Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 3863

www.rsc.org/obc

PAPER

Convenient, enantioselective hydrosilylation of imines in protic media catalyzed by a Zn-trianglamine complex†‡

Jadwiga Gajewy, Jacek Gawronski and Marcin Kwit*

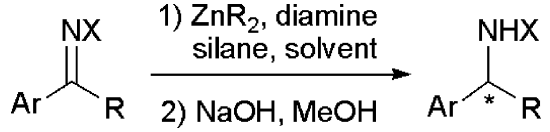
Received 13th January 2011, Accepted 25th February 2011
DOI: 10.1039/c1ob05074e

Chiral hexamine macrocycle derived from *trans*-1,2-diaminocyclohexane (DACH) in a complex with diethylzinc efficiently catalyzes the asymmetric hydrosilylation of *N*-phosphorylated aryl-alkyl or aryl-aryl ketimines in protic media with enantiomeric excess of the product approaching 100%. The cyclic structure of the trianglamine ligand increases the enantioselectivity and/or the yield of the reaction, in comparison to the catalysis by acyclic *N*,*N*′-dibenzyl-DACH ligands. Density functional theory (DFT) computations on the structure of the model ligand-zinc complex and on the structures of the pre-organized reactants together with the calculations of possible transition states allow rationalization of the direction of the asymmetric induction of the hydrosilylation reaction. This is the first example of asymmetric catalysis of the hydrosilylation reaction of ketimines with the use of a readily available and inexpensive macrocyclic trianglamine ligand.

Introduction

Chiral amines are important synthetic targets due to their occurrence in many natural products and pharmaceuticals. In the last few decades increased attention has been paid to the asymmetric hydrogenation of imines as the source of chiral amines.[1,2] However, this method requires the use of gaseous hydrogen and expensive catalysts based mainly on the ruthenium or rhodium complexes. Reductive abilities of PMHS [poly(methylhydrosiloxane)], which is a safe and inexpensive alternative to monomeric silanes, allow the synthesis of amines from activated imines without the use of gaseous hydrogen. Effective catalysts derived from transition metals such as Ti,[3] Rh,[4] Ru,[5] Cu,[6] and Re[7] were employed for enantioselective hydrosilylation of ketones and imines, however the synthesis of complex catalysts or the use of specially modified substrates was necessary.[8] The use of [Zn-amine]-catalyzed enantioselective hydrosilylation of aryl-alkyl ketones developed by Mimoun *et al.*,[9] further extended to imines (Scheme 1),[10] made a breakthrough in practical synthesis of optically active alcohols and amines *via* reduction of the carbon-heteroatom double bonds.

According to this protocol a typical catalyst system is formed *in situ* from equimolar amounts of dialkyl zinc and a secondary diamine. Enantioselectivities obtained with the use of such a catalyst depend on the structures of the diamine and the substrate,[11] as well as on the presence of an additive, and reached 96% in the case of reduction of *ortho*-substituted benzophenones.[12,13] It should be noted that the recovered product was a silyl ether, which had to be separated prior to proceeding with a somewhat sensitive hydrolysis step. The [Zn-diamine] catalytic system operating in protic conditions makes possible to avoid the hydrolysis step and to significantly improve the conversion of the substrate, however at the expense of enantioselectivity, which dropped to 55% ee in the case of acetophenone.[14,15] Imines, having phenyl or benzyl substituents at the nitrogen atom, which could not be reduced by the [Zn-diamine] complex in toluene, were reduced in the mixture of methanol and toluene (80/20, v/v). However, products of low enentiomeric excess were obtained in these cases.[15]



Scheme 1 [Zn-Diamine]-catalyzed hydrosilylation of imines.

Park *et al.* reported recently on the use of [Zn-diamine] catalysts for a highly enantioselective reduction of various activated imines in THF–methanol mixtures.[10] The authors examined *N*,*N*′-ethylenebis(1-phenylethylamine) and (*R*,*R*)-dpen derivatives (dpen = 1,2-diphenyl-1,2-ethanediamine) as the chiral ligands and diphenylsilane or PMHS as reducing agents. These authors also rationalized the use of a protic solvent as a necessary condition for easy cleavage of the strong zinc-nitrogen bond of the amine product during the catalytic cycle. Alternatively, the Zn–N(product) bond could be cleaved by the added silane.

Department of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780, Poznań, Poland. E-mail: Marcin.Kwit@amu.edu.pl; Fax: (+48)-61-829-1505

† Electronic supplementary information (ESI) available: Data on the HPLC separation of enantiomers, products literature references, spectral characterization of new compounds, computational details, total and relative energies and Cartesian coordinates for all calculated compounds. See DOI: 10.1039/c1ob05074e

‡ Dedicated to Professor Derek R. Boyd on the occasion of his 70th birthday.

Detailed analysis of the available literature precedents led us to a conclusion that in the case of [Zn-diamine]-catalyzed ketone hydrosilylation improvements could be made by judicious choice of a chiral ligand. Among many precursors of diamine ligands, enantiopure *trans*-1,2-diaminocyclohexane (DACH) appears exceptional, as it can be the source of virtually unlimited number of diamine structures. We have recently reported that chiral tetra- and hexamine macrocycles derived from DACH in complexes with diethylzinc efficiently catalyze asymmetric hydrosilylation of aryl alkyl ketones with enantiomeric excess of the product up to 89%.[11] It seemed obvious that the development of a practical and efficient catalytic system for the reduction of imines could also be based on cyclic or acyclic DACH derivatives. Herein we describe a highly enantioselective hydrosilylation of imines, catalyzed by readily available Zn-diamine catalysts. We also propose rationalization of enantioselectivity of the process, on the basis of the results of DFT calculations.

Results and discussion

From the library of available ligands we selected the three, known for their efficiency in other hydrosilylation reactions.[11,16] These ligands, shown in Fig. 1, were readily available either as acyclic DACH derivatives, such as the dibenzylDACH (**1**) and its dimethoxy derivative (**2**) or as a chiral heteraphane, trianglamine (**3**). We reasoned that the additional methoxy groups

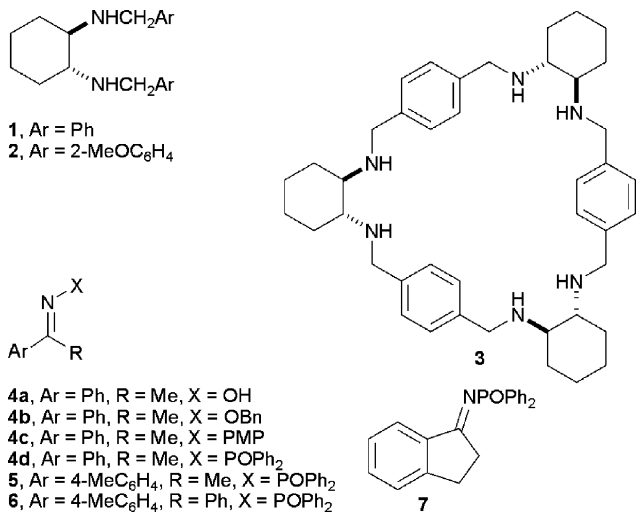


Fig. 1 Ligands **1–3** and imines **4–7** used in this study.

or macrocyclic structure of the ligand will stabilize the structure of the zinc complex and will improve reaction selectivity.

N,*N*′-Dibenzyl derivatives **1** and **2** were obtained through simple condensation of the appropriate aldehyde with DACH, followed by reduction of the imine bonds. Trianglamine **3** is readily obtained in a one-pot procedure from DACH and terephthalaldehyde, with the yield over 95%.[17]

Since the stereoselectivity of hydrosilylation reaction depends not only on the catalyst structure but also on the structure of the substrate, for the initial studies we have chosen several model imines **4a–4d**, derived from acetophenone, differing in the substitution pattern of the nitrogen atom (Fig. 1). Additionally we aimed at showing the effect of the solvent, silane and the catalyst load on the efficiency of the reaction.

Standard conditions involved generation of the zinc complex by the addition of equimolar amount of diethylzinc in hexane to a solution of the ligand in toluene (or in other solvents like dichloromethane, THF, methanol or a mixture of toluene and methanol). After 0.5 h at room temperature the imine and the silane were added and the reaction was run at room temperature for 24 h and then quenched with methanolic NaOH solution (Scheme 1). This last step could be omitted if the reaction was run under protic conditions. It should be noted that the order of addition of the reagents to the reaction vessel did affect neither the yield nor enantioselectivity of the reaction.

We initially examined the effect of *N*-substitution of the imines on the yield and enantioselectivity of the [Zn-**1**]-catalyzed hydrosilylation (Table 1). The catalyst load in all cases was 5 mol% and model imines **4a–4d** used in this study had different *N*-substituents, *i.e.* OH, OBn, *p*-methoxyphenyl (PMP) or diphenylphosphinyl ($POPh_2$) (oxime **4a** was an intermediate in the synthesis of **4d**).

Among the four imines tested two (**4a** and **4b**) did not undergo hydrosilylation under the above-mentioned conditions (Table 1, entries 1–4), regardless the silane used. The use of oxime **4a** resulted in the recovery of almost all starting material. In the case of *N*-benzyloxyderivative **4b** we did not observe any progress of the reaction, even if the reaction time was prolonged to 48 h. Although in the case of **4c** and **4d** the reactions were not complete within 24 h, promising reaction enantioselectivities (53–99% ee) were observed (Table 1, entries 5–9). Yields of isolated products were not satisfactory and prolongation of the reaction time for another 24 h had only little effect on the conversion of the substrate. It is pertinent to note that **4d** is only partially soluble in non-polar solvents and lowering the reaction temperature caused a further drop of the yield without any profound effect on enantioselectivity

Table 1 Effect of *N*-substitution on the yield and enantioselectivity of the [Zn-**1**]-catalyzed hydrosilylation of imines **4a–4d**[a]

Entry	Imine	Silane	Solvent	Conversion [%]	Yield[b] [%]	Ee[c] [%]
1	**4a**	Ph_2SiH_2	Toluene	0	0	0
2	**4a**	PMHS	Toluene	0	0	0
3	**4b**	Ph_2SiH_2	Toluene	0	0	0
4	**4b**	Ph_2SiH_2	THF	0	0	0
5	**4c**	Ph_2SiH_2	Toluene	nd	30	14
6	**4c**	$(EtO)_3SiH$	Toluene	nd	50	53
7	**4d**	Ph_2SiH_2	Toluene	99	82	92
8	**4d**	$(EtO)_3SiH$	Toluene	90	14	96
9	**4d**	PMHS	Toluene	89	28	99

[a] Reaction time 24 h, room temperature, ligand 5 mol%. [b] Isolated yields, average of two runs. [c] Determined by HPLC using a CHIRALPAK IA column.

Table 2 Effect of ligand, silane and solvent on the yield and enantioselectivity of the [Zn-diamine]-catalyzed hydrosilylation of imine **4d**[a]

Entry	Ligand	Silane	Solvent	Yield[b] [%]	Ee[c] [%]
1	**1**	Ph_2SiH_2	Toluene	82	92
2	**1**	Ph_2SiH_2	THF	71	84
3	**1**	Ph_2SiH_2	Toluene/MeOH[d]	62	92
4	**1**	$(EtO)_3SiH$	Toluene	14	96
5	**1**	PMHS	Toluene	28	99
6	**2**	Ph_2SiH_2	Toluene	82	90
7	**2**	Ph_2SiH_2	THF	70	86
8	**2**	Ph_2SiH_2	Toluene/MeOH[d]	74	87
9	**2**	$(EtO)_3SiH$	Toluene	16	98
10	**2**	PMHS	Toluene	16	94
11	**3**	Ph_2SiH_2	Toluene	66	>99
12	**3**	Ph_2SiH_2	THF	85	92
13	**3**	Ph_2SiH_2	CH_2Cl_2	64	94
14	**3**	Ph_2SiH_2	Toluene/MeOH[d]	58	97
15	**3**	Ph_2SiH_2	MeOH	54	>99
16	**3**	$(EtO)_3SiH$	Toluene	6	97
17	**3**	$(EtO)_3SiH$	Toluene/MeOH[d]	52	96
18	**3**	PMHS	Toluene	56	96
19	**3**	PMHS	Toluene/MeOH[d]	72	96

[a] Reaction conditions: ligand 5 mol%, silane 1.2 eq, room temperature, reaction time 24 h. [b] Isolated yields, average of two runs. [c] Determined by HPLC using a CHIRALPAK IA column. [d] Solvents ratio 4 : 1 (v/v).

of the reaction. The use of **4c** for hydrosilylation was further hampered by the difficulties in removing the PMP group. On the other hand, after reduction of imine **4d** the diphenylphosphinyl group could be readily hydrolyzed to give the desired amine.[18] Therefore imines substituted at the nitrogen atom by the $POPh_2$ group seemed to be the substrates of choice for hydrosilylation. Further improvements of hydrosilylation procedure were therefore limited to the model compound **4d** and the screening of ligands was conducted along with the screening of the type of silane and reaction conditions used for hydrosilylation of **4d** (Table 2, see also the ESI for the full version of Table 2†). With the catalyst load 5 mol% we observed good to excellent enantioselectivities of the hydrosilylation of imine **4d** with ligands **1–3**. The conversion values were usually high and ranged from 89% (entry 5, Table 2, ESI†) to nearly quantitative (entries 1, 3, 8, 14 and 19, Table 2, ESI†). From practical point of view, more interesting data for potential users are chemical yields of isolated products. These values ranged from low 6% (entry 16, Table 2) to high (85%, entry 12, Table 2) and better yields were obtained when a mixture of toluene and methanol was used as the reaction medium.

The data of Table 2 show that the highest enantioselectivity was achieved with the use of trianglamine **3** as a ligand in either toluene or methanol solution, and diphenylsilane as a reductor (entries 11 and 15, Table 2). The use of toluene–methanol solution (ratio 4 : 1, v/v) resulted in a small (*ca.* 3%) drop of enantioselectivity, while yield of the product increased (entry 14, Table 2). Changing the solvent from toluene to THF (entries 2, 7 and 12, Table 2) did not affect the conversion of **4d** (yields of isolated products ranged from 70% to 85%), however we observed a decrease of enantioselectivity of the reaction (drop to 84%, 86% or 92%). Dichloromethane was found a good alternative as a solvent for hydrosilylation of imines due to the high enantioselectivity of the reaction (ee 94%, entry 13, Table 2). Substituting diphenylsilane with PMHS (entries 18–19, Table 2) resulted in a 4% drop of enantioselectivity of the hydrosilylation in toluene and toluene–methanol mixture of solvents, however the yield of the isolated product was higher (entry 19, Table 2).

Table 3 Enantioselective hydrosilylation of *N*-diphenylphosphinyl ketimines[a]

Entry	Imine	Ligand	Yield[b] [%]	Ee[c] [%]
1	**5**	**1**	91	94 (*S*)
2	**5**	**2**	80	92 (*S*)
3	**5**	**3**	62	97 (*S*)
4	**6**	**1**	93	13 (nd)[d]
5	**6**	**2**	94	67 (nd)[d]
6	**6**	**3**	35	61 (nd)[d]
7	**7**	**1**	80	88 (*R*)
8	**7**	**2**	88	85 (*R*)
9	**7**	**3**	91	94 (*R*)

[a] Reducing agent Ph_2SiH_2, all reactions in toluene–methanol (4 : 1, v/v) solution, catalyst 2 mol%, room temperature, reaction time 24 h. [b] Isolated yields, average of two runs. [c] Determined by HPLC with a CHIRALPAK IA column. [d] Absolute configuration not determined.

The efficiency of the reaction could be further increased by lowering the load of the [Zn-**3**] catalyst down to 1 mol% and this surprisingly resulted in a slight increase of enantioselectivity (up to 98%) at the expense of the yield (drop to 62%). On the other hand, catalyst overload (up to 15 mol%) did not affect neither the enantioselectivity nor the yield of the reaction. Changing the ratio Zn to **3** from 1 : 1 through 2 : 1 to 3 : 1 reduced both the enantioselectivity and conversion of the substrate, which is in full agreement with our previous experimental findings for hydrosilylation of ketones.[11]

Ligand **2**, having additional methoxy groups, provided enantioselectivity of hydrosilylation reaction comparable to ligand **1** (entries 6–10, Table 2). This is in contrast to the result of asymetric hydrosilylation of various prochiral ketones, where ligand **2** provided the highest enantioselectivities of the products. In all cases the products of imines **4c** and **4d** reduction had (*S*) configurations at the stereogenic center.

Having established **3** as the best performing chiral ligand, various *N*-phosphinylimines were reduced by using 2 mol% of the catalyst, 1.2 equivs. of diphenylsilane and toluene–methanol [4 : 1 (v/v)] as a solvent. The results are summarized in Table 3.

Reduction of ketimine **5** afforded the corresponding amine of good ee (92–94%, entries 1 and 2, Table 3), trianglamine **3** gave the best result in terms of enantioselectivity (ee 97%) at the expense of the yield of the reaction (entry 3, Table 3). The same situation was also observed for cyclic substrates such as **7**: the product obtained using ligand **3** had the highest enantiomeric purity (94% ee, entry 9, Table 3). It is worth adding that the product obtained from **7** had *R* absolute configuration of the stereogenic center, probably due to a different binding pattern between the substrate and the active catalyst. Contrary to these results, ligand **2** gave the best results in terms of both enantioselectivity and chemical yield in the case of highly demanding ketimine **6** (entry 5, Table 3). In this case the only factor differentiating the faces of the substrate molecule, and by this way affecting the enantiomers ratio, was a methyl group in position 4 of one of the phenyl rings of ketimine **6**. Due to the lack of crystals suitable for X-ray crystallography

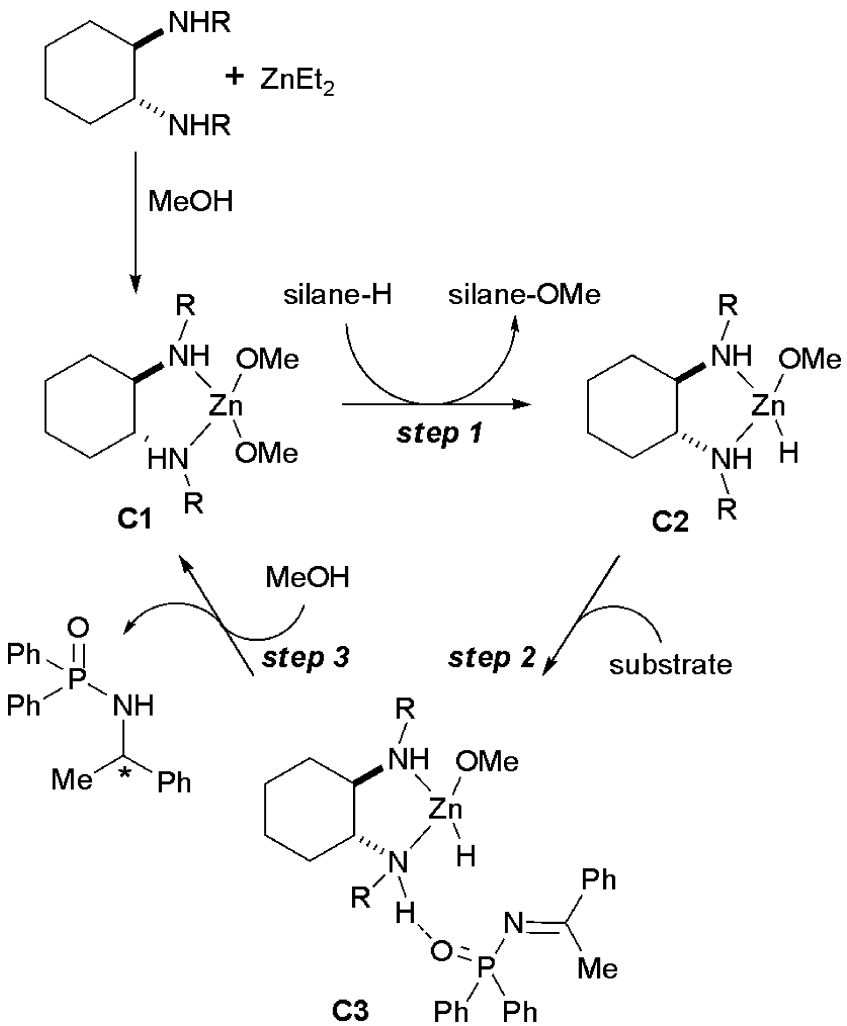
the absolute configuration of the amine obtained from ketimine **6** could not be determined.

Mechanistic and stereochemical considerations

In order to determine the factors that control the enantioselectivity of the hydrosilylation reaction using DACH-based ligands we performed DFT studies, including calculations of the structures in the possible key steps of the reaction. Preliminary calculations carried out at the PBE0/6-31G(d) level[19,20] allowed to identity the key intermediates and the transition states. For higher accuracy calculations we employed the above-mentioned PBE0 hybrid functional in conjunction with the enhanced 6-311G(d,p) basis set (see ESI for details†). Additionally, single-point calculations with the use of the same PBE0 hybrid density functional and enhanced def2-TZVPP basis set[21] were performed to get more accurate energies. The effect of the solvent was approached by single-point energy calculations at the PBE0/def2-TZVPP level with the use of the Conductor-like Screening Model (COSMO)[22] simulating methanol solution, using the optimized structures according to the generally accepted protocol.[23]

The results obtained with the use of each method showed the same trend, so we could restrict our discussion to the results obtained with the use of COSMO/PBE0/def2-TZVPP//PBE0/6-311G(d,p) method (the remaining computation results were deposited as ESI†). The relative energies (in kcal mol^{-1}) reported here refer to the computed energy differences (ΔE) and unless stated otherwise are given relative to the substrate molecule(s). In the case of molecules having multiple conformational minima, the energetic relationships were calculated and discussed by taking into account the lowest-energy conformers. All calculations were carried out with the use of either Gaussian 03[20] or Turbomole 6.0 packages.[21] In order to simplify the structures for calculations, we have chosen *N*,*N*′-dimethyldiaminoethane as a diamine and ketimine **4d** as the substrate. Since in this work dimethyldiaminoethane represents the rigid structure of DACH derivative, in all calculations we assumed a negative (H)N–C–C–N(H) torsion angle (–60°), that corresponds directly to the experimentally determined (H)N–C–C–N(H) torsion angle of (*R*,*R*)-DACH derivatives.[17] Taking into account the recent results[10,11,15] and the results of our calculations, we propose the following mechanism of the reaction (Scheme 2).

Zinc complex **C1**, formed in toluene–methanol solution from appropriate diamine and diethylzinc in the first step of the assumed catalytic cycle, undergoes the reaction with silane to provide the Zn-hydrido complex **C2** which is the effective reducing agent.



Scheme 2 Proposed reaction pathway for [Zn-diamine]-catalyzed reduction of activated imines.

The second step of the catalytic cycle controls stereoselectivity of the whole process and assumes binding the substrate to the hydrido complex **C2** with the formation of NH···O═P hydrogen bonded structure **C3** that is predisposed for hydrogen transfer from Zn to the imine group. In the last stage (*step 3*) of the catalytic cycle methanolysis of the intermediate product leads to recovery of the tetradentate [Zn-(diamino)$(OMe)_2$] species **C1** and *N*-diphenylphosphinyl amine. The formation of Zn–H species **C2** from **C1** as well as methanolysis of the intermediate product are well known,[15,16] thus we focus here mainly on the enantiodiscriminating step 2 and on the reduction stage (Scheme 2).

Whereas calculations at the PBE0/6-311G(d,p) level did not identify any stable structure characterized by a direct coordination of the substrate to the zinc atom they have demonstrated that complex **C3** can exist in two (N)H···O(═P) bonded structures **a** and **b**, which differ in the orientation of the ketimine moiety in relation to the catalyst (Fig. 2a).

There are two possible acceptor centers for a hydrogen bond in ketimine **4d**: either the imine nitrogen atom or the oxygen atom. Calculations of the atomic charges with the use of the NBO method[24] clearly show that the oxygen atom (–1.10) carries a more negative charge than the imine nitrogen atom (–0.84). Therefore, the oxygen atom in the phosphinyl group is able to form a stronger hydrogen bond with the appropriate proton donor. Calculated lengths of the NH···O(═P) hydrogen bonds are 1.96 and 1.94 Å, respectively, for **C3a** and **C3b**. The second factor that excludes formation of the NH···N(imine) hydrogen bond is steric repulsion between the ketimine phenyl group and the diamine ligand. Confirmation of the preference of the NH···O(═P) hydrogen bond over that formed by ketimine nitrogen atom was obtained by attempted calculation of the possible structure of **C2**+**4d** complex stabilized by the NH···N(imine) hydrogen bond. Regardless the initial mutual orientation of the Zn-hydrido species and the substrate, the resulting calculated structures were either **C3a** or **C3b**.

The zinc center carries a more positive charge (1.43) than any of the (N)H hydrogen atoms (0.42) and this may suggest that the zinc is the preferred coordination center. However, at the PBE0/6-311G(d,p) level of theory, we have not found any stable structure which would contain the Zn–X (*O*,N) bond, in agreement with previous findings.[16]

Coordination mode of the substrate determines the absolute configuration of the final product since the hydride attack may occur from either *re* or *si* face of the ketimine moiety. In the case of **C3**, formation of a conformer of **a** type leads to formation of (*S*)-amine, whereas from conformer **b** (*R*) enantiomer is obtained.

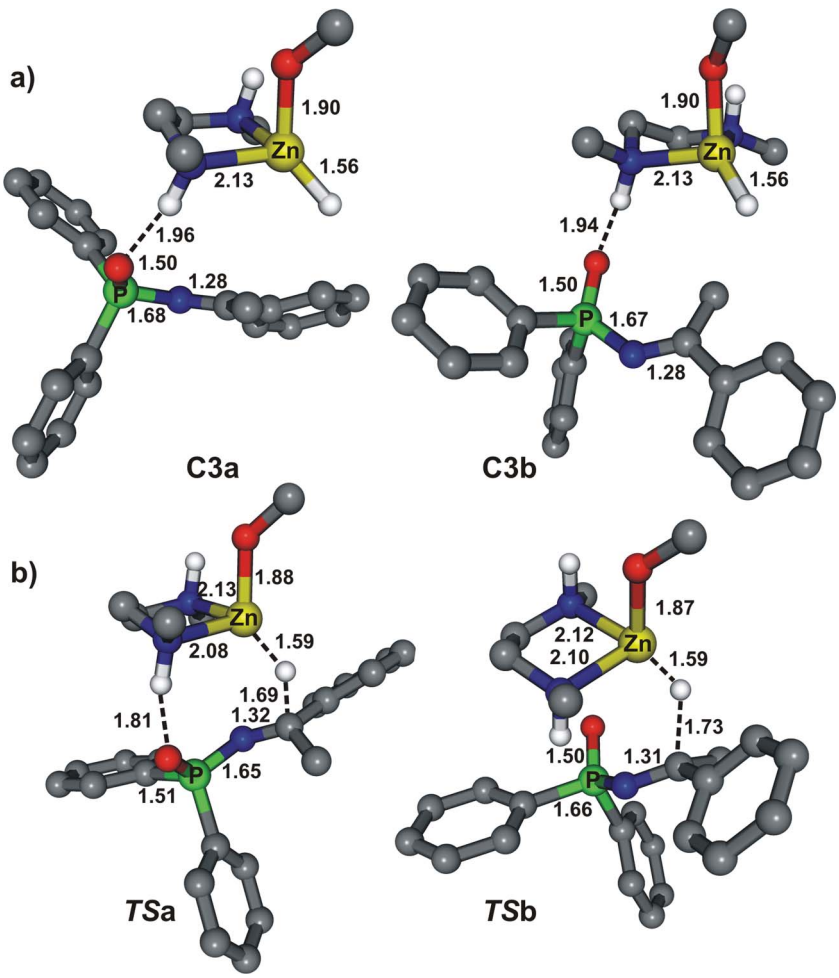
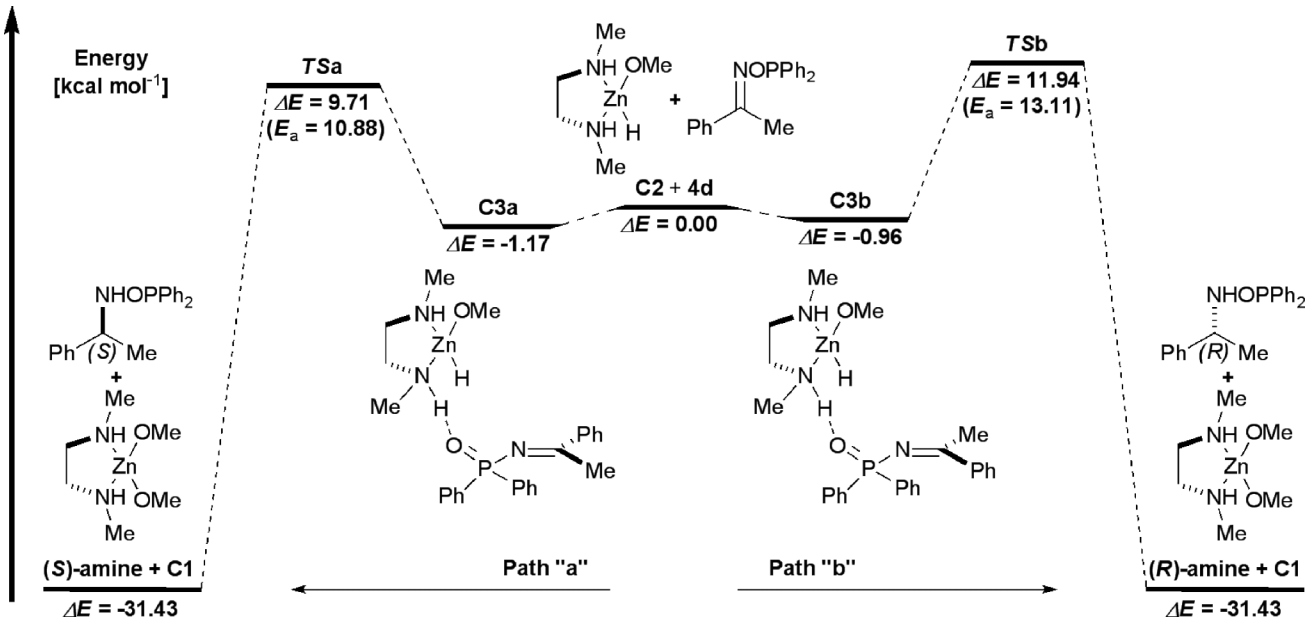


Fig. 2 Lowest-energy structures of complexes **C3** (a) and transitions states ***TS*a** and ***TS*b** (b) calculated at the COSMO/PBE0/def2-TZVPP//PBE0/6-311G(d,p) level (some interatomic distances are given in Å).



Scheme 3 Energy profile for the reduction of ketimine **4d** calculated at the COSMO/PBE0/def2-TZVPP//PBE0/6-311G(d,p) level.

Energetically more favorable is conformer **C3a**, however the calculated energy difference is only 0.21 kcal mol^{-1} and this corresponds to a 59 to 41 ratio of conformers **C3a** to **C3b**. Binding energies,[25] defined as the energy difference between **C3** complex and the sum of the reactants **C2** and **4d** are 1.17 and 0.96 kcal mol^{-1} for **C3a** and **C3b**, respectively.

Calculated transition structures ***TS*a** and ***TS*b** for reduction of the imine bond in complexes **C3a** and **C3b** are shown in Fig. 2b. The main difference is the presence of the NH $\cdots$ O(=P) hydrogen bond in ***TS*a** and its absence in ***TS*b**. This is reflected in the calculated energy difference, ***TS*a** is over 2 kcal mol^{-1} more stable than ***TS*b**. In ***TS*a** and ***TS*b** calculated interatom distances and bond lengths are different. For example, the lengths of the N–Zn bonds are 2.13 and 2.08 Å in the case of ***TS*a** and 2.12 and 2.10 Å in the case of ***TS*b**; the distance between the hydride and the acceptor carbon atom is much shorter in the case of ***TS*a** (1.69 Å *vs.* 1.73 Å). Opposite situation is observed for the P=O bonds, a longer bond (1.51 Å) is calculated for ***TS*a**, whereas for ***TS*b** its length is 1.50 Å. Characteristic NH $\cdots$ O(=P) hydrogen bond calculated for ***TS*a** is shorter by 0.15 Å than that calculated for **C3a** whereas such a bond does not exist in ***TS*b**.

In the case of ***TS*b** a long distance (3.655 Å) between the (N)H and the phosphinyl oxygen atoms excludes any attractive interactions between both fragments. These data indicate strongly that effective hydrogen transfer from zinc to the C=N bond is possible only in the transition state ***TS*a**.

Total reaction energy, defined as the energy difference between the free energies of the products and the reactants, was calculated taking as the substrates ketimine **4d**, the Zn-hydrido complex **C2** and a methanol molecule and as the products the amine and the tetradentate complex **C1**. Total reaction energy amounted to ΔE = –31.43 kcal mol^{-1}. Calculated energy profile for the reduction of imine **4d** (involving *steps 2* and *3*) is shown in Scheme 3.

Path "a" leading to the product of (*S*) absolute configuration is favored not only by the formation of a more stable initial complex **C3a**, but also by a lower activation energy E_a (defined as the energy difference between the transition state and the precursor complex). The values of E_a calculated for ***TS*a** and ***TS*b** are 10.88 and 13.11 kcal mol^{-1} and this allows to estimate enantioselectivity of the process as close to a 100%. This value remains in excellent agreement with the best experimentally obtained enantioselectivity (ee >99%) for hydrosilylation of **4d**, carried out in methanol solution. The values of E_a calculated at the PBE0/def2-TZVPP//PBE0/6-311G(d,p) level for the structures in the gas phase are 10.25 and 13.24 kcal mol^{-1} (for ***TS*a** and ***TS*b**, respectively) and again point to reaction enantioselectivity close to a 100%.

Conclusions

We reported here a convenient method for enantioselective hydrosilylation of aryl-alkyl or aryl-aryl ketimines, based on the catalysis with zinc-hexamine macrocycle, readily available from DACH. The use of inexpensive reducing agent (PMHS), generally available activated imines and protic solvent (methanol–toluene) which makes the hydrolysis of the silyl group unnecessary, are further favorable features of the procedure. Trianglamine **3**-$ZnEt_2$ (1 : 1) complex catalyzes hydrosilylation of *N*-diphenylphosphinyl ketimine **4d** in toluene solution, using diphenylsilane, with over 99% ee and moderate yield (66%) of the product. The enantioselectivity is similar to that obtained with the use of acyclic ligands **1** or **2** (ees 99 and 98%), however acyclic ligands provided the product in a lower chemical yield. Yield of the product can be significantly increased by the use toluene–methanol solution instead toluene only, with only a little drop of enantioselectivity of the reaction.

Protic conditions (addition of methanol to toluene solution) allowed the use of inexpensive poly(methylhydrosiloxane) as a reducing agent. From the economical point of view this modification is a method of choice for hydrosilylation of imines. Since trianglamine **3** can be conveniently prepared by a one-pot procedure from inexpensive tartrate salt of DACH and

terephthalaldehyde,[17] the Zn complex of **3** is a good alternative to the previously reported chiral catalysts.

In this paper we present a plausible rationalization of the observed enantioselectivity of the imine hydrosilylation, using ligands derived from (*R*,*R*)-DACH which provide preferentially amines of *S* configuration. It is related to the previous mechanistic study of Bette[15] and others[16] and is based on the DFT calculated low-energy structures of the [Zn(ligand)(OMe)(H)]-**4d** precursors, as well as on the structures of the transition states leading to the formation of the chiral product. Postulated formation of a strong NH···O(=P) hydrogen bond appears crucial for pre-organization of the reactants and determines the spatial arrangements of both the catalyst and the ketimine. In this way the enantioselectivity of the whole hydrosilylation process can be rationally accounted for.

Experimental section

NMR spectra were recorded on a Bruker BioSpin 400 (400 MHz) or Varian MR 300 (300 MHz) instruments at 25 °C using $CDCl_3$, DMSO or D_2O as solvents, purchased from Sigma–Aldrich. Chemical shifts are reported in ppm relative to the TMS (^{1}H and ^{13}C NMR spectra) or D_2O (^{31}P NMR spectra) peaks. Spectral assignments were obtained by the analysis of chemical shifts and by comparison with literature data (see Table A in the ESI for details†). Mass spectra were recorded on a AMD-402 spectrometer. HPLC analyses were performed with the use of a Hitachi LaChrom Elite system equiped with CHIRALPAK IA column at room temperature. For the data on the HPLC separation of enantiomers see Table B in the ESI.†

Imines **4a-7** were prepared according to the literature procedures (see Table A in the ESI for details†). Imine **6** was prepared following the procedure of Krzyzanowska and Stec.[18]

Imine **6**: m.p. 142–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.96–7.89 (m, 4H), 7.52–7.47 (m, 4H), 7.45–7.34 (m, 9H), 7.19 (d, J = 7.9 Hz, 3H), 2.41 (s, 3H); (400 MHz, DMSO, δ): 7.83–7.79 (m, 4H), 7.54–7.39 (m, 13H), 7.26 (d, J = 8.1 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75.44 MHz, DMSO, δ): 180.7, 141.5, 137.9, 137.7, 135.5, 135.3, 135.1, 133.8, 130.8, 130.7, 130.6, 130.5, 129.0, 128.5, 128.2, 128.1, 127.9, 127.4, 20.6; ^{31}P NMR (121.45 MHz, DMSO, δ): 14.9; HRMS-EI (m/z): $[M]^+$ calcd. for $C_{26}H_{22}NOP$, 395.14389; found 395.14595.

Product of imine **6** reduction: 177–179 °C; $[\alpha]_D$ = –2.8 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.93–7.80 (m, 4H), 7.52–7.47 (m, 2H), 7.44–7.35 (m, 4H), 7.32–7.25 (m, 5H), 7.16(q, J = 8.2 Hz, 4H), 5.45 (t, J = 10.7 Hz, 1H), 3.63 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$, δ): 143.53, 143.49, 140.50, 140.46, 136.71, 133.03, 133.01, 132.30, 132.20, 132.16, 131.77, 131.74, 131.68, 131.58, 129.10, 128.60, 128.47, 128.37, 128.26, 128.25, 127.51, 127.48, 127.03, 58.27, 51.45, 21.03; ^{31}P NMR (121.45 MHz, $CDCl_3$, δ): 22.9; HRMS-EI (m/z): $[M]^+$ calcd. for $C_{26}H_{24}NOP$, 397.15955; found 397.15824.

General procedure for the hydrosilylation of *N*-diphenylphosphinyl imines

In a 5-mL round-bottom flask $ZnEt_2$ (5.93 μL, 1 M in hexane; 5.93 μmol) and appropriate ligand (5.93 μmol) were dissolved in a mixture of freshly distilled toluene and anhydrous methanol (0.5 mL, 4 : 1, v/v) and stirred under an argon atmosphere for 30 min. Then the solution (1.5 mL, toluene–methanol, 4 : 1, v/v) of the corresponding imine (0.29 mmol) and diphenylsilane (0.066 mL, 0.36 mmol) were added to the flask. The resulting solution was stirred at room temperature for 24 h. Then NaOH (1 mL, 1 M in MeOH) was added with vigorous stirring. The reaction mixture was stirred for an additional hour at room temperature and extracted with dichloromethane (3 × 3 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with hexane–EtOAc (10 : 1) as an eluent.

Acknowledgements

This work was supported by the Ministry of Science and Higher Education, grant no. PBZ-KBN-NN204 312537. All calculations were performed at Poznań Supercomputing and Networking Center.

Notes and references

1 H. Nishiyama, K. Itoh, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, 2000, Chapter 2.
2 H. Nishiyama, in *Comprehensive Asymmetric Catalysis, Vol. 1* (ed.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999, Chapter 6.3.
3 (*a*) J. Yun and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 5640; (*b*) X. Verdaguer, U. E. W. Lange, M. T. Reding and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 6784.
4 (*a*) N. Langlois, T.-P. Dang and H. B. Kagan, *Tetrahedron Lett.*, 1973, **14**, 4865; (*b*) R. Becker, H. Brunner, S. Mahboobi and W. Wiegrebe, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 995.
5 Y. Nishibayshi, I. Takei, S. Uemura and M. Hidai, *Organometallics*, 1998, **17**, 3420.
6 B. H. Lipshutz and H. Shimizu, *Angew. Chem., Int. Ed.*, 2004, **43**, 2228.
7 (*a*) K. A. Nolin, R. W. Ahn and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 12462; (*b*) K. A. Nolin, R. W. Ahn, Y. Kobayashi, J. J. Kennedy-Smith and F. D. Toste, *Chem.–Eur. J.*, 2010, **16**, 9555.
8 B. Marciniec, (ed.) *Hydrosilylation*, Springer, Berlin 2009, part III.
9 H. Mimoun, J. Y. de Saint Laumer, L. Giannini, R. Scopelliti and C. Floriani, *J. Am. Chem. Soc.*, 1999, **121**, 6158.
10 B.-M. Park, S. Mun and J. Yun, *Adv. Synth. Catal.*, 2006, **348**, 1029.
11 J. Gajewy, M. Kwit and J. Gawroński, *Adv. Synth. Catal.*, 2009, **351**, 1055.
12 H. Ushio and K. Mikami, *Tetrahedron Lett.*, 2005, **46**, 2903.
13 (*a*) V. Bette, A. Mortreux, D. Savoia and J.-F. Carpentier, *Tetrahedron*, 2004, **60**, 2837; (*b*) V. Bette, A. Mortreux, F. Ferioli, G. Martelli, D. Savoia and J.-F. Carpentier, *Eur. J. Org. Chem.*, 2004, 3040.
14 V. Bette, A. Mortreux, C. W. Lehmann and J.-F. Carpentier, *Chem. Commun.*, 2003, 332.
15 V. Bette, A. Mortreux, D. Savoia and J.-F. Carpentier, *Adv. Synth. Catal.*, 2005, **347**, 289.
16 J. Gajewy, J. Gawronski, and M. Kwit, manuscript in preparation.
17 (*a*) J. Gawroński, H. Kołbon, M. Kwit and A. Katrusiak, *J. Org. Chem.*, 2000, **65**, 5768; (*b*) J. Gawroński, K. Gawrońska, J. Grajewski, M. Kwit, A. Plutecka and U. Rychlewska, *Chem.–Eur. J.*, 2006, **12**, 1807.
18 B. Krzyzanowska and W. J. Stec, *Synthesis*, 1978, 521.
19 (*a*) P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1966, **77**, 3865; (*b*) C. Adamo and V. Barone, *J. Chem. Phys.*, 1999, **110**, 6158.
20 M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A.

Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision D.01*, Gaussian, Inc., Wallingford CT, 2004.

21 R. Ahlrichs, M. Baer, M. Haeser, H. Horn and C. Koelmel, *Chem. Phys. Lett.*, 1989, **162**, 165 (see also www.turbomole-gmbh.com for an overview of the TURBOMOLE program).

22 (*a*) A. Klamt and G. Schüürmann, *J. Chem. Soc., Perkin Trans. 2*, 1993, 799; (*b*) A. Klamt and V. Jonas, *J. Chem. Phys.*, 1996, **105**, 9972.

23 L. Dong, S. Qin, Z. Su, H. Yang and C. Hu, *Org. Biomol. Chem.*, 2010, **8**, 3985.

24 (*a*) F. Weinhold, in, *Encyclopedia of Computational Chemistry*, P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III, P. R. Schreiner, ed., John Wiley & Sons, Chichester, UK, 1998, Vol. 3, pp. 1792–1811; (*b*) A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899; (*c*) F. Weinhold and J. E. Carpenter, in, *The Structure of Small Molecules and Ions*, R. Naaman and Z. Vager, ed., Plenum, New York, 1988, pp. 227–236; (*d*) F. Weinhold, *Computational Methods in Organic Photochemistry: Molecular and Supramolecular Photochemistry*, A. G. Kutateladze, Ed., Taylor & Francis/CRC Press, Boca Raton FL, 2005, pp. 393–476.

25 S. Sakaki, M. Sumimoto, M. Fukuhara, M. Sugimoto, H. Fujimoto and S. Matsuzaki, *Organometallics*, 2002, **21**, 3788.

