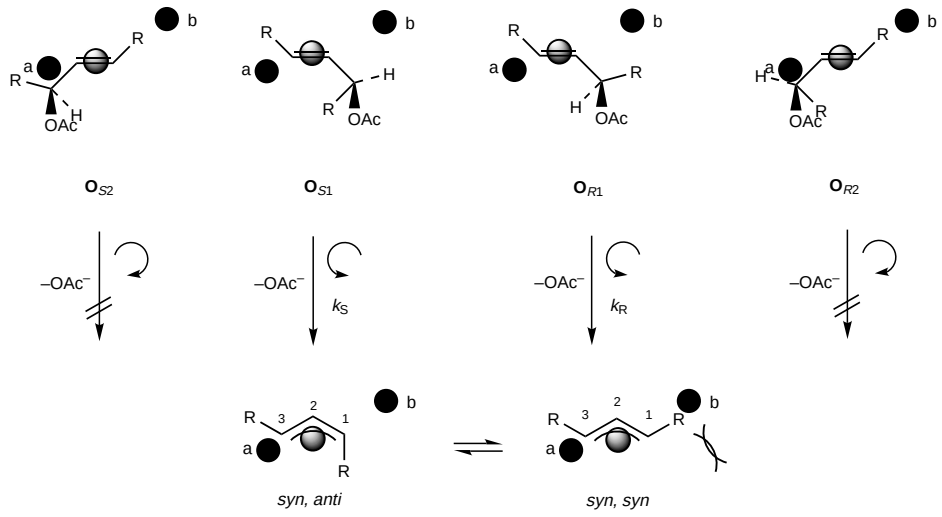
6) The first-order dependence of the rate of the overall reaction on the substrate concentration implies that the rate-determining step for the entire catalytic cycle under these conditions is either the coordination of the allyl acetate to the Pd^0 center or, more probably, the oxidative addition of the allylic substrate to Pd^0, which would necessitate that the complexation of allyl acetate to Pd^0 is weak and readily reversible.

7) The enantiomeric excess of the product results from two effects:

a) The dominance of the *syn*,*anti*-(η^3-allyl)Pd diastereomer in solution, which results from the spatial arrangement of barriers **a** and **b** in the ground state; the kinetic accessibility of this cation by isomerization of other allyl cations must be greater[11, 12] than the probability of the subsequent nucleophilic attack.

b) The selective attack of the nucleophile on the C1 atom of this cation, which is predicted to follow the PR mechanism with a late transition state[4] and avoids unfavorable rotational interactions with barrier **a**.

The PR model therefore plays a role in both the substrate-activation and product-formation steps. If the key and lock analogy is applied to this catalytic system, to obtain high enantioselectivity the key must not only be of the correct shape (7a) but will also be most effective if it can be turned only in one direction (7b).



Scheme 1. Mechanistic considerations for the kinetic chiral resolution in the Pd-catalyzed allylic alkylation of **2**. The methyl groups **a** and **b** of the chiral ligands are represented by black circles, and the Pd atom by a gray circle.

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[2] a) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3416 – 3426; b) P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2046 – 2054; c) J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsolnai, *Tetrahedron Lett.* **1994**, *35*, 1523 – 1526; d) J. M. Brown, D. I. Hulmes, P. J. Guiry, *Tetrahedron* **1994**, *50*, 4493 – 4505; e) P. S. Pregosin, R. Salzmann, A. Togni, *Organometallics* **1995**, *14*, 842 – 847; f) P. von Matt, G. Lloyd-Jones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Rüegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265 – 284; g) H. Steinhagen, M. Reggelin, G. Helmchen, *Angew. Chem.* **1997**, *109*, 2199 – 2202; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2108 – 2110.

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[5] B. M. Trost, R. C. Bunt, *J. Am. Chem. Soc.* **1996**, *118*, 235 – 236.

[6] Note that the use of an excess of BSA to deliver a constant concentration of nucleophile rapidly removes acetate ion from the reaction. This will limit both the reverse of the oxidative addition step and the possible racemization of the substrate, which would obscure kinetic resolution, and pairing of the acetate ion with the Pd cation, which is proposed to be responsable for memory effects. However, we find that pure (*R*)-**1** is not detectably racemized by the catalyst over 1 h in THF, with or without an excess of OAc^-.

[7] Since the ligand adopts a rigid envelope conformation,[4] the η^3-allyl complexes exist in *exo* and *endo* forms. In the mechanistic discussion involving **2**, we depicted only the *exo* form; similar but not identical considerations also apply to the *endo* isomer. Selected NMR data for [Pd(**B**)(η^3-dimethylpropenyl)]$^+$: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2, 298 K): major isomer (85 %): $\delta = 32.3$ (d, $^2J_{P,P} = 35.6$ Hz), 36.9 (br d, $^2J_{P,P} = 35.6$ Hz); minor isomer (15 %): $\delta = 29.9$ (br), δ 34.2 (br); 2D ^1H NOESY spectrum (400 MHz, CD_2Cl_2, 243 K): η^3-dimethylpropenyl ligand (a = *anti*, s = *syn*, c = central): major isomer: $\delta = 5.41$ (m, H_s), 4.41 (dd, $^3J_{Hc\text{-}Ha} = 12.9$ Hz, $^3J_{Hs,Hc} = 7.5$ Hz, H_c), 4.34 (m, H_a); minor isomer**:** $\delta = 5.97$ (br m, H_s), 5.12 (dd, $^3J_{Hc,Ha} = 13.0$, $^3J_{Hs,Hc} = 8.0$ Hz, H_c), 4.20 (m, H_a)**.** Details of the *endo*/*exo* isomerization and the effects of chloride ions will be reported elsewhere.

[8] The X-ray structure of the *exo* isomer of [Pd(**A**)(η^3-cyclohexenyl)]$^+$ shows one methyl group of the ligand **A** in close proximity to the organic substrate.[4] This corresponds to barrrier **a** in Scheme 1. The methyl group barrier **b** is somewhat more distant and not related to **a** by a C_2 axis.

[9] J. C. Fiaud, L. Aribi-Zouioueche, *J. Chem. Soc. Chem. Commun.* **1986**, 390 – 392.

[10] For the relative stability of such allyl complexes, see B. Akermark, S. Hansson, A. Vitagliano, *J. Am. Chem. Soc.* **1990**, *112*, 4587 – 4588.

[11] U. Burckhardt, M. Baumann, A. Togni, *Tetrahedron Asymmetry* **1997**, *8*, 155 – 159.

[12] When large quantities of malonate anion are present (i.e., with the $NaH/CH_2(COOR)_2$ method), the overall rate of the reaction is faster, and the enantioselectivity of the product greatly reduced (*ee* = 33 % (S)). We believe that the malonate anion possibly increases the rate of the oxidative addition step by coordination[11] of the carbanion to Pd^0 and thus accelerates the product-forming step. Under these conditions the rate of isomerization of the intermediate Pd allyl cations is not sufficient to obtain high enantioselectivity.

[13] T. Fukazawa, Y. Shimoji, T. Hashimoto, *Tetrahedron*: *Asymmetry* **1996**, *7*, 1649 – 1658.

[14] J. C. McKew, M. J. Kurth, *J. Org. Chem.* **1993**, *58*, 4589 – 4595.

Catalytic Enantioselective Aza Diels – Alder Reactions of Imino Dienophiles

Sulan Yao, Mogens Johannsen,* Rita G. Hazell, and Karl Anker Jørgensen*

The asymmetric catalytic hetero Diels – Alder class of reactions has attracted considerable interest due to the importance of the products formed.[1] The asymmetric oxa Diels – Alder reactions of aldehydes[2] and ketones[3] catalyzed by chiral Lewis acid catalysts can be performed with a high degree of stereoselectivity, whereas methods are still lacking for the corresponding catalytic enantioselective aza Diels – Alder reaction.[4–6] The asymmetric aza Diels – Alder reaction provides an effective route to optically active piperidine and tetrahydroquinoline heterocycles, as well as other compounds of fundamental importance.[1]

Yamamoto et al. have recently developed an enantioselective aza Diels – Alder reaction of aldimines with Danishefsky's diene using a stoichiometric amount of a chiral boron complex.[4] To our knowledge, the first catalytic enantioselective aza Diels – Alder reaction with a chiral zirconium complex as the catalyst was elegantly achieved by Kobayashi et al. for reactions of aldimines derived from 1-naphthaldehyde and 2-aminophenol, for example.[5] The highest enantiomeric excess (*ee*) obtained was 93 % with 20 mol % of the chiral zirconium catalyst.

Here we present a catalytic enantioselective aza Diels – Alder reaction of imines derived from ethyl glyoxylate with activated dienes. The optically active aza Diels – Alder adducts formed contain an ester functionality in the α-position to the nitrogen atom in the ring and an α,β-unsaturated ketone fragment. These adducts make attractive precursors for a variety of synthetic targets, such as a straightforward and very efficient route to optically active, nonnatural α-amino acids of the piperidine type.

Recently highly enantioselective hetero Diels – Alder and ene reactions of α-carbonyl esters and α-dicarbonyl compounds have been developed.[2, 3] These results prompted us to investigate whether the corresponding α-imino carbonyl compounds could be substrates in an enantioselective aza Diels – Alder reaction. We anticipated that the imino nitrogen atom and the oxygen atom would coordinate to the chiral Lewis acid complex to form a fixed chiral environment around the aldimino group.

The potential of the α-imino carbonyl compounds **1a – d** as possible substrates for the aza Diels – Alder reaction with Danishefsky's diene (**2a**) [Eq. (1); $Tos = H_3CC_6H_4SO_2$; $TMS = Me_3Si$] was investigated. Different chiral ligands, such as the 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP) ligands **3a**, **b** and the bisoxazoline ligands **4a – c**, have, in combination with various Lewis acid complexes and under

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