A Simple Chiral Cu(II) Complex as an Effective Phase-Transfer Catalyst for the Enantioselective Alkylation of Dissymmetric Glycinate Ketimines

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ABSTRACT Catalytic asymmetric benzylation of a dissymmetric *tert*-butylglycinate ketimine, incorporating 1-naphthyl and phenyl groups as the Schiff base substituents, under phase-transfer conditions was investigated. It was interesting to note that the sense of asymmetric induction of the alkylation of *Z*-imine stereoisomer is opposite to that of the corresponding *E* stereoisomer with a similar degree of enantioselectivity. More interestingly, the chiral Cu(II) complex of the Schiff base derived from (*R*)-2-phenylglycinol and 2-hydroxy-1-naphthaldehyde was found to catalyze the same reaction under solid-liquid conditions with comparable enantioselectivity (up to 60% *ee*) with respect to known cinchona alkaloid catalysts. The solvent/base-system parameter was shown to control the optimal catalytic activity. *Chirality 27:944–950, 2015.*

KEY WORDS: chiral metal complexes; *dissymmetric imines*; enolates alkylation; *hindered Schiff bases*; phase-transfer catalysis

Enantioselective α-alkylation of the enolate-forming glycinate ester frame under catalytic conditions involving the use of alkaloid or nonalkaloid-derived catalysts is a practical and well-documented process. Asymmetric alkylation of *ter*-butyl glycinate-benzophenone Schiff base using the very efficient N-alkylcinchoninium salts as catalyst is by far the most studied reaction.[1–6] Since the early reported research work on asymmetric alkylation of this substrate pioneered by O'Donnell et al.,[7,8] tremendous effort has been devoted to this area by several groups, leading in turn to the development of highly efficient catalysts.[1] In spite of this effort, the mechanism aspects of asymmetric alkylation remain unclear because of the difficulty to investigate biphasic systems and the parameters that control the transfer of chirality. For instance, it is difficult to find evidence which geometric *E* or *Z* enolate is the reacting species in the alkylation process. Moreover, most of the chiral catalysts are featured prominently at low temperature, because good asymmetric induction requires a rigid ion-paired enolate for a favorable van der Waals interaction. Therefore, the mechanism aspects of asymmetric alkylation need to be further explored in order to develop effective catalysts derived from simple structures. Although extensive studies of Schiff base asymmetric alkylation have been performed, leading to the discovery of a plethora of chiral catalysts, only very little empirical work has been carried out to characterize the effect of the imine structure within the substrate on stereoselctivity.[9–13] Moreover, in the case of dissymmetric imines, hydrogenation serves as a route to enantiomerically enriched amines with multistereogenic centers. Chiral amines are attractive targets due to their prominent representation among bioactive molecules.[14]

More than two decades ago, we reported the results of research studies aimed at the mechanism investigation of the enantioselective alkylation of prochiral glycine-derived Schiff base lithium enolates by means of alkylating agents bearing a chiral nucleofugal.[15–17] We demonstrated that switching from the symmetric benzophenone to a dissymmetric ketimine unit within the substrate has a positive impact on the enolate-enantioface differentiation by the chiral nucleofugal. In this article we will disclose the results of our research work dedicated to the study of the effect of the imine moiety on the enantioselectivity of the asymmetric α-benzylation of *ter*-butyl glycinate Schiff bases catalyzed with onium salts and organometallic complexes.

MATERIALS AND METHODS

Uncorrected melting points were determined on a Büchi 510 instrument. Optical rotations were determined on a Perkin–Elmer (Boston, MA) 240 polarimeter using the sodium D line and concentrations are given in g/100 mL. IR spectra were recorded on a Perkin-Elmer 16 PC FT instrument (in cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on Bruker (Billerica, MA) AC 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts are in ppm referenced to TMS in $CDCl_3$. Mass spectra were determined on ThermoFinnigan SSQ 7000 GC/MS. High-resolution mass spectra (HRMS) were recorded on a Micromass Zab Spectrometer at the University of Rennes (France). Elemental analyses were performed on a ThermoFinnigan Elementary Analyzer Flash EA 1112 at the UATRS, Rabat (Morocco). Single-crystal X-ray diffraction analyses were performed on a Bruker X8 APEXII CCD diffractometer. Analytical thin layer chromatography (TLC) was performed on Merck (Germany) Kieselgel 60 F254 glass plates (0.25 mm) and compounds were visualized by UV light (254 nm) or ninhydrine acid–ethanol (22.1 g, 180 mL) spray. Column chromatography was carried out on Merck Kieselgel. Chiral HPLC was performed on a Jasco (Tokyo, Japan) 875 equipped with a Chiralcel OD column, eluent: heptane/2-PrOH = 99.5:0.5, 1 ml/min, retention times: **5b** (*R*): 10.15 min; **5b** (*S*): 16.07 min.[18] Chemicals were purchased from either Sigma-Aldrich (St.

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Louis, MO) or Fluka (Buchs, Switzerland) and used as received. Solvents were distilled according to known procedures.

Syntheses

Naphthalen-1-yl(phenyl)methanimine 1. In a 25-ml two-necked flask equipped with a dropping funnel and reflux condenser fitted with a calcium chloride drying tube, were introduced magnesium turnings (0.21 g, 8.9 mmol), anhydrous THF (4 ml) and 0.2 g of 1-bromonaphthalen. When the reaction started, a moderate reflux began which was maintained by slow addition under vigorous stirring of a solution of the remaining amounts of 1-bromonaphthalen (total of 1.79 g, 8.7 mmol) in THF (8 ml). The resulting brown solution was heated under reflux for 2 h, after which time it was cooled and a solution of benzonitrile (0.85 g, 8.3 mmol, 0.95 eq) in THF (8 ml) was added. The dark solution was then heated to reflux for 4 h. The stirred mixture was cooled to room temperature before addition of absolute methanol (3 ml) and the stirring continued for 30 min. The solvents were removed in vacuo and the residual brown oil taken in ethyl acetate (30 ml). The solid which separated was collected by filtration and the filtrate concentrated to dryness in vacuo. Column chromatography on silica gel afforded pure methylenimine **1** as orange oil (1.78 g, 93%), R_f = 0.22 (0.5:9.5 EtOAc/Hexane); ^{1}H NMR δ (ppm): 7.22-7.42 (m, 3H), 7.43-7.6 (m, 4.5H), 7.70 (m, 0.5H), 7.75-7.79 (m, 2H, H2', H6'), 7.89 (m, 0.5H), 7.91-7.99 (m, 1.5H) (H2, H8), 9.01 (s, 1H, NH); ^{13}C NMR δ (ppm): 126.7 (C3'), 127.0 (C5'), 128.1 (C5), 128.4 (C7), 128.5 (C6), 128.6 (C3), 128.9 (C6'), 129.2 (C2'), 129.6 (C2), 130.4 (C8), 130.5 (C4), 130.6 (C4'), 131.3 (C9), 133.2 (C10), 133.5 (C1'), 133.6 (C1) , 178.2 (C=N); IR (KBr): 3057, 1659, 1282, 1257, 1150 cm^{-1}; MS (EI) 231 (M^+), 154; ESI-HRMS: m/z = 231.1048 (M^+); $C_{17}H_{13}N$ requires 231.1050.

***Tert*-butyl-2-(naphthalen-1-yl(phenyl)methyleneamino)acetate 2a.** Methylenimine **1** (1.7 g, 7.3 mmol) and *tert*-butylglycinate hydrochloride (1.35 g, 8.1 mmol) were dissolved in 1,2-dichloroethane (15 ml) and the resulting solution heated to reflux for 72 h. Then the crude product was subjected to column chromatography over silica gel using (0.1:9.9 EtOAc/Hexane) to purify and separate the geometric stereoisomers.

Data for imine *E*-**2a**: orange oil, (0.5 g, 20%), R_f = 0.41 (0.5:9.5 EtOAc/Hexane); ^{1}H NMR δ (ppm): 0.87-0.91 (m, 1.5H), 0.92-0.96 (m, 1.5H) (CH3), 1.26-1.43 (m, 6H) (2CH3), 3.16 (s, 2H, CH2), 7.25-7.30 (m, 1.5H), 7.31-7.35 (m, 1.5H) (H3, H7, H5'), 7.37-7.41 (m, 1H, H3'), 7.42-7.48 (m, 1H, H4'), 7.49-7.53 (m, 1H, H5), 7.53-7.55 (m, 1H, H6), 7.56-7.60 (m, 1H, H4), 7.66-7.69 (m, 1H, H6'), 7.69-7.73 (m, 1H, H2'), 7.92-7.95 (m, 1H, H2), 7.95-8.02 (m, 1H, H8); ^{13}C NMR δ (ppm): 28.83 (CH_3), 68.1 (CH_2), 77.3 (C-CH_3), 126.5 (C5, C3'), 127.1 (C5'), 128.4 (C3, C6), 128.7 (C4), 128.8 (C7), 128.9 (C2), 129 (C8), 130.1 (C2', C6'), 130.9 (C4'), 131.3 (C9), 132.4 (C10), 133.4 (C1'), 138.6 (C1), 167.8 (C=O), 170.8 (C=N); IR (KBr): 2976, 1749, 1626, 1448, 1152 cm^{-1}; MS (EI) 345 (M^+), 291, 245; ESI- HRMS: *m/z* = 345.1732 (M^+); $C_{23}H_{23}NO_2$ requires 345.1729.

Data for imine *Z*-**2a**: white solid, (1.01 g, 40%), mp = 99-101 °C, R_f = 0.32 (0.5:9.5 EtOAc/Hexane); ^{1}H NMR δ (ppm): 1.16-1.58 (m, 9H, 3CH3), 3.85-4.13 (dd, J = 13.5 and 16.2 Hz, 2H, CH2), 7.18-7.31 (m, 3H, H3, H4, H5), 7.33-7.44 (m, 2H, H6, H4'), 7.5-7.61 (m, 3H, H7, H3', H5'), 7.66-7.75 (m, 2H, H2', H6'), 7.88-8.01 (m, 2H, H2, H8); ^{13}C NMR δ (ppm): 28.0 (CH_3), 55.9 (CH_2), 81.1 (C-CH_3), 125.3 (C3', C5'), 126.5 (C5, C7), 127.1 (C6), 128.2 (C3), 128.6 (C2', C6'), 128.7 (C2), 129.1 (C8), 130.1 (C9), 130.4 (C4), 130.9 (C4'), 133.4 (C10), 133.9 (C1'), 138.7 (C1),, 169.5 (C=O), 171.3 (C=N); IR (KBr): 2976, 1749, 1626, 1448, 1152 cm^{-1}; MS (EI) 345 (M^+), 290, 246; Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.92; H, 6.74; N, 4.01.

Preparation of Catalyst 4

(–)-(*R*)-1-((2-hydroxy-1- phenylethylimino)methyl)naphthalen-2-ol 3. A suspension consisted of 2-hydroxy-1-naphthaldehyde (**0.5 g**, 2.9 mmol), (*R*)-phenylglycinol (**0.4 g**, 2.9 mmol, 1 eq), and anhydrous $MgSO_4$ (**0.48 g**) in dichloromethane (7 ml) was stirred at room temperature overnight for complete reaction. The yellow solid that precipitated was dissolved by addition of ethanol (5 ml). The resulting suspension was filtered to remove $MgSO_4$, and the filtrate concentrated to dryness in vacuo. The chiral Schiff base ligand 3 crystallized out as vivid yellow needles after addition of little hexane (0.82 g, 97%), R_f = 0.43 (5:5 EtOAc/Hexane), mp = 176 °C, $[\alpha]_D^{25}$ = -57 (c = 1, EtOH); ^{1}H NMR δ (ppm): 3.73-3.81 (m, 2H, CH2), 3.88 (t, J = 7.5 and 12 Hz, 1H, C*H), 5.00 (s, 1H, CH2O**H**), 6.75 (s, 0.5H), 6.78 (s, 0.5H), 7.11-7.28 (m, 2H), 7.3-7.39 (m, 3H), 7.41-7.49 (m, 2H), 7.55-7.58 (m, 1H), 7.70 (m, 0.5H), 7.73 (m, 0.5H), 7.78 (m, 0.5H), 7.81 (m, 0.5H), 8.68 (s, 1H), 10.2 (sb, 1H, Nap-OH); ^{13}C NMR δ (ppm): 65.9 (CH2OH), 69.9 (C*H),

120.4 (C8), 125.3 (C4'), 126.5 (C6), 126.8 (C3), 127.0 (C7), 127.1 (C6'), 127.2 (C2'), 128.1 (C5), 128.7 (C3'), 128.8 (C5'), 128.9 (C4), 129.1 (C9), 129.2 (C10), 134.7 (C1'), 138.5 (C1) , 162.2 (COH), 171.3 (C=N); IR (KBr): 3435, 3239, 2860, 1626, 1493, 1274 cm^{-1}; MS (EI) 291 (M^+), 170, 143; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.40; H, 5.81; N, 4.79.

[(+)-*R*-1-(2-hydroxy-1-phenylethylimino)methyl-2-naphthol]$_2$CuCl$_2$.H$_2$O 4. To a solution of the chiral ligand (0.7 g, 2.4 mmol) in methanol (12 ml) was added $CuCl_2.2H_2O$ (0.38 g, 2.4 mmol) and the mixture stirred at room temperature overnight. Evaporation of the solvent under reduced pressure led to a dark green solid which was washed with ether and dried in the desiccator over P_2O_5 (1.85 g, 97%), mp = 190° C (decomp.), $[\alpha]_D^{25}$ = +79 (c = 0.6, EtOH); IR (KBr): 1626, 1540, 1458, 1426, 1310, 1253, 1182, 1169, 1143, 1098, 1040, 940, 863, 740, 571, 528, 430 cm^{-1}; MS (EI) 388 (M^+), 346, 246, 172; Anal. Calcd for $C_{38}H_{34}Cl_2Cu_2N_2O_5$: C, 57.29; H, 4.30; N, 3.52. Found: C, 58.88; H, 4.01; N, 3.90.

Phase-Transfer α-Benzylation of Substrate 2

Liquid/liquid system. To a solution of **2a** (0.2 g, 0.58 mmol) in dichloromethane (2 ml) was added a solution of the chiral ammonium salt **6** (24.3 mg, 0.058 mmol) or **7** (35 mg, 0.058 mmol) and benzyl bromide (0.49 g, 2.9 mmol, 5 eq) in dichloromethane (4 ml), and under stirring, 50% aqueous NaOH (2.4 ml) was added. The mixture was then vigorously stirred at room temperature until the reaction was complete (TLC, 0.5:9.5 EtOAc/Hexane). Ether (6 ml) was added and the organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvents and purification of the residual oil by column chromatography (0.5:9.5 EtOAc/Hexane) gave Schiff base **5a** as yellow oil.

Solid/liquid system. Catalyst **4** (46 mg, 0.058 mmol) was added to a suspension of imine **2a** (0.2 g, 0.58 mmol) or **2b** (0.17 g, 0.58 mmol), benzyl bromide 0.49 g, 2.9 mmol, 5 eq) and dried solid KOH (0.32 g, 5.8 mmol, 10 eq) in dichloromethane (6 ml). After 72 h of vigorous stirring at room temperature, ether (5 ml) was added, the solid removed by filtration, and the filtrate washed with water and dried over $MgSO_4$. Evaporation of the solvents and purification of the residual oil by column chromatography (0.5:9.5 EtOAc/Hexane) afforded Schiff base **5** as a yellow oil.

Data for imine *E*-**5a**: (0.12 g, 48%), R_f = 0.37 (0.5:9.5 EtOAc/Hexane), $[\alpha]_D^{25}$ = -21.5 (c = 1, $CHCl_3$); ^{1}H NMR δ (ppm): 0.85-0.99 (m, 1.25H), 1.23-1.38 (m, 5.25H), 1.4-1.49 (m, 2.5H), 3.18-3.29 (m, 2H), 3.86-3.98 (m, 0.5H), 4.21-4.28 (m, 0.5H), 6.98-7.07 (m, 1.5H), 7.09-7.14 (m, 0.75), 7.17-7.25 (m, 2H), 7.26-7.35 (m, 2H), 7.36-7.44 (m, 2H), 7.45-7.49 (m, 1.25H), 7.5-7.58 (m, 2H), 7.6-7.8 (m, 2.5H), 7.81-7.91 (m, 2H), 7.95-8.12 (m, 1H); ^{13}C NMR δ (ppm): 27.9 (CH3), 28.0 (CH3), 28.9 (CH3), 38.7 CH2), 68.2 (C*H), 81.1 (C-CH3), 124.9 (C4"), 125.2 (C2"), 125.3 (C6"), 125.5 (C3"), 125.6 (C5"), 125.9 (C3'), 126.2 (C5'), 126.3 (C5), 126.5 (C7), 128.0 (C6), 128.1 (C3), 128.2 (C2'), 128.3 (C6'), 128.4 (C2), 128.5 (C8), 128.6 (C4), 129.7 (C4'), 130.2 (C9), 131.1 (C10), 133.0 (C1"), 138.5 (C1'), 139.8 (C1), 166.1 (C=O), 169.0 (C=N); IR (KBr) 3054, 3022, 2963, 2926, 1724, 1617, 1449, 1260, 1153 cm^{-1}; MS (EI) 435 (M^+), 380, 246, 153; ESI- HRMS: *m/z* = 435.2196 (M^+); $C_{30}H_{29}NO_2$ requires: *m/z* = 435.2198.

Data for imine Z-**5a**: (0.12 g, 50%), R_f = 0.37 (0.5:9.5 EtOAc/Hexane), $[\alpha]_D^{25}$ = +23 (c = 1, $CHCl_3$); ^{1}H NMR δ (ppm): 1.33-1.42 (m, 9H), 3.23-3.24 (d, J = 8.1 Hz, 2H), 5.86-7.89 (d, J = 9.9 Hz, 1H), 7.12-7.53 (m, 11H), 7.6-7.68 (m, 3.5H), 7.8-7.94 (m, 2.5H); ^{13}C NMR δ (ppm): 27.9 (CH3), 28.0 (CH3), 28.9 (CH3), 38.7 (CH2), 68.0 (C*H), 81.2 (C-CH3), 124.0 (C4"), 124.8 (C2"), 124.9 (C6"), 125.2 (C3"), 125.5 (C5"), 125.8 (C3'), 126.1 (C5'), 126.2 (C5), 126.3 (C7), 127.0 (C6), 127.5 (C3), 128.0 (C2'), 128.1

(C6'), 128.2 (C2), 128.4 (C8), 128.5 (C4), 129.7 (C4'), 130.2 (C9), 130.9 (C10), 133.0 (C1''), 138.1 (C1'), 138.2 (C1), 168.0 (C=O), 170.5 (C=N);

IR (KBr): 3054, 3022, 2963, 2926, 1724, 1617, 1449, 1260, 1153 cm^{-1}; MS (EI) 435 (M^+), 380, 246, 153; ESI-HRMS: m/z = 435.2195 (M^+); $C_{30}H_{29}NO_2$ requires 435.2198.

HPLC Enantiomeric Excess (ee) Determination

Transformation of imine 5a to imine 5b. Imine **5a** (0.1 g, 0.23 mmol) was dissolved in THF (3 ml) and 2 N aqueous HCl (2.5 ml) and the solution stirred at room temperature until TLC analysis indicated complete hydrolysis (~14 h). THF was removed under reduced pressure and the aqueous phase extracted with ether (3 x 1.5 ml) before complete evaporation of water in vacuo. The white solid thus obtained was dried at the desiccators (P_2O_5) for 2 h. To a solution of the amino ester hydrochloride salt (59 mg, 0.23 mmol) in dichloromethane (3 ml) was then added benzophenone methanimine[19] (41.5 mg, 0.23 mmol) and the resulting mixture stirred at room temperature overnight for complete transimination. Imine **5b** was purified by column chromatography (0.1:9.9 EtOAc/Hexane) and subjected to chiral HPLC analysis for *ee* determination. The same procedure applied to a sample of **5b** (*S*/*R*, 80/20, 60% *ee*) showed no racemization after hydrolysis and transimination processes.

RESULTS AND DISCUSSION

Syntheses

We prepared imine **2a** by means of transimination[20] protocol between methylenimine **1** and *tert*-butylglycinate hydrochloride in refluxing 1,2-dichloroethane (Scheme 1).

The choice of ketimine **2a** as substrate of the alkylation reaction underlies two main earlier established empirical guidelines; 1) contributions from this laboratory on hindered ketimines revealed that introduction of 1-naphthyl group as an imine substituent generates steric environment that facilitates separation of geometric, or even atropisomeric, Schiff base stereoisomers;[21–23] 2) the steric hindrance brought by the 1-naphthyl group enhances considerably resistance of the imine functional group towards hydrolysis, which in turn contributes to limit racemization of alkylation reaction products.

When the 1-naphthylphenylmethylenimine derivative **1** and the glycinate hydrochloride salt were heated under reflux overnight in 1,2-dichloroethane, TLC (0.5:9.5 EtOAc/Hexane) showed the appearance of new two well-resolved spots with proportions largely in favor of the less eluted one (~9:1), together with large amounts of the starting materials. These proportions change progressively with consumption of imine **1** to stabilize at (~6:4) after 72 h heating. Chromatographic separation helped to isolate the major isomer **2a** (40%) which crystallized out upon solvent removal. Then, repetitive chromatographic separation allowed us to isolate the minor isomer (20%) as an orange oil, crystallization of which proved unsuccessful.

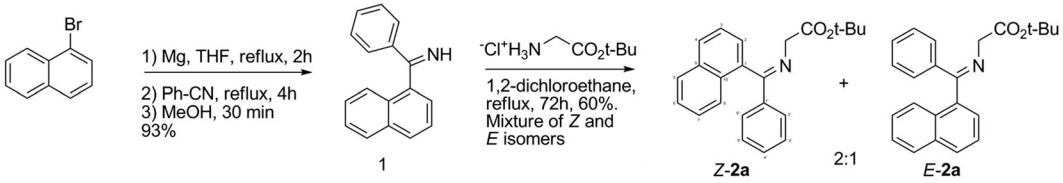
On the other hand, the Cu(II) complex **4** was readily prepared in two steps from 2-hydroxy-1-naphthaldehyde and (*R*)-(-)-2-phenylglycinol (Scheme 2). It is noteworthy that the chiral aldimine ligand **3** is stable towards hydrolysis and racemization.

A survey of the literature showed that chiral Schiff base ligands containing a naphthol fragment are seldom reported compared to salicylaldehyde derivatives. Chiral ligands derived from amino alcohols and 2-hydroxynaphthalene-1-carbaldehyde were used as catalysts, in the presence of Cu $(OAc)_2.2H_2O$, for asymmetric addition of nitroalkanes to aldehydes.[24] In the case of phenylglycinol, poor chemical yield and enantioselectivity were obtained (40%, *ee* <5%). The authors did not report on the isolation and characterization of the catalytic organometallic species generated in situ.

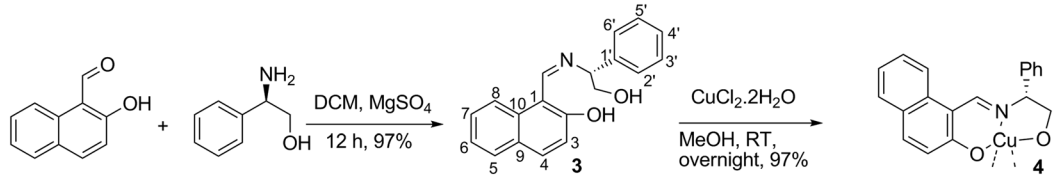
Structure Determination

A *Z* geometric configuration could be found for the major imine **2a** from X-ray analysis of a crystal grown in diluted heptane.[25] Of particular note was the out of the imino plane orientation of the 1-naphthtyl group whose plane defined a dihedral angle of 78,54° with the phenyl plane, which is almost coplanar with the imino bond plane (Fig. 1). The NMR observations were in accordance with the X-ray results as the methylene protons become magnetically different because of the 1-naphthyl orthogonal orientation, and display two doublets between 3.85 and 4.13 ppm. We believe that the steric hindrance imposed by the aryl substituents implies slow rotation of the 1-naphthyl group about the C-C bond adjacent to C=N, which in turn makes possible detection of stable conformers at the NMR time scale.

Structural information on the stereoisomeric nature of the minor imine **2a** came from the classical 2D NMR investigation. Thus, the HMBC experiment allowed assigning the imino ^{13}C=N signal which appeared downfield with respect to the imino signal of the *Z* isomer.[26] Furthermore, the methylene protons appeared as a unique singlet shifted 3.16 ppm



Scheme 1. Preparation of *ter*-butyl glycinate Schiff bases.



Scheme 2. Preparation of organometallic complex **4**.

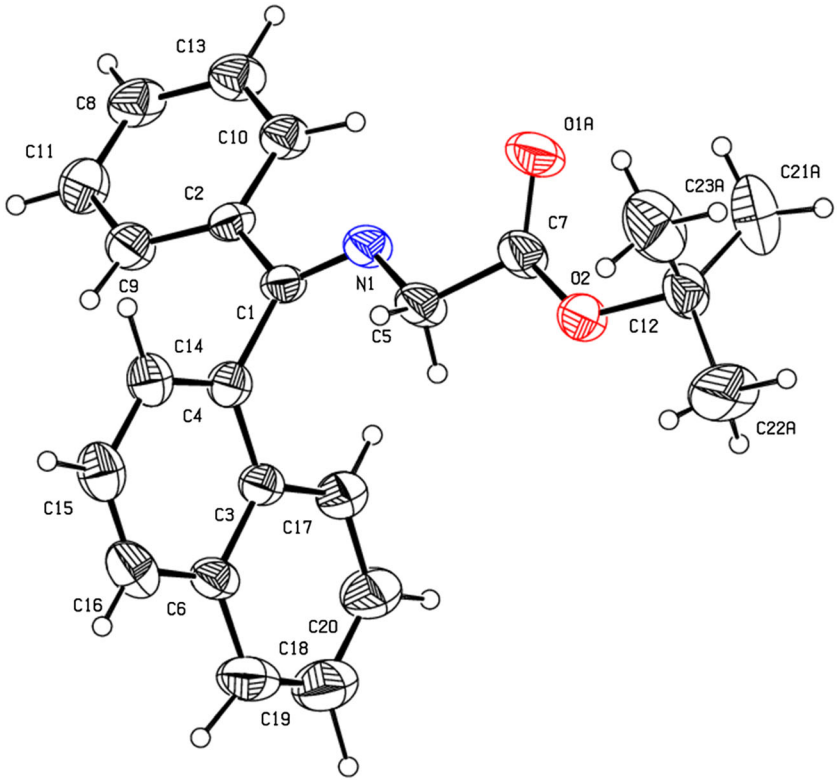


Fig. 1. ORTEP structure of imine *Z*-**2a**.

upfield. This was in line with a structure in which the methylene protons face the phenyl ring current, suggesting *E* geometric configuration. Complementary structural confirmations came from NOESY experiments that showed intense correlations between the methylene (3.16 ppm) and the ortho phenyl protons H2' and H6' (~7.7 ppm). This correlation is absent in the case of the imine geometric isomer *Z* (Fig. 2). It is worth mentioning that no *Z-E* isomerization was noticed in solution after a prolonged period of time in refluxing deuteriochloroform.

The structure of catalyst **4** was determined by means of single-crystal X-ray diffraction analysis.[27] Besides the hydrogen-bonding with one molecule of water, the three-dimensional structure of **4** revealed an asymmetric dichloro-bridged binuclear coordination in which each Cu is pentacoordinated with distorted square-pyramidal geometry, due to the existence of two Cu–Cl bond distances for each bridging theCl atom (2.2487 (Cu_1-Cl_1) Å and 2.9387 (Cu_2-Cl_2) Å) (Fig. 3). These bond distances are similar to those found in other Schiff base Cu(II) complexes.[28,29]

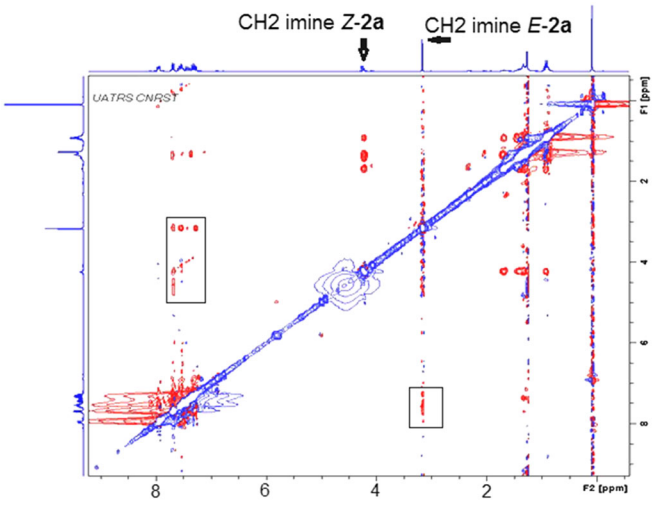


Fig. 2. NOESY experiment showing the difference in the chemical shift of the methylene protons, and their correlations with the aromatic moiety and the ester.

We first investigated the two-phase enantioselective catalytic α-benzylation of the enolate derived from Schiff bases **2** to study the impact of the imine substituents on the asymmetric induction (Scheme 2) (Table 1). For this purpose, we chose the commercially available N-benzylcinchoninium chloride **6**, the known O(9)-allyl-N-anthracenylmethylcinchonidinium bromide **7**[30] and the prepared chiral copper (II) complex **4** as catalysts[31] (Scheme 3).

Chiral quaternary ammonium salts **6** and **7**, derived from cinchona alkaloid, catalyzed the α-benzylation of the stereoisomer Z-**2a** under liquid–liquid PTC to produce (*S*)-Schiff base **5a** with good chemical yield and moderate *ee*'s (Table 1, Entries 1 and 3). By switching the substrate to the *E* stereoisomer, the alkylated Schiff base (*R*)-**5a** was obtained under the same conditions with a similar degree of enantioselectivity (Entry 3 vs. 4). This result, together with the racemic alkylated product obtained when equimolar amounts of *Z*- and *E*-**2a** were used as substrate (Entry 5), indicated that no *Z-E* isomerization occurred after deprotonation (Fig. 4).

Interestingly, the Cu(II) complex **4** catalyzed the asymmetric α-benzylation of imines Z and *E*-**2a** under solid–liquid conditions and provided a comparable degree of enantioselectivity with respect to the alkaloid-derived ammonium salts **6** and **7** (Entries 7 and 8). However, no asymmetric induction was obtained when benzophenone imine **2b** was

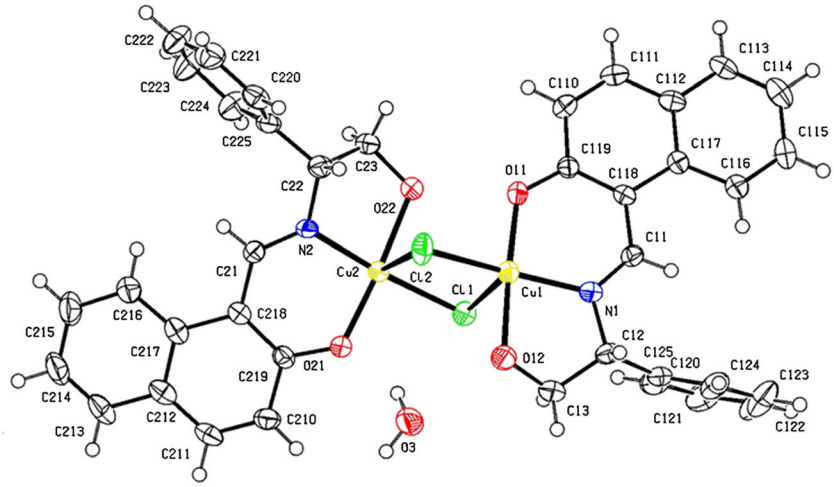


Fig. 3. Single-crystal X-ray analysis of catalyst **4**.

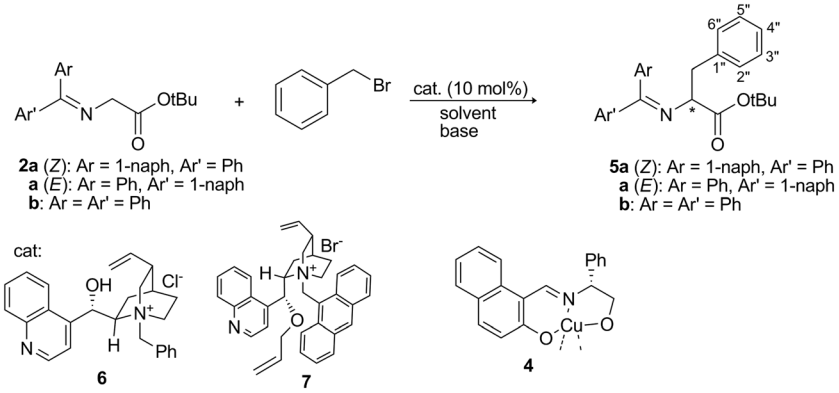
TABLE 1. Asymmetric α-benzylation of Schiff bases 2 under phase-transfer conditions

Ent.	Subst[a]	Cat.	Base	Time (h)	Yield (%)[b]	ee%[c] (%)
1	Z-**2a**	**6**	50% NaOHaq	18	90	57(*S*)
2	*E*-**2a**	**6**	50% NaOHaq	18	90	50(R)
3	Z-**2a**	**7**	50% NaOHaq	18	84	60(*S*)
4	*E*-**2a**	**7**	50% NaOHaq	18	86	53(*R*)
5	*Z*:*E*-**2a** (1:1)	**7**	50% NaOHaq	18	82	0
6	Z-**2a**	**7**	KOHs	72	—	—
7	*Z*-**2a**	**4**	KOHs	72	50	62(*S*)
8	*E*-**2a**	**4**	KOHs	72	48	60(*R*)
9	**2b**	**4**	KOHs	18	60	2(*S*)
10	*Z*-**2a**	**4**	NaOHs	72	—	—
11	*E*-**2a**	**4**	K_2CO_3:KOH (1:1)	72	—	—

[a]All reactions were performed at RT using 10 mol% of catalyst, 10 equiv. of base and 5 equiv. of benzylbromide in CH_2Cl_2.
[b]After purification of alkylated product **5**.
[c]Determined by HPLC analysis of the alkylated benzophenone imine using chiral column OD. No racemization occurred subsequent to transformation of **5a** to the benzophenone imine **5b**.

used as substrate (Entry 9), showing the beneficial steric effect on enantiotropic differentiation brought by the 1-naphthyl substituent on the imine moiety. It is worth mentioning that the Cu(II) free ligand could not provide any alkylated product, which excludes any competing nonmetal-catalyzed or uncatalyzed reactions. As far as the steric hindrance of the imine moiety is concerned, earlier studies have reported that introduction of 1- or 2-naphthyl group within the alanine aldiminoester was not beneficial to the enantioselectivity of the alkylation. Only an electronic factor was shown to be either detrimental or beneficial to stereoselectivity.[9]

Influence of the polar and nonpolar solvents on the asymmetric alkylation reaction was investigated using imine Z-**2a** as substrate, solid KOH as base, and catalyst **4**. No reaction was observed in diethylether, toluene, benzene, acetonitrile, or THF. Although diethylether is not a solvent of choice in phase-transfer reactions because of volatility and solubility problems, its use as a 5/5 mixture with DCM increased the chemical yield to 70% with no change in enantioselectivity (Table 2, Entry 4). In the absence of ether, we reasoned that the generated KBr salt, subsequent to alkylation, competes as a coordinating ligand around the Cu(II) sphere, which in turn results in catalyst poisoning and limitation of substrate transformation to a maximum of 50%. The presence of diethylether which partially dissolves KBr limits this ligand exchange. Curiously, however, among the chlorinated solvent tested only DCM gave alkylated product **5a** with 50% chemical yield and 62% *ee*. Based on these results, we studied the influence of the base on chemical yield and enantioselectivity of the α-benzylation of imine Z-**2a** under the same conditions using DCM as solvent (Table 2).



Scheme 3. Impact of the imine substituents on the sense of asymmetric induction.

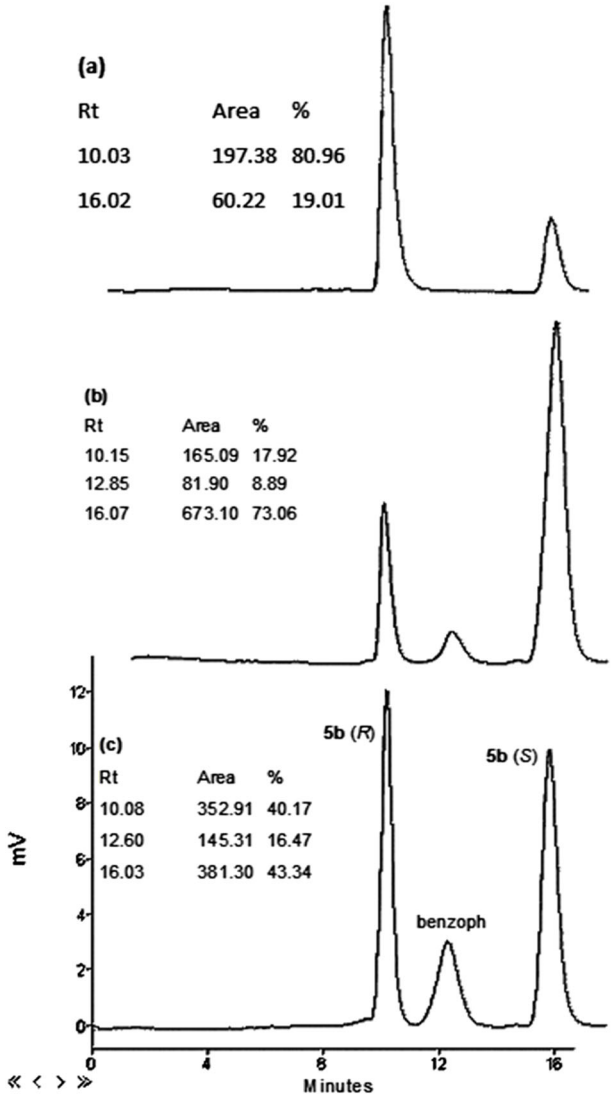


Fig. 4. Representative chiral HPLC trace: (**a**) alkylation of imine *E*-**2a**; (**b**) alkylation of imine *Z*-**2a**; (**c**) alkylation of equimolar amounts of *E* and *Z*-**2a**. Complex **4** was used as the catalyst in all cases. Attempts to separate enantiomers of imine **5a** using different chiral HPLC columns were unsuccessful.

The data in Table 2 show that solid KOH/DCM is the only base/solvent-system in which catalyst **4** was found to be active, with 10 molar equivalents of the base being the optimum. The relatively high pKa of the α–methylene protons of the ketimine substrate is thought to be responsible for the prolonged reaction time. Complexation of the alkali ion is believed to activate the ion pair derived from the substrate and the base. This process seems to be slow under solid–liquid conditions and favorable with potassium ion in DCM. Surprisingly, no reaction was observed when a mixture of potassium carbonate and potassium hydroxide (10 molar equiv. each) was used as a base in an attempt to enhance the reactivity. In the presence of stronger bases and a small alkali ion, such as Cs_2CO_3, $NaNH_2$, NaH, and LiOH, the chiral ligand **3** appeared in the reaction medium, showing a decomplexation of the Cu(II) catalyst prior to alkylation. Similarly, no alkylated product was formed using NaOH, $BaCO_3$ and Ba(OH)2, although catalyst **4** showed more stability towards these bases.

The asymmetric induction induced by the metal complex catalyst **4** provides a reference to study the mechanistic

TABLE 2. Asymmetric α-benzylation of Schiff base *Z*-2a under phase-transfer conditions catalyzed by complex 4; influence of the base (S/L system)

Ent.	Base[a]	Molar eq.	Time (h)	Yield (%)[b] **5**	ee% (%)[c] (R:S)
1	KOHs	2.5	72	—	
2		5		—	
3		10		50	62 (19:81)
4		10		70[d]	62 (19:81)
5		20		50	62 (19:81)

[a]All reactions were performed at RT using 10 mol% of catalyst and 5 equiv. of benzylbromide in CH_2Cl_2.
[b]After purification of alkylated product **5**.
[c]Determined by HPLC analysis of the alkylated benzophenone imine using chiral column OD. No racemization occurred subsequent to transformation of **5a** to the benzophenone imine **5b**.
[d]Diethylether was used as cosolvent (5/5).

aspects of the alkylation reaction. X-ray crystallographic analysis of substrate Z-**2a** revealed the nitrogen and the sp2 oxygen atoms oriented *cis* to each other in the solid state, and the naphthyl group almost orthogonal to the imino bond. In solution, the NOESY experiment showed a correlation between the α-methylene and t-butylester groups protons of both *Z*- and *E*-imines (Fig. 2). Deprotonation of such structures would most likely generate an enolate with *E*-geometric configuration, rigidified by additional interaction between the nitrogen and the alkali ion. The same *E*-enolate configuration has been suggested by Lygo et al.[32] as a plausible intermediate in the case of asymmetric PTC alkylation of benzophenone glycine Schiff bases catalyzed by cinchona onium salts. Formation of product (*S*)-*Z*-**5a** implies benzylation of the enolate (*si*) face. Accordingly, the favorable ion-pairing assembly and ligand exchange from catalyst **4** and the enolate is one in which the catalyst disfavors an approach of the electrophile to the (*re*) face of the enolate. In contrast, phase-transfer alkylation of the -imine *E*-**2a** catalyzed by the organometallic complex **4** suggests a transition state involving an enolate with *E*-geometric configuration and benzylation of the enolate (*re*) face, since no isomerization occurs subsequent to deprotonation (Entry 5, Table 1). Obviously, in both cases the naphthyl group of the substrate imposes an arrangement between the chiral catalyst **4** and the enolate within the ion-pairing, and coordination with the Cu center, for minimum steric hindrance and the favorable approach of the alkylating agent (Fig. 5.). The absence of enantiose-lectivity in the case of benzophenone glycine Schiff base **2b** (Table 1, Entry 9) reinforces this statement.

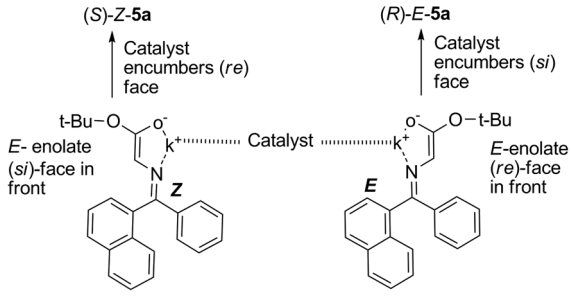


Fig. 5. Possible transition states of the enantioselective alkylation of *Z* and *E*- imine-derived enolates.

CONCLUSION

The catalytic properties and performance of most earlier developed chiral phase-transfer catalysts have been studied, choosing the asymmetric alkylation of the symmetric benzophenone glycine Schiff base derivatives as a reaction model. We have demonstrated in this preliminary study that the imine substituents have an impact on the asymmetric induction by alkylating a dissymmetric ketimine as a substrate. We have found that the observed stereoselectivity of the alkylation depends on the geometric configuration of the imine substrate. The enantioselectivity is opposite, with a similar degree switching from *Z* to *E* stereoisomer, which excludes any *Z*/*E* isomerization subsequent to substrate deprotonation. More important, introduction of the 1-naphthyl group as a substituent within the imine moiety helped to use a simple and effective Cu(II) complex, incorporating a ligand possessing one stereogenic center, as a chiral phase-transfer catalyst. Hence, fine-tuning of the catalyst structure is necessary to enhance the reactivity and to reach a favorable chiral environment for a better transfer of the chiral information.

ACKNOWLEDGMENTS

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LITERATURE CITED

1. Maruoka K. Asymmetric phase transfer catalysis. Weinheim, Germany: Wiley-VCH; 2008.
2. Ooi T, Maruoka K. Recent advances in asymmetric phase-transfer catalysis. Angew Chem Int Ed 2007;46:4222–4266.
3. Hashimoto T, Maruoka K. Recent development and application of chiral phase-transfer catalysts. Chem Rev 2007;107:5656–5682.
4. Albanese D. New applications of phase-transfer catalysis in organic synthesis. Mini-Rev Org Chem 2006;3:195–217.
5. O'Donnell MJ. The enantioselective synthesis of α-amino acids by phase-transfer catalysis with achiral Schiff base esters. J Acc Chem Res 2004;37:506–517.
6. Maruoka K, Ooi T. Enantioselective amino acid synthesis by chiral phase-transfer catalysis. Chem Rev 2003;103:3013–3028.
7. O'Donnell MJ, Bennett WD, Wu S. The stereoselective synthesis of alpha-amino acids by phase-transfer catalysis. J Am Chem Soc 1989;111:2353–2355.
8. O'Donnell MJ, Wu S, Huffman JC. A new active catalyst species for enantioselective alkylation by phase-transfer catalysis. Tetrahedron 1994;50:4507–4518.
9. Belokon YN, Davies RG, Fuentes JA, Parson T, North M, Pertrosyan A. The influence of imine structure, catalyst structure and reaction conditions on the enantioselectivity of the alkylation of alanine methyl ester imines catalyzed by Cu(ch-salen). Tetrahedron Lett 2001;42:8093–8096.
10. Achard T, Belokon YN, Fuentes JA, North M, Parsons T. Influence of aromatic substituents on metal(II)salen-catalyzed asymmetric synthesis of α -methyl α -amino acids. Tetrahedron 2004;60:5919–5930.
11. Ooi T, Kameda M, Maruoka K. Molecular design of C_2-symmetric chiral phase-transfer catalyst for practical asymmetric synthesis of α-amino acids. J Am Chem Soc 1999;121:6519–6520.
12. Ooi T, Takeuchi M, Kameda M, Maruoka K. Practical Catalytic enantioselective synthesis of α,α-dialkyl-α-acids by chiral phase-transfer catalysis. J Am Chem Soc 2000;122:5228–5229.
13. Ooi T, Takeuchi M, Daisuke O, Maruoka K. Advantage of anaerobic conditions in highly enantioselective synthesis of α,α-dialkyl-α-amino acids by chiral phase-transfer catalysis. Synlett 2001;2001:1185–1187.
14. Nugent TC. Chiral amine synthesis: methods, developments and applications. Weinheim, Germany: Wiley-VCH; 2010.
15. Duhamel P, Valnot JY, Jamal Eddine J. Synthèse Asymétrique à l'Aide d'Agents à Nucléofuges Chiraux: Alkylation Enantiosélective de la Glycine. Tetrahedron Lett 1982;28:2863–2866.
16. Duhamel P, Jamal Eddine J, Valnot JY. Enantioselective synthesis of enolate derived from glycine: influence of the imine moiety. Tetrahedron Lett 1984;25:2355–2358.
17. Duhamel P, Jamal Eddine J, Valnot JY. Enantioselective methylation of glycine: influence of the structure of the chiral nucleofugal. Tetrahedron Lett 1987;28:3801–3804.
18. Baptise T, Perrard T, Audouard C, Plaquevent JC, Cahard D. Solution- and solid-phase approach in asymmetric phase-transfer catalysis by chinchona alcaloid derivatives. Synthesis 2001;2001:1742–1746.
19. Pickard PL, Tolbert TL. Diphenyl ketimine [diphenylmethylenimine]. Org Synth 1964;44:51.
20. O'Donnell MJ, Polt RL. A mild and efficient route to Schiff base derivatives of amino acids. J Org Chem 1982;47:2663–2666.
21. Gmouh S, Jamal-Eddine J, Valnot JY. Sterically hindered ketiminium salts: a new generation of phase-transfer catalysts. Tetrahedron 2000;56:8361–8366.
22. Retmane A, Gmouh S, Runghen M, Valnot JY, Maddaluno J, Toupet L, Oulyadi H, Jamal Eddine J. Synthesis, separation and structure determination of atropisomeric ketimines: precursors of new potential chiral ligands and phase-transfer catalysts. Tetrahedron: Asymmetry 2008;19:1523–1531.
23. Bafqiren H, Jamal Eddine J. Water enables transimination between hindered ketimines and β-aminoalcohols and selective protection of a vicinal diamine backbone. Tetrahedron 2010c;66:7028–7034.
24. Ran DQ, Shen TH, Zhou XC, Li JQ, Cui FN, Ma CA, Song QB. Asymmetric Henry reaction catalyzed by chiral Schiff base. Russ J Organ Chem 2013;49:849–852.
25. Crystal structure data for Z-2a: $C_{23}H_{23}NO_2$ Triclinic, P-1, a = 9.3294 (3) Å, b = 10.6186 (3) Å, c = 11.6829 (6) Å , α = 105.815 (2)°, β = 102.516 (2)°, γ = 110.448 (1)°, Z = 2, R[$F^2 > 2\sigma(F^2)$] = 0.074. CCDC-779591 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
26. Earlier studies on the mechanism of the isomerizationof N-alkylketimines showed that the E-imino $^{13}C = N$ signal is shifted downfield with respect to the Z-imino oneCasarini D, Lunazzi L, Macciantelli D. Conformational studies by dynamic NMR. Part 48. Conformational preferences and stereomutational processes of the rotational enantiomers of hindered naphthyl imines and immonium salts. J Chem Soc Perkin Trans 2 1992;1992:1363–1370.
27. Crystal structure data for compound 4: $[Cu_2Cl_4\text{-}(C_{19}H_{14}NO_2)_2]H_2O$, Orthorhombic, $P2_12_12_1$, a = 13.5518 (3) Å, b = 14.5475 (3) Å, c = 16.9070 (3) Å, α = β = γ = 90.0°, Z = 4, R[$F^2 > 2\sigma(F^2)$] = 0.042. CCDC-779592 contains the supplementary crystallographic data for this paper.
28. Qi Z-P, Wang AD, Zhang H, Wang XX. Di-μ-chlorido-bis(chloride{2,2'[3-(1H-imidazol-4-ylmethyl)-3-azapentane-1,5-diyl]diphthalimide}copper(II)). Acta Cryst 2009;E65:m1507–m1508.
29. Pradeep CP, Zakharias PS, Das SK. Synthesis and characterization of a chiral dimeric copper(II) complex: crystal structure of $[Cu_2(\mu\text{-}Cl)_2(HL)_2]\cdot H_2O$ (H_2L = S-(-)-2-[(2-hydroxy-1-phenyl-ethylimino)-methyl]-phenol). J Chem Sci 2005;117:133–137.
30. Corey EJ, Xu F, Noe MC. A rational approach to catalytic enantioselective enolate alkylation using a structurally rigidified and defined chiral quaternary ammonium salt under phase-transfer conditions. J Am Chem Soc 1997;119:12414–12415.
31. For use of metal complexes as chiral phase-transfer catalysts, see: North M. Crown ethers, taddol, nobin and metal(salen) complexes as chiral phase-transfer catalysts for asymmetric synthesis. In: Maruoka K, editor. Asymmetric phase-transfer catalysis. Weinheim, Germany: Wiley-VCH; 2008. Chap. 8, p 173–185.
32. Lygo B, Andrews BI. Asymmetric phase-transfer catalysis utilizing chiral quaternary ammonium salts: asymmetric alkylation of glycine imines. Acc Chem Res 2004;37:518–525.