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^{31}P NMR assays for rapid determination of enantiomeric excess in catalytic hydrosilylations and transfer hydrogenations

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ABSTRACT

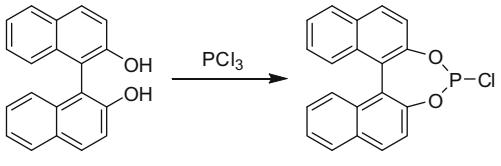
Chiral chlorophosphine (*S*)-(1,1′-binaphthalen-2,2′-dioxy)chlorophosphine (*S*)-**2** was tested for its performance as a chiral-derivatizing agent (CDA) using solutions of various alcohols, amines, and *N*-BOC amino acids. Based on ^{31}P NMR spectroscopy, the enantiomeric excess was determined within less than 5 min per sample, reaching an accuracy of ±1%. One-pot procedures for a combination of the method with typical homogenous catalytic transformations of prochiral ketones were established. Hydrosilylation products may be analyzed after conversion into alcohols using HF bound to PS-vinyl pyridine co-polymer beads. Transfer hydrogenations simply require solvent evaporation prior to the use of the CDA.

1. Introduction

Rapid progress in asymmetric synthesis and increasing demand for enantiopure compounds require development of accurate and reliable techniques for the determination of enantiomeric excess (ee).[1–3] Currently, accurate analyses of mixtures of enantiomers are dominated by chromatographic methods.[2] Progress has been made in the rapid analysis of enantiomers by chiral GC, which has become a powerful tool for high throughput ee determination.[3] However, problems arise from decomposition or racemization at elevated temperatures.[4] Hence, the advent of combinatorial methods for asymmetric catalysis triggered the progress of several alternative approaches.[3,5,1a] Recent reports of rapid assays cover a broad range of technologies including reaction microarrays,[6] mass spectrometry,[7] imprinted polymers,[8] supramolecular systems[9] as well as chromogenic,[10] enzymatic,[11] or immuno assays.[12] Specifically NMR-based determinations of ee have gained interest, due to the speed and simplicity of the related protocols.[13] These rely on the use of chiral shift reagents,[14] chiral transition metal complexes,[15] or chiral-derivatizing agents (CDAs/CSAs).[13,16] In particular, CDAs have become of great importance for the analysis of configuration and enantiomeric excess.[17] Discrete diastereomers generated by this method show chemical inequivalent shifts that are typically five times higher than the use of other chiral reagents.[13] Since Mosher introduced MPTA (α-methoxy-α-(trifluoromethyl)-phenylacetic acid) for the resolution of chiral amines in 1969,[18] a broad range of reagents have been used to monitor the respective diastereomeric shifts by ^{1}H and heteronuclear NMR spectroscopy.[13,19] Of all nuclei applied, ^{31}P seems to be most attractive since it combines the economic use of non-deuterated solvents with good sensitivity, narrow line width, large chemical shift dispersion, responsiveness to structural changes in diastereomeric adducts, and the simplicity of broad band decoupled ^{31}P NMR spectra.[20]

In spite of their favorable properties, to the best of our knowledge there are very few reports about the applications of phosphorus-based CDAs in catalyst screening. We attribute this fact to the high sensitivity of these reagents towards protic and nucleophilic components, which are typical for protocols of many asymmetric catalytic reactions, for example, transfer hydrogenations or hydrosilylations. However, a reactive functionality is intrinsic for an effective conversion of alcohol, amine, or carboxylic acid-directed CDAs. Hence, the key to a rapid CDA-based evaluation of asymmetric catalysts is post-catalytic procedures, which efficiently remove unwanted reactive components without necessitating demanding or expensive sample preparation.

We here report an efficient protocol for ^{31}P NMR-based determination of enantiomeric excess in catalytic reactions. This protocol utilizes the BINOL-derived CDA (*S*)-**2** or (*R*)-**2** introduced by Tang and co-workers for discrimination of chiral alcohols or amines, which is comfortably available from economic precursors (Fig. 1).[21]



(*S*)-**1** (*R*)-**1** (*S*)-**2** (*R*)-**2**

Figure 1. Synthesis of chiral-derivatizing agents (*R*)- and (*S*)-(1,1′-binaphthalen-2,2′dioxy)chlorophosphine (*S*)-**2** and (*R*)-**2**.[21]

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2. Results and discussion

(1,1′-Binaphthalen-2,2′-dioxy)chlorophosphines (*S*)-**2** and (*R*)-**2** are availible in a one-step one-day synthesis from trichlorophosphine and (*R*)- or (*S*)-BINOL, respectively (Fig. 1).[21] The chiral-derivatizing agents are obtained in quantitative yield and can be stored under argon for months without any sign of decomposition. In the presence of a tertiary amine such as NEt_3, CDAs (*S*)-**2**, or (*R*)-**2** react cleanly with alcohols, amines, or carboxylic acids to the respective phosphite derivatives. Since the phosphorus atom is located on the C_2-axis of the chelating BINOL-frame, it is not stereochemically active and only two diastereomers can be formed (Fig. 2). Correspondingly, for non-enantiopure samples, two resonances were observed by ^{31}P NMR, which exhibit identical chemical shifts for either enantiomer of the CDA. Hence, in contrast to chiral GC or HPLC, the signal originating from each enantiomer of a compound can be assigned by conversion of an enantiomerically pure sample with both enantiomers of the CDA.

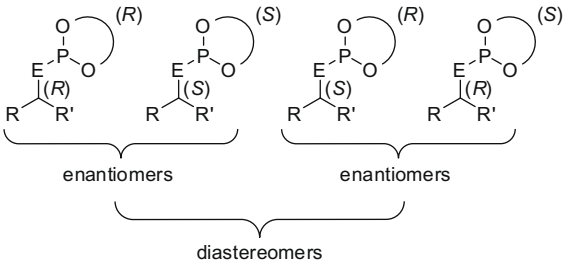
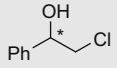
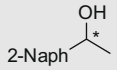
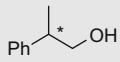
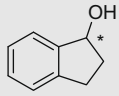
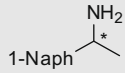
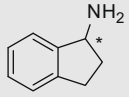


Figure 2. Illustration of the correlation between structure and observed ^{31}P NMR resonances. E = O, NH, COO.

The two diastereomeric ^{31}P NMR signals for both enantiomers of the compounds tested are listed in Table 1. Except for entry 4, base line separation of the signals was achieved on a 400 MHz spectrometer in all cases. In general, $\Delta\delta$ values are highest for substrates possessing an aryl group on the α-carbon, and decrease depending on the nature of the functionality in the order: alcohols > amines > carboxylic acids. For benzylic alcohols, diastereomeric shifts ranging from 6.72 to 5.19 ppm were observed (entries 1–4). Smaller signal separation results for benzyl amines (4.46–2.01 ppm, entries 7 and 8). For aliphatic compounds diastereomeric signals are split by less then 1 ppm. The observed trend is in agreement with values reported for other compounds.[21] Broadening the scope of the method, we found that CDAs (*S*)-**2**/(*R*)-**2** are also well suited to determine the configuration and enantiomeric excess of carboxylic acids. We therefore tested a range of N-protected amino acids, which show $\Delta\delta$ values larger than 1 ppm. Despite the broad applicability, the method tested encounters some limitations. For an alcohol with a stereogenic center at the β-position (entry 4), the observed $\Delta\delta$ value of 0.02 ppm does not give base line separation of the signals. Compounds with more than one CDA-reactive functional group such as diols, amino alcohols, diamines, or unprotected amino acids lead to complex signal patterns, which cannot be used for quantification of enantiomeric excess.

We examined the accuracy of the method over the full range of enantiomeric ratios probing samples of known ee, which were received by mixing enantiomerically pure (*R*)- and (*S*)-1-phenyl ethanol (Fig. 3). Differences between determined and theoretical values are less than ±1%, and do not show any systematic trend. While conversion of CDAs (*S*)-**2** or (*R*)-**2** with all nucleophiles tested is completed within less than 5 min, kinetic resolution impairs quantifications of enantiomeric ratios, if the CDA is the limiting component. Thus, for racemic 1-phenylethanol 63% ee (*S*) is derived from ^{31}P NMR analysis, if a (*S*)-**2**/alcohol ratio of 1:20 is applied. Using excess of (*S*)-**2** leads to correct values. To account for this effect, samples, which might still contain substances consuming the chlorophosphite reagent, a CDA/product ratio of at least 1.5:1 was applied.

Table 1
^{31}P NMR chemical shift δ and shift differences $\Delta\delta$ in ppm of products formed from (*S*)-(1,1′-binaphthalen-2,2'dioxy)chlorophosphine (*S*)-**2** and alcohols, amines, or amino acids

Entry[a]	Substrate	(*R*,*S*)//(*S*,*R*)	(*S*,*S*)//(*R*,*R*)	$\Delta\delta$
1		141.03	147.65	6.62
2		144.01	137.29	6.72
3		143.90	138.03	5.87
4		137.41	137.43	0.02
5		135.61	140.80	5.19
6		142.93	143.85	0.92
7		151.11	149.10	2.01
8		150.04	146.37	4.46
9		145.67	150.13	4.46
10		152.49	152.17	0.32
11		151.28	151.56	0.28
12	Boc-Ala-OH	140.56	141.80	1.24
13	Boc-Ile-OH	139.14	141.11	1.97
14	Boc-Leu-OH	139.48	141.06	1.51
15	Boc-Val-OH	139.00	140.57	1.58

[a] Conditions: CDA/substrate/Et_3N = 2:1:4. Solvent: THF.

Generally, the use of deuterated solvent is not necessary for catalytic runs, as ^{31}P NMR shifts can be referenced to the signal of excess CDA. Due to the good NMR sensitivity of the ^{31}P nuclei, only 500 μL of a 36 mM substrate solution are necessary to obtain satisfactory signal to noise ratio after 150 pulses, which translates to a measurement time of less than 5 min. Such product concentrations are typical for catalytic screenings.

Having established the scope and accuracy of the method, we examined its applicability for on-line ee determination in combination with standard catalytic protocols. Asymmetric hydrosilylation has become a versatile tool for the synthesis of chiral

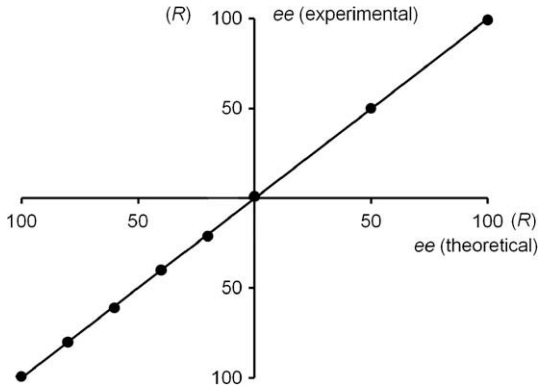
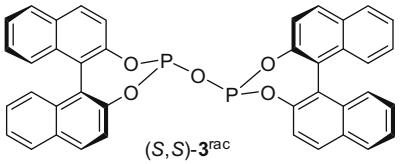


Figure 3. Correlation between theoretical and calculated enantiomeric excess for defined mixtures of (*R*)- and (*S*)-1-phenyl ethanol. The latter were calculated from the integral ratios of the respective diastereomeric ^{31}P NMR resonances after conversion with (*S*)-**2**.

alcohols.[22] Here, the originally produced silanols need to be converted to alcohols prior to application of the CDA.[23] Generally, small quantities of water present in reagents or solvent consume the CDA under formation of the oxo-bridged dimer **3**^{rac}, giving rise to an intense signal at 134.23 ppm. (**3**^{meso} is formed additionally from racemic mixtures of CDA; $\delta(^{31}P) = 133.11$ ppm). To minimize the excess of CDA required, anhydrous proton and fluoride-based cleavage protocols were investigated, including addition of *p*TsOH, trifluoroacetic acid, or tetrabutyl ammonium fluoride in alcoholic or THF solution. The cleanest and most effective method turned out to be fluoride-induced desilylation with HF bound to PS-vinyl pyridine co-polymer beads (SP-py/HF). Conversion is completed within 10 min after which the solid-phase reagent can conveniently be removed by filtration. Figure 4 depicts the reaction sequence applied for the CDA-based evaluation of the asymmetric hydrosilylation catalysts. With the exception of **6** all catalysts tested achieve high to near quantitative conversion within 24 h (Table 2). Unsurprisingly, no asymmetric induction was found using achiral NHC–Rh(I) systems **5** and **6**. For all enantiomeric excesses detected, ees values of up to 81% for the CuH/BINAP system were seen. The CuH catalysts, which have been developed based on the original 'Styker's reagent' by Lipshutz et al. and Yun et al. were generated in situ from $Cu(OAc)_2$, diphenyl silane and chiral diphosphines.[24,25] Controls revealed a divergence of less than 2% for the enantiomeric excess determined using CDA **1** in the *one-pot* procedure versus values obtained by chiral GC. The observed ees correspond well with available literature values; for example, Yun et al. reported 79% ee (*S*) for conversion of acetophenone using CuH/BINAP at 0 °C in toluene.[25] Our slightly reduced ee (entry 1 in Table 2) may be attributed to the higher reaction temperature and a change of solvent. Interestingly, determination of yields based on the consumption of the defined amount of CDA added differed by less then 7% from GC-derived values. Thus, in catalytic hydrosilylations, CDA (*S*)-**2** can be applied for ^{31}P NMR-based parallel quantification of enantiomeric excess and reaction yields.



In addition to asymmetric hydrosilylation, Rh and Ru catalyzed transfer hydrogenations have developed into a versatile tool for the generation of chiral alcohols from prochiral ketones.[26] Thus, we investigated options to apply CDA (*S*)-**2**/^{31}P NMR-based determination of enantiomeric excess in combination with typical transfer hydrogenation protocols. Initial investigations revealed that for procedures employing aqueous formate as a reducing agent, tedious work-up procedures or residual water limited the usability of our technique. A common method for transfer hydrogenations uses catalysts generated in situ from precursors such as $[(\eta^6\text{-arene})RuCl_2]_2$ or $[(Cp^*)RhCl_2]_2$ and amino alcohols in *i*PrOH as solvent and hydrogen sources.[26,27] The high reactivity of the P–Cl moiety in (*S*)-**2** toward alcohols requires complete removal of the solvent

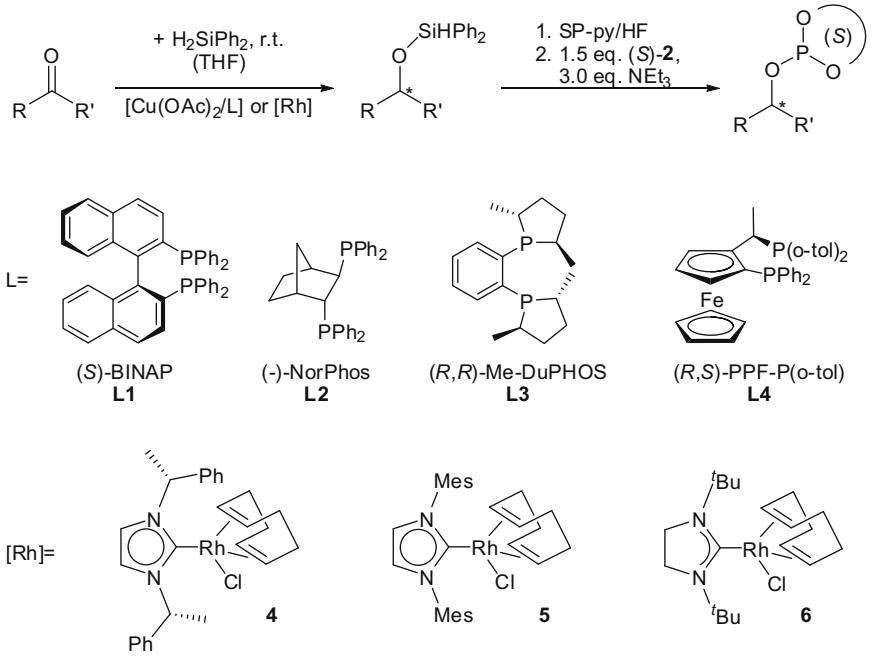


Figure 4. Hydrosilylation of ketones employing chiral copper[24,25] or rhodium[29,30] catalysts. For results see Table 2.

Table 2
Results for the hydrosilylation of prochiral ketones (see Fig. 4)

Entry [a]	Catalyst[b]	Ketone[c]	Yield[d] (%)	ee[e] (%)
1	$Cu(OAc)_2$/**L1**	**K1**	>99	75 (*S*)
2	$Cu(OAc)_2$/**L1**	**K2**	>99	81 (*S*)
3	$Cu(OAc)_2$/**L1**	**K3**	>99	81 (*S*)
4	$Cu(OAc)_2$/**L2**	**K1**	86	20 (*S*)
5	$Cu(OAc)_2$/**L2**	**K2**	79	24 (*S*)
6	$Cu(OAc)_2$/**L2**	**K3**	79	39 (*S*)
7	$Cu(OAc)_2$/**L3**	**K1**	92	33 (*R*)
8	$Cu(OAc)_2$/**L3**	**K2**	90	47 (*R*)
9	$Cu(OAc)_2$/**L3**	**K3**	85	42 (*R*)
10	$Cu(OAc)_2$/**L4**	**K1**	>99	46 (*S*)
11	$Cu(OAc)_2$/**L4**	**K2**	>99	51 (*S*)
12	$Cu(OAc)_2$/**L4**	**K3**	>99	48 (*S*)
14	**4**	**K1**	70	1 (*S*)
15	**4**	**K2**	98	15 (S)
16	**4**	**K3**	72	9 (*S*)
17	**5**	**K1**	>99	0
18	**5**	**K2**	>99	0
19	**6**[f]	**K1**	78	0
20	**6**[f]	**K2**	98	0

[a] Reaction time 24 h.
[b] **L1**–**L4** see Figure 4.
[c] **K1**: acetophenone, **K2**: 2-acetonaphthone, **K3**: 1-indanone.
[d] Conversions determined by GC against diethyleneglycol dibutyl ether (internal standard).
[e] Ees determined by ^{31}P NMR spectroscopy using CDA (*S*)-**2**.
[f] Reaction time 7 days.

Table 3
Results for the transfer hydrogenations of prochiral ketones (see Fig. 5)

Entry[a]	Catalyst[b]	Ketone[c]	Yield[d] (%)	ee[e] (%)
1	[Ru]/**L5**	**K1**	64	89 (*R*)
2	[Ru]/**L5**	**K2**	91	85 (*R*)
3	[Ru]/**L5**	**K3**	88	93 (*R*)
4	[Rh]/**L5**	**K1**	57	73 (*R*)
5	[Rh]/**L5**	**K2**	68	78 (*R*)
6	[Rh]/**L5**	**K3**	74	81 (*R*)
7	[Rh]/**L6**	**K1**	69	28 (*S*)
8	[Rh]/**L6**	**K2**	82	21 (*S*)
9	[Rh]/**L6**	**K3**	69	33 (*S*)

[a] Reaction time 2 h.
[b] [Ru] = $[(p\text{-cymene})RuCl_2]_2$, [Rh] = $[(Cp^*)RhCl_2]_2$; **L5, L6** see Figure 4.
[c] **K1**: acetophenone, **K2**: 2-acetonaphthone, **K3**: 1-indanone.
[d] Conversions determined by GC against diethyleneglycol dibutyl ether (internal standard).
[e] Ees determined by ^{31}P NMR spectroscopy using CDA (*S*)-**2** .

prior to the addition of the CDA, which can most easily be achieved by evaporation. The resulting protocol is depicted in Figure 5. Using amino alcohol **L5**, good to high enantiomeric excess was observed in combination with both transition metal catalyst precursors, with Ru being slightly superior to Rh. Chiral induction resulting from less rigid **L6** was poor. Again, obtained results correspond well with GC control and available literature values. For example, Wills et al. reported ees of 91% (*S*) and 86% (*S*) for conversion of acetophenone and acetonaphthone, respectively, using the other enantiomers of **L6** in combination with $[(p\text{-cymene})RuCl_2]_2$ under similar conditions.[27]

3. Conclusion

BINOL-derived chiral-derivatizing reagents (*S*)-**2** and (*R*)-**2** are well suited for the ^{31}P NMR-based determination of enantiomeric excess in solutions containing chiral alcohols, amines, or amino acids. The accuracy of the method has been verified. Maximum deviations from theoretical values were less than ±1% in all cases tested with a total acquisition time for the ^{31}P NMR of less than 5 min. The technique can be used in combination with standard protocols for catalytic asymmetric hydrosilylations and transfer hydrogenations of prochiral ketones, without introduction of tedious work-up procedures. Conversion of the hydrosilylation products into alcohols is easily achieved using hydrogen fluoride coordinated to pyridine on solid support, while the chiral alcohols from transfer hydrogenations can directly be analyzed after removal of all volatiles. The one-pot protocols established here are straight forward to parallelize. Due to a unique combination of parallel workup, inexpensive reagents, and non-deuterated solvents as well as short ^{31}P NMR acquisition time, the method seems to be advantageous for enantiomeric excess determination in catalyst screenings and may easily be extended to other phosphorus-based CDAs.[20]

4. Experimental

4.1. General remarks

All reactions were performed under an argon atmosphere using standard Schlenk glassware or a glove-box. NMR measurements were recorded on JEOL JNM-GX 400. ^{31}P NMR chemical shifts are reported relative to external phosphoric acid (δ = 0.0 ppm). $Cu(OAc)_2 \cdot H_2O$, amino alcohols, phosphine ligands, (*S*)-BINOL (*R*)-BINOL, and all chiral alcohols, amines as well as amino acids were obtained from commercial sources and used without further purification. Complexes **4**–**6** were synthesized according to literature procedures.[28–30] Derivatizing agents (*S*)- and (*R*)-(1,1′-binaphthalen-2,2′-dioxy) chlorophosphine (*S*)-**2** and (*R*)-**2** were synthesized as described previously.[21]

4.2. Derivatization of (*R*)- or (*S*)-(1,1′-binaphthalen-2,2′-dioxy)chlorophosphine 1 with amines, alcohols, amino acids, and phosphorus acids

(*S*)-(1,1′-Binaphthalen-2,2'-dioxy)chlorophosphine (CDA (*S*)-**2**, 63 mg, 0.18 mmol) and triethylamine (48 μL, 0.36 mmol) were dissolved in 600 μL THF. After the addition of the chiral racemic or enantiomerically pure nucleophilic reagent (0.12 mmol), triethyl-

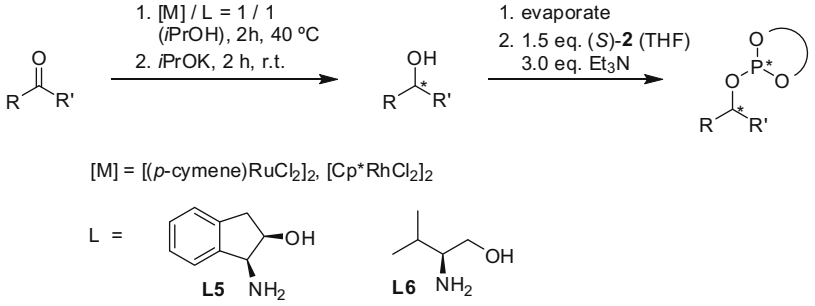


Figure 5. Transfer hydrogenation of ketones employing in situ-generated chiral Ru(II) or Rh(III) catalysts. For results see Table 3.

ammonium chloride was allowed to settle, before the reaction mixture was analyzed by ^{31}P NMR spectroscopy.

4.3. NMR parameters

To achieve high accuracy in the quantification of NMR signals, a $\pi/2$ pulse delay of five times the longest T_1 has to be maintained.[31] However, T_1 values may exceed 10 s for phosphites.[32] Additional effects like different variations in NOE signal enhancement for broad band decoupled heteronuclear experiments or non-linear instrumental responses may hamper comparability of quantifications for different resonances. Using 1-phenyl ethanol as a test system, we achieved variances <1% for the diastereomers resulting from conversion with CDA (*S*)-**2** after using the following parameters: relaxation delay: 2 s, x-offset: 100 ppm, x-sweep: 200 ppm, pulse angle: 45° acquisition time: 1 s.

4.4. Hydrosilylation employing Cu-catalysts

Copper(OAc)$_2$-hydrate (0.7 mg, 3.8 μmol) and diphosphane (3.8 μmol) were placed in a glass vial equipped with a stirring bar and dissolved in THF (120 μL), before diphenylsilane was added (22.3 μL, 0.12 mmol). After stirring for 10 min, a solution of ketone (0.12 mmol) and bis(ethyleneglycol) dibutylether (0.06 mmol) in 0.5 mL thf was added. After stirring the solution for the time given in Table 2, the silyl ether was cleaved using HF/pyridine on solid phase (3 equiv based on amount of silane). After stirring for 60 min, the solution was filtered into a NMR tube and 500 μL THF containing CDA (*S*)-**2** (63 mg, 0.18 mmol) and triethylamine (48 μL, 0.36 mmol) were added. Triethylammonium chloride was allowed to settle, before the reaction mixture was analyzed by ^{31}P NMR spectroscopy.

4.5. Hydrosilylation employing Rh(I)-catalysts

At first, NHC–Rh(I) catalyst (1.2 μmol) was placed in a glass vial equipped with a stirring bar and dissolved in THF (120 μL), before diphenylsilane was added (33.4 μL, 0.18 mmol). Then, a solution of ketone (0.12 mmol) and bis(ethyleneglycol) dibutylether (0.06 mmol) in 0.5 mL THF was added. After stirring the solution for the time given in Table 2, the silyl ether was cleaved using HF/pyridine on solid phase (3 equiv based on amount of silane). After stirring for 60 min, the solution was filtered into a NMR tube and 500 μL THF containing CDA (*S*)-**2** (63 mg, 0.18 mmol) and triethylamine (48 μL, 0.36 mmol) were added. Triethylammonium chloride was allowed to settle, before the reaction mixture was analyzed by ^{31}P NMR spectroscopy.

4.6. Transfer hydrogenation employing Rh(III)- and Ru(II) catalysts

A solution of the catalyst precursor {A: $[(Cp^*)RhCl_2]_2$ (0.15 mg, 0.24 μmol) or B: $[(p\text{-cymene})RuCl_2]_2$ (0.14 mg, 0.24 μmol)} and the respective amino alcohol (0.48 μmol), dissolved in isopropanol (0.3 mL) were placed in a glass vial equipped with a stirring bar and warmed to 40 °C for 2 h. Then, a solution of ketone (0.12 mmol) and bis(ethyleneglycol) dibutylether (0.06 mmol) in 0.5 mL THF was added, before the reaction was started by addition of potassium isopropanolate (5 μL of a 0.2 M solution in isopropanol). After 2 h, the reaction was quenched with acetic acid (0.2 mL, 3 mmol), and volatiles were removed in vacuo. The residue was redissolved using 600 μL THF containing CDA (*S*)-**2** (63 mg, 0.18 mmol) and triethylamine (48 μL, 0.36 mmol). Triethylammonium chloride was allowed to settle, before the reaction mixture was analyzed by ^{31}P NMR spectroscopy.

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