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Orthopalladated complexes as phase-transfer catalysts for asymmetric alkylation of achiral Schiff base esters

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Abstract The asymmetric *C*-alkylation of benzophenone Schiff base glycine esters has been achieved using a palladium(II) chiral complex as a phase-transfer catalyst. The aromatic moiety around the metal center and various physicochemical parameters were investigated to study their effect on the asymmetric alkylation reaction under phase-transfer conditions. Moderate enantioselectivity(30–40%) was achieved under room temperature conditions, which is a significant improvement compared to no enantioselectivity with a chiral palladium-salen complex reported earlier. Computer simulation studies indicate that coordination of the metal center with Z-enolate forming a square planar complex provides a favorable steric environment where the α-carbon atom of the enolate is available for enantioselective alkylation.

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Introduction

Asymmetric phase-transfer catalysis has been recognized as a convenient tool for the synthesis of optically active α-amino acid targets [1–6]. Several advantages like operational simplicity, mild reaction conditions in aqueous media, environmental benefits and suitability of large scale reactions have make phase-transfer reactions highly useful in academia and industry. The first general synthesis of racemic amino acids by phase-transfer catalysis (PTC) based on the alkylation of glycine ester Schiff bases was reported in 1978 [7]. Several chiral catalysts derived from the cinchona alkaloids afforded optically active amino acids in a room temperature enantioselective PTC process [8–14]. In these reactions, a variety of alkyl halides were used and either enantiomer of the product could be prepared by selective use of the pseudoenantiomeric cinchonidine- or cinchonine-derived catalysts. Catalysts derived from cinchonine and cinchonidine have been used extensively in chiral PTC because the alkaloid precursors are less expensive and can be easily tailored to give effective phase-transfer catalysts. Polymer-supported quaternary ammonium salts have also been successfully used in the asymmetric alkylation reaction by various groups [15–20].

Although there are successful catalysts for phase-transfer alkylation reaction, formation of C–C bonds through direct alkylation using an orthopalladated complex was unknown. In 1998, Belokon et al. reported [21, 22] the use of sodium taddolate as a catalyst for the asymmetric alkylation of alanine enolates. In subsequent years, this group used chiral metal–salen complexes as phase-transfer catalysts for asymmetric synthesis of α-methyl α-amino acids. No model or mechanistic part has however been discussed in their reported work [23]. The recent review [24] on asymmetric alkylation reactions by Najera et al.

indicated that Cu(II) and Ni(II) salen complexes give impressive enantioselectivity under PT conditions. No enantioselectivity could be observed with the Pd-salen and Pt-salen complexes under similar conditions. We have been interested for some time in the application of phase-transfer catalysis to the preparation of amino acid derivatives. The optically active orthopalladated phenanthrylamine phase-transfer catalyst has been produced and explored for asymmetric glycine alkylation very recently by us [25]. The sterically hindered orthopalladated complex provided asymmetric induction in benzophenone Schiff base substrates under biphasic conditions. Prompted by the successful results from the phenanthrylamine moiety in PTC, we focused on different orthopalladated complexes, hypothesizing that with the proper alignment of the ammonium centers, optimum enantioselectivity would be observed.

We explored different reaction conditions such as temperature variation from as low as −20 to 60 °C, different alkylating agents from simple alkyl halides to robust substituted aromatic halides and various solvents or solvent mixtures in different ratios to promote effective displacement reactions under phase-transfer conditions. Simultaneous computer simulation and model studies have been made to focus on the nature of interactions involved and to account for the role played by the many variables in asymmetric induction mechanism. We believe that the area of asymmetric induction by phase-transfer catalysis will continue to grow as new catalysts, reagents and reaction conditions are investigated as this methodology finds application in the total synthesis of complex molecules.

Experimental

Analytical grade reagents and freshly distilled solvents were used throughout our investigation. The palladium complexes were prepared and characterized as per standard literature methods with slight modifications done to suit our experimental conditions. The Schiff base derivatives of glycine were chromatographed on grade V basic alumina with ethyl acetate in hexane as eluant. Vibrational, electronic and ^{1}H NMR spectra were taken with Perkin Elmer 883, Shamadzu MPC-3700 and Bruker 400-MHz instruments, respectively. The enantioselectivity was determined by chiral HPLC analysis (chiracel OD, hexane:2-propanol (99.5:0.5), flow rate 1 mL/min, 20 °C, $\lambda = 254$ nm). Optical rotation studies wherever necessary were determined on a Perkin Elmer 241 polarimeter using 1% solution in CH_2Cl_2.

For kinetic studies, the reaction was performed in a 50-mL three-necked round-bottomed flask submerged in a water bath whose temperature was maintained at 20 °C. Mechanical stirring was performed at a constant agitation rate by a magnetic stirrer. Initial products were dissolved in CH_2Cl_2 and were added to the reactor. The start of the reaction was measured after the addition of 50% aqueous NaOH solution to the organic layer. Samples (0.1 mL) were removed from the reactor after every 1 h, and the concentrations of initial Schiff base were monitored by HPLC assay.

Synthesis of di-μ-acetatobis[(S,S)-9-(1-(dimethylaminoethyl))-10-phenanthrenyl-C,N] dipalladium(II)[26]; **Complex-I**

The orthopalladated complex (I), as reported in the literature [26], has been prepared by a slightly modified method. The racemic form of 1-(9-phenanthryl)-ethylamine was obtained in 60% yield upon the acid hydrolysis of the reaction product between 9-acetyl phenanthrene and ammonium formate at 180 °C. The racemic primary amine was resolved using L(+)tartaric acid (Merck) as the resolving agent. The enantiomer (−) variety was obtained as a white solid in 30% yield. Methylation of the isolated enantiomer with formic acid and formaldehyde gave the corresponding *N,N*-dimethyl substituted amine as a colorless oil in 60% isolated yield. Dipalladium acetato-bridged complex (**complex-I**) was prepared by refluxing the substituted amine with palladium(II) acetate in refluxing acetic acid for 12 h [25]. This resulted in the formation of the bridged complex as gray powder in 50% isolated yield. The optically active μ–chloro dimer (**complex-II**) could be obtained efficiently by simply treating the palladium acetato-bridged complex in CH_2Cl_2 with a solution of ammonium chloride in water (yield ∼ 70%). The corresponding bromo complex (**complex-III**) was similarly obtained in 60% isolated yield using a solution of ammonium bromide.

The purity of the complexes was checked by TLC, IR and ^{1}H NMR spectral data. ^{1}H NMR (Complex-I)-(DMSO-d_6):δ(ppm) = 2.1(s,6H), 2.41(d,3H), 2.47(d,3H), 2.66(s,3H), 2.75(s,3H), 2.88 (s,6H), 4.22(q,1H), 4.27 (q,1H), 7.4–8.7(m, 16H, aromatics); IR(KBr, pellets) 3100, 1734, 1610, 1535, 1398, 1166, 870, cm^{-1}. Anal. Found: C, 57.9; H, 5.1; N, 3.3 Calcd for $C_{36}H_{36}(CH_3COO)_2N_2Pd_2$: C, 58.1; H, 5.1; N, 3.4.

^{1}HNMR(Complex-II)(DMSO-d_6):δ(ppm) = 2.43(d,3H), 2.49(d,3H), 2.69(s,3H), 2.77(s,3H), 2.89 (s,6H), 4.25 (q,1H), 4.31(q,1H), 7.4–9.0(m,16H, aromatics); IR(KBr, pellets)3096, 1614, 1530, 1160, 870, 650 cm^{-1}. Anal. Found: C, 55.2; H, 4.6; N, 3.5 Calcd for $C_{36}H_{36}Cl_2N_2Pd_2$: C, 55.4; H, 4.6; N, 3.6.

^{1}HNMR(Complex-III)(DMSO-d_6):δ(ppm) = 2.41(d,3H), 2.49(d,3H), 2.67(s,3H), 2.76(s,3H), 2.88 (s,6H), 4.22(q,1H), 4.3(q,1H), 7.4–8.7(m,16H, aromatics); IR(KBr, pellets)

3094, 1612, 1538, 1174, 872 cm^{-1}. Anal. Found: C, 49.5; H, 4.1; N, 3.2 Calcd for $C_{36}H_{36}Br_2N_2Pd_2$: C, 49.7; H, 4.1; N, 3.2.

Synthesis of di-μ-chloro-bis[(S,S)-(1-(dimethylamino-ethyl))-2-Naphthylamine-C,N] dipalladium(II) [26, 27]; **Complex-IV**

μ-dichloro-bis[(*S,S*)-(1-(dimethy1amino)ethyl]-2-naphthalenyl-dipalladium(II)] was prepared from (*S*)-dimethy[1-(1-naphthylethyl]amine and lithium tetrachloropalladate(II) in the presence of triethylamine (1 eq.) in methanol (yield 88–90%) as described below.

Palladium chloride (36.5 g) was dissolved in methanol (400 mL) containing lithium chloride (18 g), and the solution was filtered. To the filtrate was slowly added (*S*)-dimethyl[1-(1-ethyl-2-naphthyl)]amine (82.2 g). After 6 h of stirring, the reaction mixture was filtered and the yellow solid isolated. It was washed with cold methanol and diethyl ether and then dried in vacuo (68.0 g, 88% yield). Recrystallization of this material from dichloromethane-methanol mixture afforded the product as orange crystals, mp 178 °C (62.5 g, 88–89%).

Anal. Found: C, 49.3; H, 4.6; N, 4.2 (Calcd for $C_{28}H_{32}Cl_2N_2Pd_2$: C, 49.4; H, 4.7; N, 4.1) ^{1}H NMR (DMSO-d_6): 1.91, (m, 6H), 2.72 (s, 3H), 2.79 (s, 3H), 2.96 (s, 3H), 3.0 (s, 3H), 4.18 (br q, 1H) 4.22 (br q, 1H), 7.1–7.8 (m, 12H, aromatics). $[\alpha]_D$ +170.2 (c 1.0, CH_2Cl_2).

Synthesis of di-μ-chloro-bis[(S,S)-(1-(dimethylamino-ethyl))-benzylamine-C,N] dipalladium(II) [28] **Complex V**

μ-dichloro-bis[(*S,S*)-(1-(dimethy1amino)ethyl)-benzyl-amine-
C,N]dipalladium(II) was prepared from (*S*)-dimethy[1-(1-phenylethyl)]amine and lithium tetrachloropalladate(II) in the presence of triethylamine (1 eq) in methanol (yield 78–80%) as described below.

Palladous chloride (18.2 g) was dissolved in methanol (200 mL) containing lithium chloride (8.0 g), and the solution was filtered. To the filtrate was slowly added (*S*)-dimethyl[1-(1-ethyl-2-phenyl)]amine (41.2 g). After 4 h of stirring, the reaction mixture was filtered and the white solid isolated. It was washed with cold methanol and diethyl ether and then dried in vacuo (30.5 g, 80% yield). Recrystallization of this material from dichloromethane-methanol mixture afforded the product as white crystals, mp 164 °C (26.2 g, 74%). The (R)–(–) form of the benzylamine complex was obtained similarly (**Complex VI**) by using the same procedure with (*R*)-dimethy[1-(1-phenylethyl)]amine (97%, Aldrich chemicals) in approximately 60% yield.

Anal. Found: C, 41.3; H, 4.6; N, 4.7 (Calcd for $C_{20}H_{28}Cl_2N_2Pd_2$: C, 41.1; H, 4.8; N, 4.8). ^{1}H NMR (DMSO-d_6): 1.76, (d, 6H), 2.69 (s, 6H), 2.74 (s, 6H), 4.3 (q, 2H), 7.2–7.7 (m, 8H, aromatics). $[\alpha]_D$ +162.2 (c 1.0, CH_2Cl_2).

Preparation of ethyl-*N*-diphenylmethylene glycinate [29, 30]

The Schiff base ethyl-*N*-diphenylmethylene glycinate was prepared in 77% isolated yield by refluxing benzophenone (2.6 g, 14.3 mmol) with glycine ether ester (3.0 g, 21.5 mmol) in toluene (100 mL), containing a trace of boron trifluoride etherate ($BF_3{\cdot}Et_2O$). After refluxing for 24 h with a provision for removal of water (Dean Stark apparatus), the crude product was obtained as an orange liquid. This was distilled (195–200 °C/10^{-1} mbar) and then recrystallized (ether/hexane) to give pure light yellow solid (mp = 49–50 °C). ^{1}H NMR and C^{13} NMR correspond to the literature value [29], and the product is stable in air at room temperature for extended periods of time.

^{1}H NMR(DMSO-d_6):δ(ppm) = 1.2 (t, 3H), 4.2 (q, 2H), 4.2 (s, 2H), 7.1–7.7 (m, 10H); ^{13}C NMR: 14.2, 55.7, 60.9, 127.6, 128, 128.7, 128.8, 130.4, 135.9, 139.2, 170.6, 171.8.

Experimental procedure for the Pd-catalyzed asymmetric alkylation

Palladium complex (0.05 mmol) was dissolved in methylene chloride (1 mL). Aqueous KOH solution (50%, 0.5 mL) was added to a vigorously stirred solution of the Schiff base (0.2 g, 0.70 mmol), metal complex and benzyl bromide (1.2 eq, 0.1 mL, 0.85 mmol) in methylene chloride. The course of the reaction was followed by TLC (eluent, *n*-hexane/ethylacetate, 90/10) until the starting material was consumed. The suspension was diluted with diethylether, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. Purification of the residue by flash column chromatography on alumina 90 active basic (0.063–0.200 mm) afforded the alkylated product as a colorless oil (yield generally >80%).

Results and discussion

Catalytic alkylation of benzophenone imine glycinate

The orthopalladated dimeric complexes (Catalyst-I–V) and the dimeric R-complex of the benzylamine variety (catalyst-VI) were prepared by known literature methods [26–28] (slight modifications undertaken as revealed in the experimental section). These were then used as catalyst precursors for phase-transfer alkylation reactions. With

ethyl-*N*-diphenylmethylene glycinate as substrate (substrate-I) and methyl iodide as reactant (alkylating agent), we achieved 35–40% enantiomeric excess (chiracel OD, hexane:2-propanol (99.5:0.5); flow rate 1 mL/min, 20 °C, $\lambda = 254$ nm). *tert*-Butyl-*N*-diphenylmethylene glycinate (substrate II) was used under similar phase-transfer conditions to explore the steric effect. The temperature in all the runs was maintained at 20 °C since lowering the temperature up to −20 °C did not have much impact on the percentage yield or the product composition (Table 1). Chilling the reaction mixture, instead, lowered the rate of conversion. A 50% aqueous sodium hydroxide solution and 1.2 equivalents of the alkylating agent have been used in most of the runs under biphasic conditions. The effect of various bases and different solvents on enantioselectivity is discussed separately.

Though the ee obtained was modest, it was the first report of a chiral palladium complex to induce asymmetric induction under phase-transfer conditions. Palladium and Platinum salen complexes (Scheme 1) employed as phase-transfer catalysts by different groups for such studies did not yield any ee (Table 1).

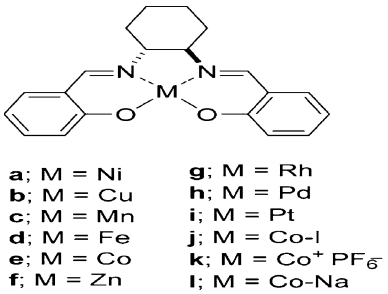
Like the highly efficient cinchona alkaloid systems previously employed for the above-mentioned reactions by various groups, we believe that the enantioselectivity in our case is attributed to the rigid orthometalated aromatic rings (Scheme 2).

To verify, we prepared the three sets of catalysts based on naphthylamine (catalyst-IV) and benzylamine moiety (catalyst-V) as shown in Scheme 3, and the catalytic studies were made under similar conditions. The naphthylamine complex has been found to be slightly superior

Table 1 Metal–salen complexes and the corresponding % ee obtained in asymmetric alkylation reactions [24]

Entry	Metal	Complex	Yield (%)	ee (%)
1	Ni^{+2}	1a	54	30
2	Cu^{+2}	1b	91	81
3	Mn^{+2}	1c	15	01
4	Fe^{+2}	1d	34	03
5	Co^{+2}	1e	82	80
6	Zn^{+2}	1f	39	01
7	Rh^{+2}	1g	92	14
8	Pd^{+2}	1h	56	01
9	Pt^{+2}	1i	55	00
10	Co^{+3}	1j	46	07
11	Co^{+3}	1k	66	00
12	Co^{+1}	1l	21	00

Methyl ester as substrate/50% aq NaOH/$C_6H_5CH_2Br$(electrophile)/toluene/RT/18 h



Scheme 1 Metal–salen complexes used in asymmetric alkylation reactions [24]

to its closely related benzyl analog in alkylation reactions (Table 2, comparison of catalytic runs 8, 9 and runs 12, 13).

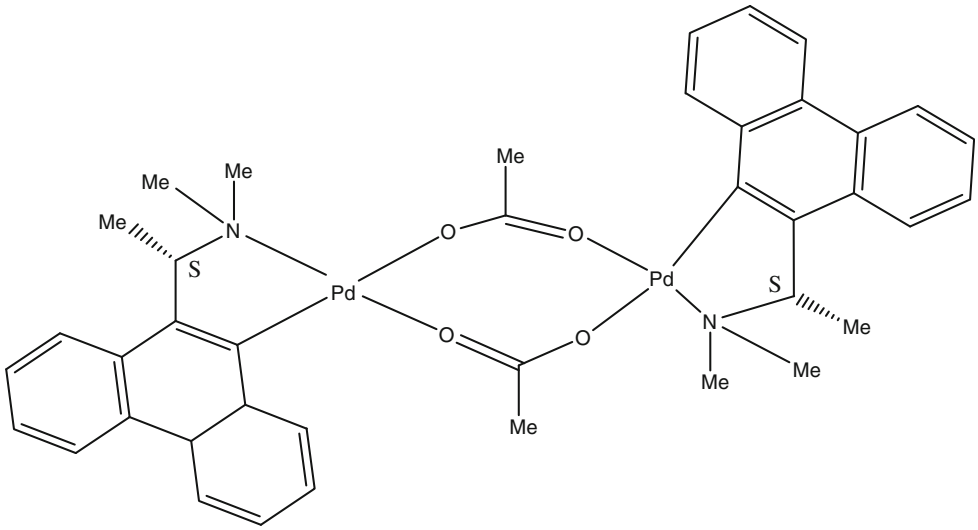
Alkylation of the Schiff bases was explored using the six set of catalysts (10 mol%) in dichloromethane with 50% aqueous KOH at 20 °C. T he highest enantioselectivity was achieved when methyl iodide was used as the electrophile for the alkylation of *tert*-butyl glycinate benzophenone Schiff base (40%, Table 2, entry 6). Under similar conditions and using the same set of catalyst and the Schiff base, lower enantioselectivity (15–20%) was noticed with benzyl bromide as electrophile (Table 2, entry 14–16). Though we expected better enantioselectivity with these alkylating agents due to their extended planarity and steric bulkiness compared to methyl iodide, we witnessed the opposite. Lower enantioselectivity was however observed when the ethyl ester was used as the substrate for alkylation compared to the *tert*-butyl glycine esters as evident from the catalytic runs 1, 3, and 5, 6 (Table 2). Though the difference in ee content is small, the trend of increased bulkiness giving better selectivity is evident both from the viewpoint of different glycine esters and different chiral palladium complexes used in our studies. Acetato-, chloro- or bromo-bridged ligands attached to palladium make no difference as far as product yield, rate of alkylation or the enantioselectivity is concerned.

The enantiomeric R-complex of palladium (complex-VI) was also studied as the catalyst in the enantioselective alkylation reaction of *tert*-butyl glycinate under similar optimized conditions to find the match-mismatch effect. The mismatch effect was evident as the R-variety of the palladium complex gave the R-product and the S-variety produced the S-product in major amounts (Table 2) under similar phase-transfer conditions.

Influence of bases and solvents

Different bases with varied concentrations were tried to optimize the yield as well as the ee content of the alkylated products. It was observed that 50% aqueous NaOH and

Scheme 2 Orthopalladated phenanthryamine complex employed in asymmetric alkylation reaction



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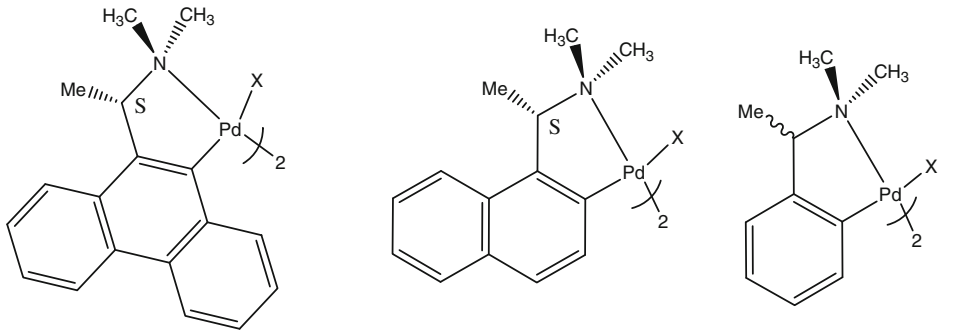
Scheme 3 Orthopalladated complexes used as catalysts in enantioselective alkylation reaction



X=OAc, catalyst-Ⅰ (S, enantiomer)
X=Cl, catalyst-Ⅱ (S, enantiomer)
X=Br, catalyst-Ⅲ (S, enantiomer)

X=C l, catalyst-Ⅳ

X=C l
catalyst-Ⅴ (S, enantiomer)
catalyst-Ⅵ (R, enantiomer)

KOH solutions are more effective than solid–liquid phase-transfer alkylation reactions employing solid bases like KOH, K_2CO_3, NaOH, $CsOH.H_2O$ (Sigma) or Cs_2CO_3. Using the much weaker base K_2CO_3 either in solid state or in aqueous solution retards the rate of alkylation and nearly 20 h is needed to accomplish the same product yield (80%). Organic solvents like toluene, chloroform, dichloromethane and chlorobenzene were tried either individually or as mixed solvents in our investigation to improve the ee of the alkylated products. We did not notice any significant difference either in the rate or product composition. Effect of relative amount of aqueous NaOH and dichloromethane as solvent on the rate of PTC alkylation reveals that with decrease in ratio beyond 1:4, the rate drop is significant (Fig. 1). We have therefore performed the catalytic reactions using 0.5 mL 50% aqueous NaOH solution and 1 mL of CH_2Cl_2 or toluene:chloroform (2:1) under ambient temperature conditions.

Asymmetric alkylation of benzophenone imine glycinate using different electrophiles

Having optimized the reaction conditions, the alkylation of *tert*-butyl benzophenone imine glycinate with a range of other electrophiles was investigated and the results are given in Table 3. For cinchona alkaloid catalyzed reactions, it is known that the steric bulk of the glycine ester and that of the alkylating agent are both important for efficient asymmetric induction. However, this is not the case for catalysis in our chiral palladium complexes. Though the more bulky *tert*-butyl glycinate gave a slightly better enantioselectivity compared to the ethyl esters, the benzylic alkyl halides under the standard conditions gave a low chemical yield and also low enantiomeric excess. Simple alkyl halides like MeI and EtI exhibited the highest activity and allylic bromides also gave good chemical yields and moderate enantiomeric excesses.

Table 2 Alkylation of glycine derivatives under phase-transfer conditions using chiral orthopalladated complex

Entry No.	Catalyst used	Substrate	Electrophile	Solvent	Pdt/yield (%)[a]	ee (%)[b]
1	**Complex-I**	I	CH_3I	CH_2Cl_2	Ia/84	24
2	**Complex-I**	I	CH_3I	PhMe:$CHCl_3$	Ia/70	26
3	**Complex-I**	II	CH_3I	CH_2Cl_2	IIa/86	38
4	**Complex-II**	I	CH_3I	CH_2Cl_2	Ia/88	30
5	**Complex-II**	I	CH_3I	PhMe:$CHCl_3$	Ia/86	33
6	**Complex-II**	II	CH_3I	PhMe:$CHCl_3$	IIa/90	40
7	**Complex-III**	II	CH_3I	PhMe:$CHCl_3$	IIa/85	38
8	**Complex-IV**	II	CH_3I	PhMe:$CHCl_3$	IIa/88	30
9	**Complex-V**	II	CH_3I	PhMe:$CHCl_3$	IIa/85	25
10	**Complex-VI**	II	CH_3I	PhMe:$CHCl_3$	IIa/86	28
11	**Complex-VI**	I	CH_3I	PhMe:$CHCl_3$	Ia/84	22
12	**Complex-VI**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/78	12
13	**Complex-IV**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/75	15
14	**Complex-III**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/75	18
15	**Complex-II**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/78	17
16	**Complex-I**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/84	15
17[c]	**Complex-I**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/70	05
18[d]	**Complex-I**	II	$C_6H_5CH_2Br$	PhMe:$CHCl_3$	IIb/72	17

Alkylating agent: benzyl bromide(b)/methyl iodide(a), $T = 20$ °C, time = 12 h

* Absolute configuration of products was determined to be (S) from literature data for catalysts I–V and (R) for catalyst-VI

[a] Isolated crude oil before column chromatography

[b] Determined by ^{1}H NMR, HPLC and optical rotation studies

[c] A higher temperature of 50 °C was employed

[d] A lower temperature of −20 °C was employed

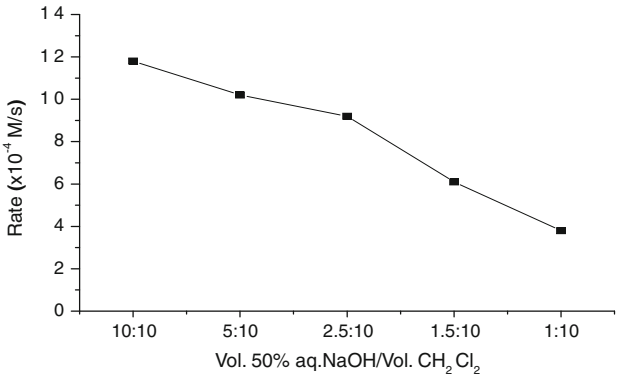


Fig. 1 Effect of relative amount of aqueous NaOH on rate of PTC alkylation

Table 3 Alkylation of *tert*-butyl-*N*-(diphenylmethylene)glycinate (substrate II) with different electrophiles under phase-transfer conditions

Alkylating agent	Product yield (%)	Enantiomeric excess (%)
$C_6H_5CH_2Br$	78	15
4-$O_2NC_6H_4CH_2Br$	70	10
CH_2=$CHCH_2Br$	84	30
PhCH=$CHCH_2Br$	80	22
CH_3I	90	40
CH_3CH_2I	88	35

Catalyst: orthopalladated μ–chloro dimer (complex-II, 10 mol%); solvent: PhMe:$CHCl_3$(2:1); $T = 20$ °C; time = 12 h; Base = 50% Aq. KOH

Catalyst recovery and reuse

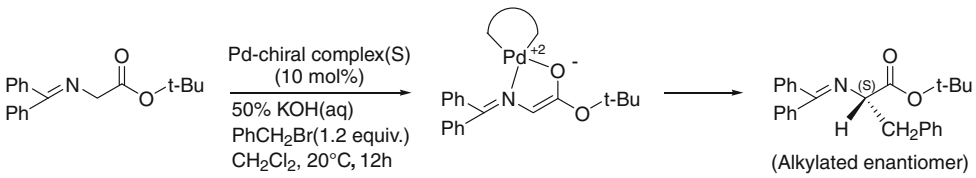
In contrast to commonly used cinchona alkaloid derived catalysts, the chiral palladium complexes are stable and suffer no decomposition under phase-transfer conditions. As a result, we recovered the benzylamine chloro complex (catalyst-V) from the reaction mixture by simple decantation. After quenching the reaction with deionized water and diethyl ether, the catalyst appeared as a white solid between the lower aqueous layer and the upper organic layer. After stirring vigorously for 5 min, this white solid adhered to the reaction vessel. The solid was easily separated by simple decantation and reused without further purification. The recovered catalyst under the same phase-transfer alkylation condition showed the same catalytic efficiency (86% yield, 26% ee) with methyl iodide.

Computational studies with the chiral palladium complex

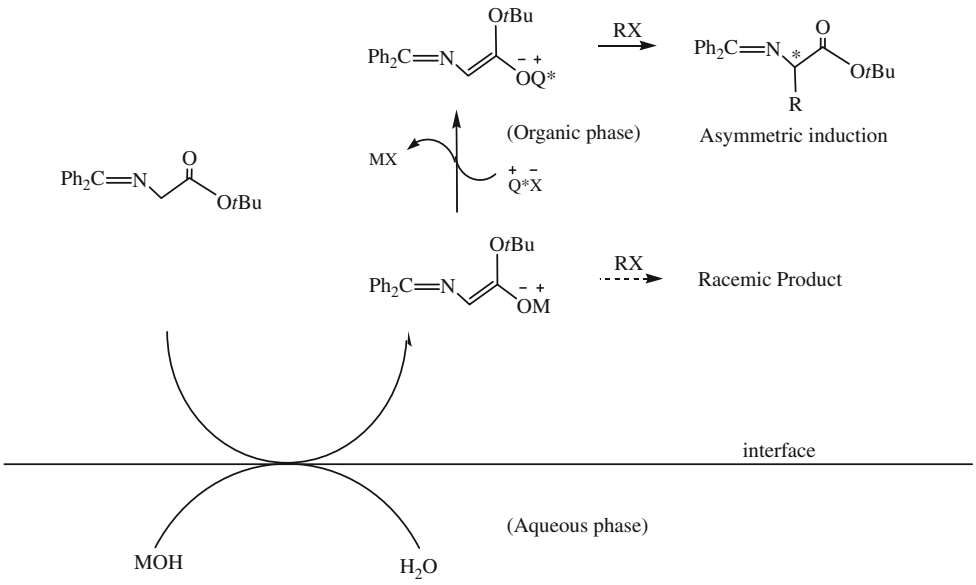
Computer simulations have been made to examine the complexes formed and the nature of interactions between the chiral phase-transfer catalyst and enolates that are known to be alkylated enantioselectively. A similar molecular recognition technique and computational tool has been employed by Lipkowitz et al. [31] although their catalysts, used as asymmetric templates, were derived from the cinchona alkaloid family. It has already been reported [32] that the benzophenone imine anions can exist as E- or Z-enolates and that with a metal ion like lithium the Z-enolate has been found to be more stable. The palladium metal in our studies should therefore associate with the N and O^- atoms simultaneously to stabilize the Z-enolate by orbital interactions or by coulombic attractions (Scheme 4). The four-coordinated square planar geometry of the palladium complex with the enolate has therefore been considered as a computational tool to initialize the energy minimization steps.

A detailed molecular mechanism has been described for the phase-transfer catalyzed enantioselective alkylation of an enolate with the chiral quaternary cinchonidinium salt by Corey et al. [33, 34]. In their mechanistic model, contact ion pairing takes place between the anionic oxygen of the enolate and just one of the tetrahedral faces of the cationic nitrogen of the alkaloid species (Scheme 5). For the chiral palladium complexes, the bridged dimer species spontaneously dissociates into the monomer solvent adduct and immediately combines with the Z-enolate to form a stable square planar species. This mode of bonding actually prevents the enolate component to be solvated or racemized in strongly basic solution and explains why the different bridging ligands in complexes I to III do not affect enantioselectivity. The enolate with the catalyst is successfully transferred to the organic layer where it is lined up in the sterically most favorable geometry with the alkyl halide (alkylating agent). Only the appropriate *re* face or the *si* face of the α-carbon of the enolate is available for electrophilic attack leading to the observed R and S products, respectively.

The interactions between the Z-enolate form of glycine derivative and palladium chiral catalysts were theoretically investigated using the Gaussian 03 program [35]. The geometry optimizations and thermodynamic corrections without including the bulk solvent effect were performed with hybrid Becke 3-Lee–Yang–Parr (B3LYP) exchange–correlation functional with the 6-31+G* basis sets for C, H, N and O, and LanL2DZ(ECP) basis sets for S and Pd. In order to obtain the most stable geometries, all kinds of possible interaction patterns were optimized. No restrictions on symmetries were imposed on the initial structures. All stationary points were verified as minima by full



Scheme 4 Coordination of the Pd-chiral complex to the Z-enolate under PT conditions



Scheme 5 General phase-transfer mechanism for asymmetric alkylation of active methylene compounds

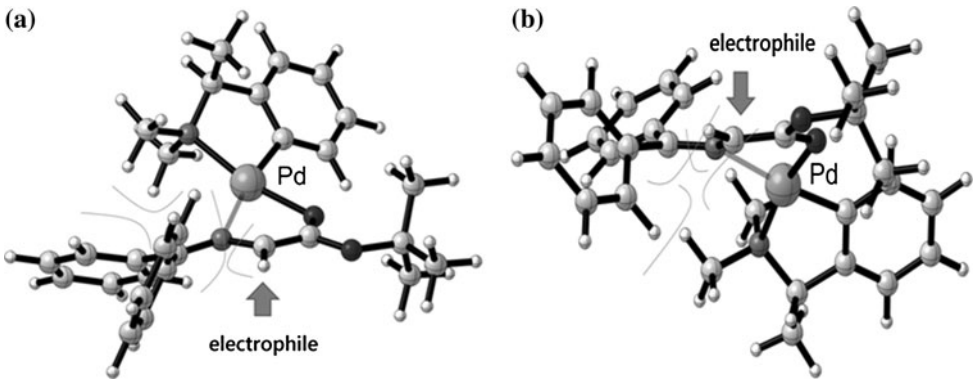


Fig. 2 Chiral palladium benzyl complex (S-enantiomer) coordinated to Z-enolate

calculation of the Hessian and a harmonic frequency analysis. *tert*-Butyl-*N*-diphenylmethyleneglycinate has been taken as the reference substrate in all model computational studies with chiral palladium complexes.

Analysis based on findings

The palladium catalyst with S-ligand (complex V) coordinates to Z-enolate in a square planar fashion. The complex with *si* face exposed to give the S-enantiomer (Fig. 2a) is calculated to be more stable than the one with *re* face exposed to give the R-enantiomer (Fig. 2b) by 3.5 kJ/mol.

The palladium catalyst with R-ligand (complex VI) also coordinates to Z-enolate in a square planar fashion. In this case, the complex with *re* face exposed to give the R-enantiomer is calculated to be more stable than the one with *si* face exposed to give the S-enantiomer by almost 3.5 kJ/mol. The electrophile is not accounted for in the modeling study and it is assumed that the low energy structures derived from the model are the ones leading to product.

Conclusion

A new design for asymmetric phase-transfer catalysts has been discussed. Orthopalladated chiral complexes were found to be effective catalysts in asymmetric phase-transfer alkylation reactions. The rigid orthometallated phenanthrylamine moiety provided maximum asymmetric induction followed by the less constrained naphthylamine and benzylamine palladium complexes. The energy differences between the most stable *si* and the most stable *re* structures correlate with the experimental findings. Though the ee content reported is moderate compared to ee reported with cinchona-based alkaloids, the use of palladium catalysts and computer simulation work to evaluate the nature of interactions could provide new insights into the enantioselective alkylation reactions. Further work on optimization of the catalyst design and change of conditions by incorporating additives to improve enantioselectivity is underway.

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