Regio- and Enantioselective Catalytic Hydrophosphorylation of Vinylarenes

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Received: December 23, 2004; Accepted: February 10, 2005

Abstract: Regioselective and stereoselective hydrophosphorylation of vinylarenes **1** with pinacol H-phosphonate **2** can be achieved with transition metal catalysts. The use of rhodium catalysts such as the Wilkinson complex leads to the *anti*-Markovnikov adducts **3** as the only observable reaction products. In contrast, palladium catalysts give high selectivities for the Markovnikov adducts **4**. In the presence of (*R*,*S*)-BINAPHOS as a chiral ligand, significant enantioselectivities have been obtained for the first time in hydrophosphorylation reactions.

Keywords: asymmetric catalysis; hydrophosphorylation; palladium; P ligands; rhodium

Introduction

The addition of compounds containing phosphorus-hydrogen bonds to C–C double or triple bonds provides an atom-economic method for the synthesis of organophosphorus derivatives. This transformation can be promoted by radical initiators or by adding catalytic amounts of acid or base.[1] In the last decade, several examples of carbon-phosphorus bond forming reactions have been reported which are catalyzed by transition metal complexes.[2,3] In particular, recent pioneering studies indicate that complexes of palladium[4] and rhodium[5] show a promising potential as catalysts for the direct addition of H-phosphonates to olefinic double bonds.

Among organophosphorus compounds, arylalkylphosphonic esters and the corresponding acids exhibit particularly interesting biological activities.[6] 2-Arylalkylphosphonates can be synthesized by base-catalyzed *anti*-Markovnikov addition of H-phosphonates[7] or by hydrogenation of vinylphosphonates.[8] Synthetic methodologies for the branched 1-arylalkylphosphonates comprise again hydrogenation of suitable precursors,[9] alkylation of deprotonated diesters of benzylphosphonic acids with methyl halides,[10] Arbuzov reaction of triethyl phosphite with 1-arylethyl bromides,[11] Michaelis–Becker reaction of dialkyl phosphite with 1-arylethyl bromides[12] and other methods requiring multistep procedures.[13] Optically active 1-arylethylphosphonates have been obtained *via* enantioselective methylation of benzylphosponic acid derivatives bearing chiral auxiliaries,[14] Ir(I)- or Ru(II)-catalyzed hydrogenation of 1-arylalkenylphosphonates and phosphonic acids[15] and by photo-Arbuzov rearrangement of optically active 2-(1-phenylethoxy)-1,3,2-dioxaphosphorinanes.[16]

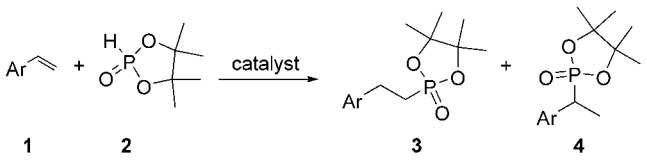
The synthesis of arylalkylphosphonic esters by catalytic hydrophosphorylation of alkenylarenes could open an elegant and versatile alternative to the above-mentioned methods. Obviously, the synthetic utility of this approach critically depends on the catalyst's ability to control the regioselectivity of the addition (Markovnikov *vs.* *anti*-Markovnikov) and the enantioselectivity in the case of the Markovnikov adduct.

In order to identify suitable catalysts and to investigate the factors controlling selectivity for such transformations, we have studied the addition of pinacol H-phosphonate (4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide, **2**) to styrene (**1a**) and related vinylarenes **1b–f** as the benchmark reaction. Herein we report the highly regioselective synthesis of 1- and 2-arylethylphosphonic esters **4** and **3** using palladium and rhodium catalysts, respectively. In particular, we found that the chiral phosphine/phosphite ligand (*R*,*S*)-BINAPHOS allows for the first time the introduction of significant levels of enantioselectivity in the formation of the Markovnikov products **4**.

Results and Discussion

Wilkinson's catalyst [$RhCl(PPh_3)_3$] was found to be a very efficient catalyst for the hydrophosphorylation of

 DOI: 10.1002/adsc.200404390



1 2 3 4

a: Ar = Ph
b: Ar = 4-ClC_6H_4
c: Ar = 4-*t*-BuC_6H_4
d: Ar = 4-$CH_3C(O)OCH_2C_6H_4$
e: Ar = 2-naphthyl
f: Ar = 6-CH_3O-2-naphthyl

Scheme 1.

1a with **2** leading exclusively to the formation of the linear adduct **3a** at 100 °C. In contrast to alkyl-substituted terminal olefins, no addition of supplementary ligands like dppb[5] is necessary to achieve full conversion within a standard reaction time of 10 hours (Table 1, entry 1). Even at 70 °C, full conversion can be achieved at prolonged reaction times (Table 1, entry 2). A variety of vinylarenes, both electron-rich and electron-deficient, reacted with more than 99% selectivity and high yield in the presence of this rhodium catalyst (Table 1, entries 3–6). Noteworthy, this approach represents a complementary methodology for the synthesis of 2-arylethylphosphonates containing base-sensitive functional groups like **1d**, which are not accessible via existing procedures.[7]

Table 1. Rh-catalyzed hydrophosphorylation of vinylarenes with **2**.[a]

Entry	Substrate	T [°C]	t [h]	Conv. (yield)[b] [%]	**3**:**4**[c]
1	**1a**	100	10	>99 (85)	>99:1
2	**1a**	70	20	>99	>99:1
3	**1b**	100	10	>99 (82)	>99:1
4	**1c**	100	10	>99 (75)	>99:1
5	**1d**	100	10	>99 (78)	>99:1
6	**1e**	100	10	>99 (80)	>99:1

[a] Catalyst: [$RhCl(PPh_3)_3$], 5 mol %; vinylarenes in two-fold excess with respect to **2**; solvent: dioxane.
[b] Conversion of **2** according to ^{31}P NMR and isolated yields after column chromatography.
[c] Isomer **4** was not detectable by ^{31}P NMR.

In contrast to rhodium catalysts, Pd systems are known to lead preferentially to the Markovnikov adducts **4** in hydrophosphorylation reactions.[4] The protocol originally developed by Tanaka and co-workers requires the use of preformed complexes having the general structure [Me_2PdL_2] (L_2 = 2 $CyPPh_2$ or dppb).[4] As one of the goals in the present study was an efficient screening of potential lead structures for asymmetric hydrophosphorylation, initial experiments aimed to find a simple palladium precursor for a reliable *in situ* protocol. Using [$Pd_2(bda)_3]\cdot CHCl_3$ together with 2 equivalents of $CyPPh_2$ per palladium gave only 28% conversion after 24 hours at 70 °C. However, full conversion was achieved under identical conditions when [CpPd(allyl)][17] was used as palladium precursor.

Table 2 summarizes representative results obtained with catalyst systems generated *in situ* from this precursor and achiral ligands under various conditions.

In the absence of additional ligand, [CpPd(allyl)] did not catalyze the reaction (Table 2, entry 1). The activity and selectivity of the *in situ* system with dppb [dppb = 1,4-bis(diphenylphosphino)butane] as ligand compared well with that of the preformed complex [Me_2Pd(dppb)] (Table 2, entry 2 *vs.* 3). The use of two equivalents of the monodentate ligand $CyPPh_2$ led to full conversion within a standard reaction time of 20 h even at 70 °C (Table 2, entry 5), but selectivity towards the Markovnikov adduct **4** was lower than that reported for [$Me_2Pd(CyPPh_2)_2$] at 100 °C (Table 2, entry 4). The regioselectivity of the *in situ* system can be improved to synthetically useful levels by using 3 equivs. of the mon-

Table 2. Pd-catalyzed hydrophosphorylation of vinylarenes with **2**.[a]

Entry	Pd source/Ligand	L/[Pd]	Substrate	Conv. (yield)[b] [%]	**3**:**4**[c]
1	[CpPd(allyl)]/-	–	**1a**	0	–
2	[CpPd(allyl)]/dppb	1	**1a**	100	50:50
3[d]	[Me_2Pd(dppb)]	1	**1a**	95	45:55
4[d]	[$Me_2Pd(CyPPh_2)_2$]	2	**1a**	not reported	5:95
5[e]	[CpPd(allyl)]/$CyPPh_2$	2	**1a**	100 (78)	21:79
6[e]	[CpPd(allyl)]/$CyPPh_2$	3	**1a**	85	13:87
7	[CpPd(allyl)]/$CyPPh_2$	3	**1b**	100 (84)	6:94
8	[CpPd(allyl)]/$CyPPh_2$	3	**1c**	100 (71)	11:89
9	[CpPd(allyl)]/$CyPPh_2$	3	**1d**	0	–
10	[CpPd(allyl)]/$CyPPh_2$	3	**1f**	>99 (85)	5:95

[a] Reactions conditions: [Pd] = 5 mol %; vinylarenes in two-fold excess with respect to **2**; T = 100 °C; t = 20 h; solvent = dioxane.
[b] Conversion of **2** according to ^{31}P NMR and isolated yields for the mixture of isomers after column chromatography.
[c] Determined by ^{31}P NMR.
[d] Data taken from ref.[4a]
[e] T = 70 °C.

odentate ligand (Table 2, entry 6). Thus, the optimized *in situ* procedure comprises the incubation of a dioxane solution of the ligand and [CpPd(allyl)] (in a 3:1 ratio for monodentate ligands and a 1.1:1 ratio for bidentate ones) in the presence of **2** at 100 °C for 40 min, followed by addition of the vinylarene **1a–f** to start the reaction. Both electron-donating (Table 2, entry 7 and 10) and -withdrawing (Table 2, entry 8) groups are tolerated and the reactions proceeded smoothly with high regioselectivity. In contrast to the Rh-catalyzed hydrophosphorylation (Table 1, entry 5), 4-vinylbenzyl acetate (**1d**) was unreactive under Pd-catalyzed conditions (Table 2, entry 9).

With a reliable procedure for the *in situ* preparation of Pd-based catalysts in hand, a broad variety of chiral ligands was tested for asymmetric hydrophosphorylation. An overview of typical results is provided in Figure 1.[18] The monodentate phosphine ligands NMDPP and (*R,S*)-CCDPP contain the cyclohexyldiphenylphosphine framework and favor the formation of the branched adduct **4**. However, both chiral ligands are not able to induce noticeable enantioselectivity. Similar disappointing results were obtained with other monodentate ligands such as the Feringa-type phosphoramidites. Bidentate chiral bis(diphenylphosphino) ligands such as BINAP, BPPM or NORPHOS gave moderate to good regioselectivities, but ees did not exceed 11%. Initially, electronically dissymmetrical phosphorus ligands of the phosphine-phosphite or the phosphine-phosphoramidite type gave similar poor enantioselectivities. However, enantioselectivities of up to 39% could be achieved by employing Josiphos-type ligands, albeit with low regioselectivities. This indicated that two different binding sites might be a preferred ligand motif for this transformation.

Indeed, it turned out that (*R,S*)-BINAPHOS[18] is able to induce both a high level of regioselectivity and significant enantioselectivity in the Pd-catalyzed hydrophosphorylation of vinylarenes. Under the standard screening conditions, 42% ee at a regioselectivity of 89% were obtained for the formation of (−)-**4a** from **1a** and **2**. Increasing the ligand to metal ratio did not lead to a pronounced improvement of enantioselectivity, but proved detrimental for the regioselectivity.[19] Reducing the reaction temperature to 70 °C still led to nearly quantitative conversion at prolonged reaction times, providing (−)-**4a** with 56% ee and 93% regioselectivity. Very high regioselectivity of up to 96% with similar levels of asymmetric induction varying from 29% to 54% were also observed with the [CpPd(allyl)]/(*R,S*)-BINAPHOS catalyst system for the hydrophosphorylation of other vinylarenes **1c**, **1e** and **1f** (Table 3, entries 4–6).

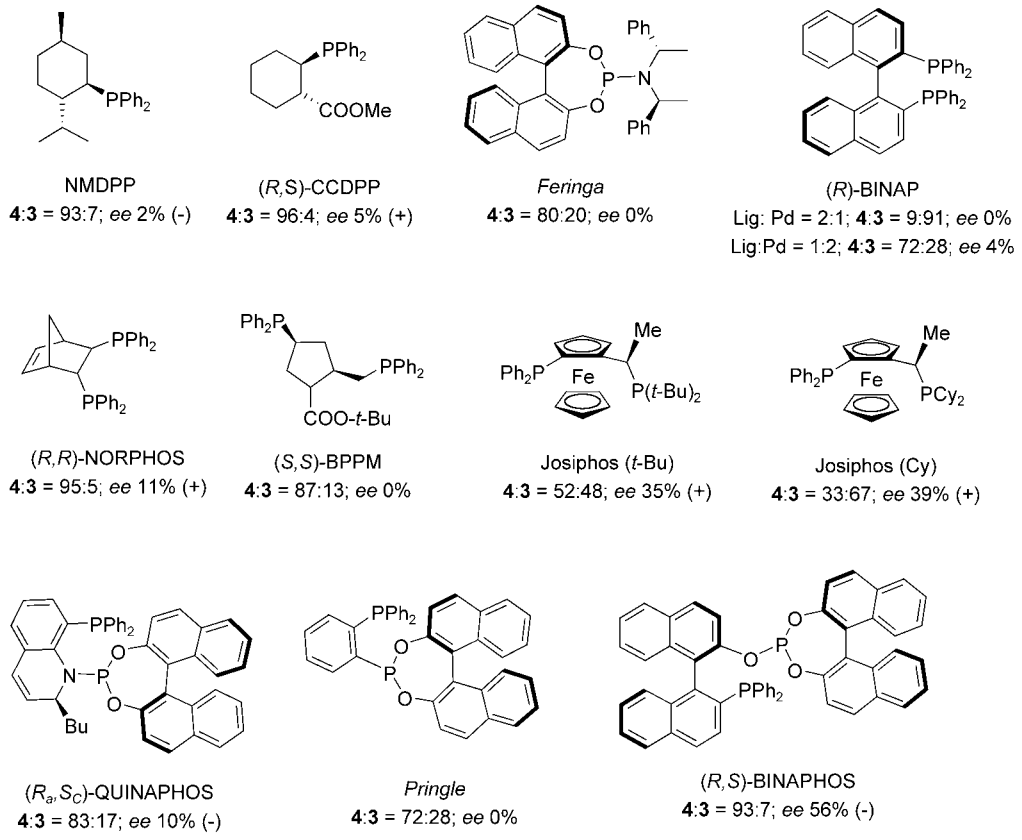


Figure 1. Selected results from the ligand screening for Pd-catalyzed asymmetric hydrophosphorylation.

Table 3. Enantioselective hydrophosphorylation of vinylarenes with **2** using the [CpPd(allyl)]/(*R*,*S*)-BINAPHOS catalyst system.[a]

Entry	Substrate	*T* [°C]	*t* [h]	Conv. (yield)[b] [%]	**3**:**4**[c]	*ee* [%]
1	**1a**	100	35	>99 (85)	11:89	42
2[d]	**1a**	100	35	>99	33:67	50
3	**1a**	70	70	>99	7:93	56
4	**1c**	100	35	>99 (65)	9:91	54
5	**1e**	100	35	>99 (80)	4:96	39
6	**1f**	100	35	>99 (85)	9:91	29

[a] Reactions conditions: [CpPd(allyl)] and (*R*,*S*)-BINAPHOS both 5 mol %; vinylarenes in two-fold excess with respect to **2**; solvent = dioxane.
[b] Conversion of **2** according to ^{31}P NMR and isolated yields for the mixture of isomers after column chromatography.
[c] Determined by ^{31}P NMR.
[d] 2:1 ligand to metal ratio.

Conclusion

We have shown that the metal-catalyzed hydrophosphorylation of vinylarenes can be controlled to provide either the linear (*anti*-Markovnikov) or the branched product with greater than 95% regioselectivity. Rhodium-based catalysts lead preferentially to the linear products, whereas Pd systems generally give the branched compound as the major product. Bidentate ligands with two different binding sites were identified as promising lead structures for asymmetric hydrophosphorylation. An *in situ* catalyst formed from (*R*,*S*)-BINAPHOS and [CpPd(allyl)] led to more than 90% regioselectivity and enantioselectivities in the 50% range for the hydrophosphorylation of styrene and related vinylarenes. This reaction is the first example for enantioselective hydrophosphorylation, adding a new possibility to the still very limited number of enantioselective P–H bond additions across double bonds.[20]

Experimental Section

General Remarks

All chemicals were purchased from Aldrich, Avocado or Strem and used as received. Manipulations were carried out under argon using standard Schlenk or glove-box techniques. Solvents were distilled under argon from appropriate drying agents. Compounds [CpPd(allyl)],[17] pinacol H-phosphonate (**2**),[21] and ligands (*R*,*S*)-CCDPP,[22] (R_a,S_C,S_C)-*Feringa*,[23] (*S*,*S*)-BPPM,[24] (*R*)-*Pringle*,[25] (R_a,S_C)-QUINAPHOS,[26] and (*R*,*S*)-BINAPHOS[18] were prepared according to literature procedures. NORPHOS and Josiphos-type ligands were gifts of Prof. Henri Brunner (University of Regensburg) and Dr. Hans-Ulrich Blaser (Solvias AG), respectively.

NMR spectra were recorded on a Bruker DPX 300 spectrometer, operating at 299.6 MHz (^{1}H) and 121.3 MHz (^{31}P), respectively. Chemical shifts are given in ppm relative to TMS (internal standard) for ^{1}H and to H_3PO_4 (external standard) for ^{31}P. GCs were recorded on a Sichromat 2–4 chromatograph equipped with an FID detector. HPLC analyses were carried out on a Jasco system equipped with a DAD detector. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

General Procedure for Rh-Catalyzed Hydrophosphorylation of Vinylarenes 1a–e with Pinacol H-Phosphonate (2)

Vinylarene **1a–e** (2 mmol) was added to a dioxane solution (2 mL) of [$Rh(PPh_3)_3Cl$] (46 mg, 0.05 mmol) and pinacol H-phosphonate (**2**; 164 mg, 1 mmol). The reaction mixture was stirred at 100 °C for a standard reaction time of 10 h. ^{31}P{^{1}H} NMR (C_6D_6) of the crude reaction mixture showed **3a–e** as the only detectable products. Compounds **3a–e** were purified through column chromatography [SiO_2, 230–400 mesh (Merck), eluent: hexane:*i*-PrOH = 10:1].

General Procedure for Pd-Catalyzed Hydrophosphorylation of Vinylarenes 1a–f with Pinacol H-Phosphonate (2)

A dioxane solution (2 mL) of [CpPd(allyl)] (7.4 mg, 0.035 mmol), phosphorus ligand (0.105 mmol or 0.038 mmol in the case of monodentate or bidentate, respectively) and pinacol H-phosphonate (**2**; 115 mg, 0.7 mmol) was heated at 100 °C for 45 min. Then, vinylarene **1a–f** (1.4 mmol) was added and the reaction mixture stirred at the same temperature for the desired time (see Tables 2 and 3). Conversion of **2** and the ratio between **3** and **4** were determined by analyzing a sample of the crude reaction mixture by means of ^{31}P{^{1}H} NMR (C_6D_6) and confirmed by GC analysis for the substrate **1a**. The products **3a–f**/**4a–f** were purified through column chromatography [SiO_2, 230–400 mesh (Merck), eluent: hexane:*i*-PrOH = 10:1].

4,4,5,5-Tetramethyl-2-(2-phenylethyl)-1,3,2-dioxaphospholane 2-Oxide (3a): ^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 6H), 1.52 (s, 6H), 2.16–2.23 (m, 2H), 3.00–3.15 (m, 2H), 7.23–7.34 (m, 5H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.6.

2-[2-(4-Chlorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (3b): ^{1}H NMR ($CDCl_3$): δ = 1.33 (s, 6H), 1.59 (s, 6H) 2.20–2.31 (m, 2H), 3.24–3.12 (m, 2H),

7.08–7.18 (m, 2H), 7.45–53 (m, 2H); ^{31}P NMR ($CDCl_3$): δ = 42.1.

2-{2-[4-(*tert*-Butyl)phenyl]ethyl}-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (3c): ^{1}H NMR (C_6D_6): δ = 1.32 (s, 6H), 1.61 (s, 6H), 1.67 (s, 9H), 2.32–2.50 (m, 2H), 3.40–3.55 (m, 2H), 7.34 (d, 2H), 7.65 (d, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.8.

4-[2-(4,4,5,5-Tetramethyl-2-oxido-1,3,2-dioxaphospholan-2-yl)ethyl]benzyl Acetate (3d): ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 6H), 1.51 (s, 6H), 2.10 (s, 3H), 2.10–2.22 (m, 2H), 3.0–3.08 (m, 2H), 5.08 (s, 2 H), 7.23 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.5.

4,4,5,5-Tetramethyl-2-[2-(2-naphthyl)ethyl]-1,3,2-dioxaphospholane 2-Oxide (3e): ^{1}H NMR ($CDCl_3$): δ = 1.38 (s, 6H), 1.54 (s, 6H), 2.22–2.34 (m, 2H), 3.18–3.27 (m, 2H), 7.35–7.39 (m, 1H), 7.45–7.52 (m, 2H), 7.67–7.73 (m, 2H), 7.80–7.85 (m, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.5.

4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaphospholane 2-Oxide (4a): ^{1}H NMR ($CDCl_3$): δ = 1.14 (s, 3H), 1.18 (s, 3H), 1.42 (s, 3H), 1.45 (s, 3H), 1.67 (dd, J = 7.4 Hz, J = 18.6 Hz, 3H), 3.16 (dq, J = 7.4 Hz, J = 21.2 Hz, 1H), 7.20–7.37 (m, 5H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.0. Enantiomeric excess was determined *via* GC; column: Chirasil-Dex-CB (25 m, d = 250 μm, d_{film} = 0.25 μm); carrier: H_2 (1.0 bar); conditions: 250 °C//100 °C/1 °C min^{-1}/150 °C/70 min isotherm//300 °C; (+)-**4a** = 68.7 min; (−)-**4a** = 69.3 min.

2-[1-(4-Chlorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (4b): ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3H), 1.30 (s, 3H), 1.49 (s, 3H), 1.53 (s, 3H), 1.71 (dd, 3H, J = 7.3 Hz, J = 18.5 Hz), 3.20 (dq, 1H, J = 7.3 Hz, J = 20.9 Hz), 7.28–7.40 (m, 4H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 41.1.

2-[1-(4-*tert*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (4c): ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 3H), 1.26 (s, 3H), 1.37 (s, 9H), 1.50 (s, 3H), 1.52 (s, 3H), 1.74 (dd, 3H, J = 7.4 Hz, J = 18.7 Hz), 3.24 (dq, 1H, J = 7.4 Hz, J = 21.2 Hz), 7.27–7.32 (m, 2H), 7.33–7.39 (m, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.3. Enantiomeric excess was determined *via* HPLC; column: Chiralcel OJ-H (length: 250 mm, i. d. 4.6 mm), eluent: *n*-heptane:2-propanol = 99:1; flow rate 0.5 mL/min; **4c** (minor) = 34.5 min; **4c** (major) = 40.7 min; **3c** = 101.7 min.

4,4,5,5-Tetramethyl-2-[1-(2-naphthyl)ethyl]-1,3,2-dioxaphospholane 2-Oxide (4e): ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 3H), 1.23 (s, 3H), 1.46 (s, 3H), 1.51 (s, 3H), 1.83 (dd, 3H, J = 7.3 Hz, J = 18.6 Hz), 3.40 (dq, 1H, J = 7.3 Hz, J = 21.6 Hz), 7.48–7.61 (m, 3H), 7.81–7.93 (m, 4H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 41.8. Enantiomeric excess was determined *via* HPLC; column: Chiralcel OJ-H(length: 250 mm, i. d. 4.6 mm), eluent: *n*-heptane:2-propanol = 90:10; flow rate 0.5 mL/min; **4e** (minor) = 33.0 min; **4e** (major) = 41.8 min; **3e** = 53.1 min.

2-[1-(6-Methoxy-2-naphthyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-Oxide (4f): ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 3H), 1.22 (s, 3H), 1.46 (s, 3H), 1.51 (s, 3H), 1.81 (dd, 3H, J = 7.4 Hz, J = 18.6 Hz), 3.63 (dq, 1H, J = 7.4 Hz, J = 21.0 Hz), 3.93 (s, 3H), 7.13–7.21 (m, 2H), 7.48–7.51 (m, 2H), 7.72–7.78 (m, 2H); ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 42.0. Enantiomeric excess was determined *via* HPLC; column: Chiralcel OJ (length: 250 mm, i. d. 4.6 mm), eluent: *n*-heptane:2-propanol = 80:20; flow rate 0.5 mL/min; **4f** (minor) = 19.6 min; **4f** (major) = 29.4 min; **3f** = 42.5 min.

Acknowledgements

We thank Prof. Brunner for a sample of NORPHOS and Dr. Hans-Ulrich Blaser for the SOLVIAS Ligand Kit. We thank Mike Schmitkamp for technical assistance. M. O. S. thanks the DAAD for a fellowship. Additional financial support from the Deutsche Forschungsgemeinschaft (SFB 380) is gratefully acknowledged.

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