Synthesis of \( \alpha \)-Amino Acids via Asymmetric Phase Transfer-Catalyzed Alkylation of Achiral Nickel(II) Complexes of Glycine-Derived Schiff Bases

Yuri N. Belokon,*† Natalia B. Bespalova,† Tatiana D. Churkina,† Ivana Cisařová,‡ Marina G. Ezerinitskaya,§ Syuzanna R. Harutyunyan,† Radim Hrdina,‖‡ Konstantin A. Kochetkov,† Oleg V. Larionov,† Konstantin A. Lyssenko,† Michael North,‖ Miroslav Polášek,‖§ Alexander S. Peregudov,† Vladimir V. Prisyazhnyuk,† and Štěpán Vyskočil*†‡∥

Contribution from A. N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, 117813, Moscow, Vasiliev 28, Russian Federation, Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 303, 12840 Prague 2, Czech Republic, Department of Chemistry, Joseph Black Building, University of Glasgow G12 8QQ, United Kingdom, Institut de Chimie Moléculaire d’Orsay, Laboratoire de Synthèse Asymétrique (UPRESA 8075), Université de Paris Sud, 91405-Orsay Cedex, France, Department of Chemistry, King’s College, Strand, London, WC2R 2LS, United Kingdom, and J. Heyrovsky Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, 18223 Prague 8, Czech Republic

Received April 4, 2003; E-mail: yubel@ineos.ac.ru; P.Kocovsky@chem.gla.ac.uk; stepanv@natur.cuni.cz

Abstract: Achiral, diamagnetic Ni(II) complexes 1 and 3 have been synthesized from Ni(II) salts and the Schiff bases, generated from glycine and PBP (7) and PBA (11), respectively, in MeONa/MeOH solutions. The requisite carbonyl-derivatizing agents pyridine-2-carboxylic acid(2-benzoyl-phenyl)-amide 7 (PBP) and pyridine-2-carboxylic acid(2-formyl-phenyl)-amide 11 (PBA) were readily prepared from picolinic acid and \( \alpha \)-aminobenzophenone or picolinic acid and methyl \( \alpha \)-anthranilate, respectively. The structure of 1 was established by X-ray crystallography. Complexes 1 and 3 were found to undergo C-alkylation with alkyl halides under PTC conditions in the presence of \( \beta \)-naphthol or benzyltriethylammonium bromide as catalysts to give mono- and bis-alkylated products, respectively. Decomposition of the complexes with aqueous HCl under mild conditions gave the required amino acids, and PBP and PBA were recovered. Alkylation of 1 with highly reactive alkyl halides, carried out under the PTC conditions in the presence of 10% mol of (S)- or (R)-2-hydroxy-2′-amino-1,1′-binaphthyl 31a (NOBIN) and/or its N-acyl derivatives and by (S)- or (R)-2-hydroxy-8′-amino-1,1′-binaphthyl 32a (iso-NOBIN) and its N-acyl derivatives, respectively, gave rise to \( \alpha \)-amino acids with high enantioselectivities (90–98.5% ee) in good-to-excellent chemical yields at room temperature within several minutes. An unusually large positive nonlinear effect was observed in these reactions. The Michael addition of acrylic derivatives 37 to 1 was conducted under similar conditions with up to 96% ee. The \( ^1 \)H NMR and IR spectra of a mixture of the sodium salt of NOBIN and 1 indicated formation of the two components. Implications of the association and self-association of NOBIN for the observed sense of asymmetric induction and nonlinear effects are discussed.

Introduction

The synthesis of nonproteinogenic \( \alpha \)-amino acids remains a subject of considerable interest because of their great importance in biology, medicine, and synthetic chemistry.1 An increasingly popular approach to chiral \( \alpha \)-amino acids with a tertiary \( \alpha \)-carbon atom relies on the C–C bond formation via alkylation of glycine derivatives, such as N-(diphenylmethylene)glycine tert-butyl ester with alkyl halides, developed by O’Donnell et al.2 Catalytic asymmetric versions of this reaction are being sought, and following the seminal work by O’Donnell et al.2c on asymmetric alkylation with cinchona alkaloid derivatives as chiral phase-transfer catalysts (PTC), dramatic improvements have been achieved.3 Purely synthetic, chiral C2 symmetrical ammonium salts have recently been prepared and shown to be highly efficient in the same set of reactions.4 Nevertheless,
Chart 1. Synthesis of Ni(II) Complexes 1 and 2

Scheme 1. Synthesis of Ni(II) Complexes 1 and 2

Despite the recent progress in the catalytic asymmetric synthesis of \(\alpha\)-amino acids, asymmetric PTC alkylation of glycine or alanine derivatives still represents the simplest and most straightforward route to a variety of enantiomerically enriched \(\alpha\)-amino acids.

Previously, we have reported on the synthesis and application of the square-planar nickel(II) complex 1 (Chart 1) in asymmetric Michael reaction, catalyzed by \((R,R)\)-TADDOL \([(4R,5R)\]

2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethylene)], which led to 4-methylglutamic acid with low enantiomeric excess (28\% ee). More recently, we employed NOBIN (2-amino-2-hydroxy-1,1'-binaphthyl) as a novel type of PTC catalyst in the alkylation reaction of \(N\)-(phenylmethylene)alanine esters producing \(\alpha\)-methyl-\(\alpha\)-amino acids with modest enantiomeric excess (68\% ee).

Herein, we report on the introduction of one or two alkyl groups (identical or different) into the achiral Ni(II) complex 1, derived from the Schiff base of glycine and pyridine-2-carboxylic acid(2-benzoyl-phenyl)-amide 7 (PBP), in a selective, stepwise manner. This approach represents a viable route to the preparation of either racemic or enantiomerically enriched \(\alpha\)-monosubstituted \(\alpha\)-amino acids or \(\alpha,\alpha\)-disubstituted \(\alpha\)-amino acids. Also reported is the achiral Ni(II) complex 3, obtained from the Schiff base of glycine and pyridine-2-carboxylic acid(2-formyl-phenyl)-amide 11 (PBA) as a convenient substrate for the preparation of achiral, highly constrained \(\alpha,\alpha\)-disubstituted \(\alpha\)-amino acids. Finally, we explore asymmetric catalytic C-alkylation of 1 with alkyl halides and Michael acceptors under PTC conditions, using NOBIN, iso-NOBIN, and their derivatives as catalysts.

Results

Synthesis and Structure of Ni(II) Complexes 1 and 3. Complexes 1 and 3 were prepared from glycine, Ni(NO\(_3\))\(_2\); and the respective ligand precursors 7 (PBP) and 11 (PBA) in the presence of KOH or MeOn in methanol (Schemes 1 and 2). The red-colored, crystalline, diamagnetic complexes 1 and 3 can be purified by chromatography or crystallization from CHCl\(_3\). Racemice complexes 1 and 3 can be used in the same way, using \((\pm)\)-alanine instead of glycine. The ketone precursor 7 (PBP) was obtained by condensation of the in situ-generated chloride of \(\alpha\)-picolinic acid (5) with \(\alpha\)-aminobenzenophene (6),
as reported in our preliminary communication,7a an improved
Figure 2. Scheme illustrating the formation of the heterochiral dimers in
the crystal of (±)-2. The other position of the disordered ligand is omitted
for clarity.

The dihedral angles between the Ni(1)O(1)N(1)N(2)N(3)
plane and the phenyl ring in 1 and (±)-2 differ slightly (90.8° and
108.8°, respectively). The difference most likely originates
in the steric interaction of the methyl substituent and the Ph
group in (±)-2 that is absent in 1. The effect of the methyl
group is also reflected in the supramolecular assembly of the
complexes. Although both complexes 1 and (±)-2 are assembled
into centrosymmetric dimers, the nature of the interaction
between the stacks is different. The heterochiral dimer of 1
is interconnected by the weak Ni(1)•••N(1) contacts [Ni(1A)••
N(1A) 3.287(2)Å] and by the interaction of the N(3) atom with
the π-system of the pyridine ring [N(3)•••C(2A) 3.319(3)Å]
(Figure 1). By contrast, the presence of the methyl group in
(±)-2 makes this stacking-type interaction impossible, and as a
result, the interdimer interactions are limited to only a weak
contact of the nickel atom with the carbonyl group [Ni(1)••
O(3A) 3.287(2)Å] (Figure 2).

Synthesis of Racemic Amino Acids by Alkylation of Ni-(II)
Complexes 1 and 3. The alkylation of both 1 and 3 with
alkyl halides was carried out in the presence of Bu4NBr, Bu4-
NCl, or β-naphthol as PTC catalysts in CH2Cl2 with solid NaOH
as a base (Scheme 3), and the reaction was monitored by TLC.
After completion, the reaction mixture was neutralized and the
red-colored solid residue was purified either by chromatography
or crystallization. In most cases the yields exceeded 95%,
and the purification was not necessary. Decomposition of the
resulting complexes 12, 13–16, and 22–24 was effected by
diluted methanolic HCl within 5 min at 50 °C to produce the
corresponding mono- and bis-alkylated amino acids 17, 18–
21, 25, and 26, respectively. The process was easily followed
by the change of the solution color from red to blue. The
hydrochlorides of 7 (PBP) and 11 (PBA) were removed by
filtration in almost quantitative yields, and NiCl2 and the amino
acid were easily isolated by ion exchange chromatography. The
results of the alkylation are summarized in Table 2.

At a 1:1 molar ratio of the alkylation agent to the substrate,
the monoalkylation of the ketimine complex 1 proceeded
quantitatively both in CH2Cl2 under PTC conditions and in DMF
in the presence of NaOH or NaH (Table 2, entries 1–4). The
use of sterically hindered alkyl halides such as i-PrI gave rise
to mono-alkylated products with 1, even at a 3:1 ratio to the
substrate in DMF (Table 2, entry 5). On the other hand, bis-
alkylation of 1 can be performed by employing 2–3 equiv of
the more reactive alkylation agents, such as benzy1 and allyl
bromide (Table 2, entries 6 and 7) in DMF. α,α′-Dibromo-o-
xylenne can be employed to give cleanly the corresponding

Table 1. Selected Bond Lengths (Å) and Angles in Complexes 1 and (±)-2

<table>
<thead>
<tr>
<th>atoms</th>
<th>bond/angles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ni(1)–O(1)</td>
<td>1.851(2)</td>
</tr>
<tr>
<td>Ni(1)–N(1)</td>
<td>1.876(3)</td>
</tr>
<tr>
<td>Ni(1)–N(2)</td>
<td>1.861(3)</td>
</tr>
<tr>
<td>Ni(1)–N(3)</td>
<td>1.845(2)</td>
</tr>
<tr>
<td>O(1)–C(21)</td>
<td>1.289(4)</td>
</tr>
<tr>
<td>O(2)–C(21)</td>
<td>1.231(4)</td>
</tr>
<tr>
<td>O(3)–C(6)</td>
<td>1.220(4)</td>
</tr>
<tr>
<td>N(1)–C(1)</td>
<td>1.333(4)</td>
</tr>
<tr>
<td>N(1)–C(5)</td>
<td>1.352(4)</td>
</tr>
<tr>
<td>N(2)–C(6)</td>
<td>1.381(4)</td>
</tr>
<tr>
<td>N(2)–C(7)</td>
<td>1.395(4)</td>
</tr>
<tr>
<td>N(3)–C(13)</td>
<td>1.292(4)</td>
</tr>
<tr>
<td>N(3)–C(20)</td>
<td>1.486(4)</td>
</tr>
<tr>
<td>O(1)–Ni(1)–N(1)</td>
<td>90.8(1)</td>
</tr>
<tr>
<td>O(1)–Ni(1)–N(2)</td>
<td>176.7(1)</td>
</tr>
<tr>
<td>O(1)–Ni(1)–N(3)</td>
<td>87.6(1)</td>
</tr>
<tr>
<td>N(1)–Ni(1)–N(2)</td>
<td>86.0(1)</td>
</tr>
<tr>
<td>N(1)–Ni(1)–N(3)</td>
<td>176.0(1)</td>
</tr>
<tr>
<td>N(2)–Ni(1)–N(3)</td>
<td>95.6(1)</td>
</tr>
</tbody>
</table>
that various reactions could be easily performed on the groups of the side chains. As an illustration, a ruthenium-catalyzed ring-closing metathesis was carried out with the diallylglycine complex 14, which resulted in a ready formation of 1-amino-1-carboxycyclopent-3-ene 28 after decomplexation of the intermediate 27 (Scheme 4).

Synthesis of Enantiomerically Enriched p-Amino Acids by Asymmetric Alkylation of the Ni(II) Complex 1 with Alkyl Halides, Catalyzed by NOBIN, iso-NOBIN and Their Congeners 31–32. Asymmetric alkylation of 1 in CH₂Cl₂ (Scheme 5) was carried out in the presence of cinchonine derivative 29, (R,R)-TADDOL 30, NOBIN 31a (and its derivatives 31d–h), and iso-NOBIN 32a (and its derivatives 32b–g) as catalysts (Chart 2). Catalysts 29 and 30 gave low chemical yields (less than 50%) even after prolonged treatment (1 h), and the ee of the resulting phenylalanine (17a) was in the range of 5–16% (Table 3, entries 1–3). By contrast, NOBIN-type binaphthyls 31 and 32 proved much more efficient.

Thus, benzylation of 1, catalyzed by (R)-NOBIN 31a (or its enantiomer) in toluene (Scheme 5), gave the mono-alkylated complex 12a in a 50% chemical yield, and the released phenylalanine (17a) was of 89% ee (Table 3, entry 4). The reaction carried out in CH₂Cl₂ gave (R)-Phe [or (S)-Phe] in 88–90% chemical yield with 96–97% ee within 8 min (Table 3, entries 5 and 6). As expected, the increase in solvent polarity (MeCN) diminished the ee of the alkylation (Table 3, entry 7), whereas (CH₂)₂Cl₂ served as a good substitute for CH₂Cl₂ (Table 3, entries 8 and 9), allowing the reaction to be carried out at higher temperatures (up to 70 °C) without a significant loss in the product ee (Table 3, entry 9).

The nature of the base was important in these reactions as the transition from solid NaOH to KOH and then to CsOH brought the ee of the reaction progressively from 96% to 16% and finally to 10% (Table 3, compare entries 6, 10, and 11). Switching from solid NaOH to 50% aqueous NaOH was detrimental to the enantioselectivity, which fell from 96% ee to 55% ee; simultaneously, the chemical yield dropped to a meager 5% after 1 h (Table 3, entry 12). Significantly, solid NaH proved to be almost as efficient as NaOH (Table 3, compare entries 6 and 13).

An attempt at using BINOL (31b) or 2,2′-diamino-1,1′-binaphthyl (31c) as catalysts resulted in both low ee and chemical yields of the product (Table 3, entries 14 and 15). The modifications of 31a by replacing the NH₂ group with NMe₂ (31d) or NHPhe (31e) invariably decreased the efficiency of the reaction by slowing the rate and decreasing the enantioselectivity to 3–5% ee (Table 3, entries 16 and 17). N-Formyl NOBIN 31f was also inactive (Table 3, entry 18), whereas modest restoration of reactivity was observed for the (R)-N-acetyl derivative 31g, which gave the final (S)-Phe of 28% ee (Table 3, entry 19). Interestingly, the latter instance constitutes the reversal of the sense of chirality as compared to the catalysis by (R)-NOBIN (Table 3, compare entries 6 and 19). The introduction of three fluorine atoms into the N-acetyl moiety (31h) resulted in a total loss of catalytic activity (Table 3, entry 20).

(S)-iso-NOBIN (32a) proved to be a fairly efficient catalyst for the production of (S)-Phe with 87.5% ee and 36% chemical.

yield after 13 min (Table 3, entry 21). (S)-N-Acyl derivatives 32b–d also turned out to be catalytically active, furnishing phenylalanine of 71–92% ee with reversed sense of chirality, as compared to the parent catalyst 32a of the same configuration (Table 3, entries 22–24). The size of the acyl groups was identified as a decisive factor: the larger that group, the higher the ee. However, introduction of an N-tosyl group (32e) ruined the catalytic activity (Table 3, entry 25). By contrast, the NOBIN-catalyzed benzylation of monoalkylated complexes 2 and 4 (derived from alanine) proved to be very slow and exhibited low asymmetric inductions (Table 3, entries 26 and 27).

Table 3 summarizes the alkylation of substrate 1 with different alkyl halides catalyzed by (S) or (R)-NOBIN 31a under optimal conditions (as in Table 3, entry 6). As can be seen from the data, all the activated alkyl halides participated in the reaction, affording the alkylated products in good chemical yields and high ee (92–98.5%) at room temperature within 4–30 min (Table 3, entries 1–7). As expected, unactivated alkyl halides were much less efficient so that relatively low yields of the alkylated product were obtained within short time intervals (Table 3, entries 8, 9, and 11), although the ee of the resulting amino acids was still good. The yields could be improved by using larger amounts of NOBIN (Table 3, entry 9). Longer reaction times resulted in a gradual decrease of the ee of the final amino acid because of a partial racemization of the final complex (Table 3, entry 10). The introduction of electron-withdrawing groups into the side chain of the amino acid moiety could also be used as a base in the reaction.
made racemization faster, as illustrated by the decline of ee in the alkylation with tert-butyl bromoacetate (Table 4, entries 12–14).

The intermediate alkylated complexes can be purified either by chromatography or by crystallization before releasing the amino acid. With the crystallization procedure, the ee of the complex or recovered amino acid was further improved (Table 14). The reaction was carried out at 70 °C.

Another interesting feature of the NOBIN catalysis was the observation of a significant positive nonlinear effect (NLE)10 for the alkylation of 1 with BnBr (Figure 4). In practical terms, this means that even the catalyst of 30% ee is sufficient to bring about the same level of asymmetric induction as the enantiomerically pure catalyst.

The solubility of 1 in CH2Cl2 [or (CH2)2Cl2] was found to greatly increase in the presence of sodium NOBIN-ate (Figure 5). Since the solubility experiments were always conducted under excess of insoluble 1, the observed straight line dependence of the concentration of 1 in solution versus the concentration of sodium (S)- or (R)-NOBIN-ate reflects the formation of a well soluble complex formed between 1 and the enantiomerically pure NOBIN-ate in a 1:1 ratio with an equilibrium constant of 165 M−1. Self-association of the racemic mixture of sodium NOBIN-ates, which effectively decreases the concentration of active monomeric sodium NOBIN-ate, appears to be the most plausible explanation for the ineffectiveness of the racemate.

**Synthesis of Enantiomerically Enriched α-Amino Acids by Asymmetric Michael Addition of the Ni(II) Complex 1 to Michael Acceptors 37, Catalyzed by NOBIN, iso-NOBIN, and Their Congeners 31–32.** Since enolates react with alkyl halides via SN2 mechanism, the above asymmetric alkylation is limited to the use of good electrophiles, such as benzyl, allyl, and primary alkyl halides. Further extension of this methodology should, therefore, be sought in the area of nucleophilic addition to suitable electrophiles, such as Michael acceptors or aldehydes.
Asymmetric Michael addition of substrates 1, 2, and 4 to Michael acceptors, catalyzed by TADDOL, NOBIN, iso-NOBIN (30–32), and their derivatives was conducted in CH₂Cl₂ in the presence of a base (NaH or NaOH; Scheme 6). The resulting alkylated complexes could be isolated from the reaction mixture by chromatography and analyzed as such or directly decomposed without prior isolation. The enantiomeric purity of the amino acids obtained by decomposition of the latter complexes was determined by chiral GLC. While PBP (7) was easily recovered in most cases, the recovery of the catalysts was attempted only in the case of 32b (70% yield); its reuse did not lead to any noticeable loss of the ability to effect asymmetric induction.

TADDOL 30 did catalyze the reaction but the asymmetric induction was relatively low at the beginning of the reaction (40% ee by extrapolation to 0% conversion) and progressively decreased as the reaction proceeded. As can be seen from the experimental data summarized in Table 5, unsubstituted NOBIN 31a still catalyzed the addition of 1 to methyl acrylate (37a), but gave poor asymmetric induction even at low temperatures (Table 5, entries 1–3). In addition, the sense of chirality of the product was reversed, as compared with the alkyl halide alkylation product (Table 5, entries 1–3; compare with Tables 3 and 4).

N-formyl NOBIN 31f was still a poor asymmetric catalyst (Table 5, entry 4), but the N-acetyl derivative 31g exhibited an improved asymmetric induction with the same sense of chirality of the products for both alkyl halide alkylation and Michael addition reactions (Table 3, entry 19; Table 5, entry 5). N-BOC-NOBIN 31i was less efficient than 31g but still retained some asymmetric catalytic efficiency (Table 5, entry 6).

Asymmetric Michael addition of substrates 1, 2, and 4 to Michael acceptors, catalyzed by TADDOL, NOBIN, iso-NOBIN (30–32), and their derivatives was conducted in CH₂Cl₂ in the presence of a base (NaH or NaOH; Scheme 6). The resulting alkylated complexes could be isolated from the reaction mixture by chromatography and analyzed as such or directly decomposed without prior isolation. The enantiomeric purity of the amino acids obtained by decomposition of the latter complexes was determined by chiral GLC. While PBP (7) was easily recovered in most cases, the recovery of the catalysts was attempted only in the case of 32b (70% yield); its reuse did not lead to any noticeable loss of the ability to effect asymmetric induction.

TADDOL 30 did catalyze the reaction but the asymmetric induction was relatively low at the beginning of the reaction (40% ee by extrapolation to 0% conversion) and progressively decreased as the reaction proceeded. As can be seen from the experimental data summarized in Table 5, unsubstituted NOBIN 31a still catalyzed the addition of 1 to methyl acrylate (37a), but gave poor asymmetric induction even at low temperatures (Table 5, entries 1–3). In addition, the sense of chirality of the product was reversed, as compared with the alkyl halide alkylation product (Table 5, entries 1–3; compare with Tables 3 and 4).

N-formyl NOBIN 31f was still a poor asymmetric catalyst (Table 5, entry 4), but the N-acetyl derivative 31g exhibited an improved asymmetric induction with the same sense of chirality of the products for both alkyl halide alkylation and Michael addition reactions (Table 3, entry 19; Table 5, entry 5). N-BOC-NOBIN 31i was less efficient than 31g but still retained some asymmetric catalytic efficiency (Table 5, entry 6).

The behavior of iso-NOBIN 32a turned out to be similar to that of NOBIN 32a, with low asymmetric efficiency and the sense of chirality of the Michael adduct opposite to that of the alkyl halide alkylation product (compare Table 5, entry 7, with Table 3, entry 21). By contrast, N-acyl derivatives of iso-NOBIN
Scheme 6. Asymmetric Michael Addition

- For conditions and results, see Table 5.

32b–d and 32f proved to be highly efficient catalyst in the addition of 1 to methyl acrylate (37a) (Table 5, entries 8, 13, 14, and 16), with the ee of the product as high as 96%. There is a tendency toward increased enantioselectivity of the catalyst as the size of the side chain of the acyl moiety becomes larger with the ee increased from 90–94% ee for N-acetyl derivative 32b to 96% for the catalysis by N-pivalyl derivative 32d. However, further increase in the steric bulk of the acyl moiety, as in the adamantyl derivative 32f, reduced the ee to 84% (Table 5, entry 16). Unfortunately, partial racemization accompanied the reaction catalyzed by 32b (and most likely those catalyzed by all the other derivatives of NOBIN and iso-NOBIN), with the ee of the product falling from 90–94% to 83% and 68% as the reaction time was increased from 2 min to 20 and 60 min (Table 5, entries 8, 9, and 10). Replacement of the N-acyl group by the N-p-toluenesulfonyl moiety (32e) resulted in a dramatic decrease in the effectiveness of the catalyst, with only 8% ee and the chemical yield of 75% after 40 min (Table 5, entry 15). Finally, 32g, a modification of 32b in which the NHAc group was replaced by Br, was still an efficient chemical catalyst (as was 2-naphthol) although the ee of the reaction was only 13% (Table 5, entry 18).

The addition of 4 to methyl acrylate was also catalyzed by 32b and 32f to give the corresponding complexes of α-methylglutamic acid with 30–39% ee (Table 5, entries 11 and 17). Under similar conditions, with 32b as catalyst, substrate 2 reacted very slowly, affording the Michael adduct in 9% yield with inferior enantioselectivity (31% ee) after 240 min (Table 5, entry 12). The enantiomeric purity of the product can be increased up to 88% ee by carrying the reaction of 4 in toluene (Table 5, entry 11).

Other Michael acceptors included methyl metacrylate (37b), which reacted with 1 to produce the (S,R)/(S,S) isomers in ca. 7:1 ratio when catalyzed by 32b (Table 5, entry 19). Under the same conditions, acrolein and acrylamide were found to be unsuitable substrates, with low ee (Table 5, entries 20 and 25). Another substrate, 37d, having the NH protons of acrylamide replaced by alkyl groups, reacted with 1 to give the Michael adduct with good enantioselectivity (80, 86, and 75% ee), when 32b, 32d, and 32f, respectively, were employed as catalysts (Table 5, entries 21–23).

Attempts to carry out a C=C bond forming cascade by trapping the intermediate enolate with benzyl bromide or aldehydes failed, as only the products of the initial Michael addition were found in the solutions. A positive nonlinear effect was also observed in the Michael addition of 1 to 37a promoted by 32b (Figure 6).

3H NMR and IR Analysis of the Mixtures of 1 and Sodium Salt of NOBIN (31a) and N-Acetyl-NOBIN (31g). Figure 7 illustrates the changes that occur in the 3H NMR spectra of both 1 and sodium NOBIN-ate in CD2Cl2 when mixed at a 1:1 and 1:3 ratio, respectively. The most salient features of the spectra are the significant shifts of almost all the protons of sodium NOBIN-ate, with one of the protons shifted by 0.4 ppm to lower fields (from 6.2 to 6.6 ppm). The chemical shifts of the protons of 1 were influenced to a lesser extent, but they all became broadened. At a 1:3 ratio of 1 to sodium NOBIN-ate, the broadening became even more evident. By contrast, very few changes were observed in the spectra of mixtures of 1 and the sodium salt of 31g even at a 1:3 ratio.

An IR study of the solutions of 31a, the sodium salt of 31a, and their mixtures with 1 was conducted to assess the mutual interactions. The IR spectrum of NOBIN 31a in CCl4 exhibits one band for ν(OH) at 3527 cm⁻¹ and two bands (νas and νs) at 3482 and 3394 cm⁻¹ for the NH2 group. The NH stretches have the same values as those for β-naphthylamine whereas the ν(OH) is 81 cm⁻¹ lower compared to that for β-naphthol. On decreasing the concentration by 3 orders of magnitude, no band at higher frequency could be attributed to the free OH group. The low-frequency shift of ν(OH) and the lack of concentration dependence indicate that the OH group in NOBIN is involved in an intramolecular H-bonding. Note that if this were an OH···N or NH···O hydrogen bond, the NH stretches would also differ from those for β-naphthylamine. In addition, this type of H-bonding could hardly take place because the naphthyl moieties in NOBIN are not coplanar. Thus, it seems reasonable to assume that the OH group of NOBIN is H-bonded to one of the neighboring naphthlene π-systems. In contrast to free NOBIN, sodium NOBIN-ate in the solution is associated via intramolecular coordination of the NH groups with the sodium cations as demonstrated by the IR spectrum of sodium NOBIN-ate in dichloromethane, in which the two bands for NH stretches appeared at 3406 and 3324 cm⁻¹, i.e., by 76 and 70 cm⁻¹ lower, respectively, than those for pure NOBIN (vide supra).

The IR spectrum of the Ni substrate 1 in the region of CO stretches exhibits two bands: the band at 1645 cm⁻¹ is assigned to amide I mode, while the other band at 1675 cm⁻¹ is assigned to νasym of the carboxyl group (νsym of the carboxyl group is observed at 1329 cm⁻¹). The difference between νasym and νsym modes is 346 cm⁻¹, which is typical for monodentate coordination of the ionized carboxylic group with metal cations.  

The IR spectra of the mixtures of free NOBIN and 1 in dichloroethane or dichloromethane in a wide range of ratios of various ratios were recorded in dichloroethane and compared to the spectra of the initial substances. In the range of CO stretches, the intensity of νasym of the carboxyl group gradually decreased with the increase in the NOBIN-ate excess. All changes in the IR spectra were reversible. The IR spectra were also measured in CD₂Cl₂ with a 3:1 sodium NOBIN-ate to complex 1 ratio in parallel with the ¹H NMR experiment. Analysis of the IR spectra can be summarized as follows: (1) There is no interaction between the NH₂ group of NOBIN-ate and any fragment of complex 1. (2) The frequency of the νasym mode of the carboxyl group decreases in the presence of NOBIN-ate. Unfortunately, the solvent and NOBIN-ate absorption mask a large part of the spectrum, and therefore, it is difficult to determine the position of the new band. (3) The bands of the CH₂ group at 2927 and 2855 cm⁻¹ were still observed in the spectrum of the mixture, indicating that the CH₂ group of complex 1 was not involved in the interaction with NOBIN-ate.

**Discussion**

Evidently, the glycine-derived complex 1 is a very convenient substrate for the synthesis of racemic α-amino acids, retaining one α-proton of the original glycine moiety. Simple alkylation of 1 under PTC conditions with alkyl halides of varying activities resulted in the selective formation of mono-alkylated products, from which a set of racemic α-amino acids could be released by decomplexation (Table 2, entries 1–5). As expected, steric hindrance imposed by the phenyl substituent at the C=ßN moiety of 1 provided for much more efficient mono-alkylation of the glycine moiety, as compared to 3 (Table 2, compare entries 3 and 5 with 10 and 11).

O’Donnell discussed in detail similar differences in the behavior of the Schiff bases of glycine esters of benzophenone and benzaldehyde and attributed the predominant mono-alkylation of benzophenone substrate to the diminished CH acidity.

---


---

**Table 5. Asymmetric Michael Addition of Ni(II) Complexes 1, 2, and 4 (Scheme 6)**

<table>
<thead>
<tr>
<th>entry</th>
<th>Ni(II) complex</th>
<th>catalyst</th>
<th>base (mol %)</th>
<th>acrylic acid derivative</th>
<th>time (min)</th>
<th>yield (%)</th>
<th>ee of amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-31a</td>
<td>NaH</td>
<td>10</td>
<td>37a</td>
<td>3</td>
<td>40</td>
<td>26 (S)</td>
</tr>
<tr>
<td>2</td>
<td>(R)-31a</td>
<td>NaH</td>
<td>10</td>
<td>37a</td>
<td>15</td>
<td>33 (S)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(R)-31a</td>
<td>NaH</td>
<td>10</td>
<td>37a</td>
<td>30</td>
<td>15</td>
<td>33 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(R)-31f</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>6</td>
<td>65</td>
<td>2 (R)</td>
</tr>
<tr>
<td>5</td>
<td>(R)-31g</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>3</td>
<td>50</td>
<td>55 (S)</td>
</tr>
<tr>
<td>6</td>
<td>(R)-31i</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>2</td>
<td>70</td>
<td>30 (S)</td>
</tr>
<tr>
<td>7</td>
<td>(R)-32a</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>3</td>
<td>50</td>
<td>13 (S)</td>
</tr>
<tr>
<td>8</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>2</td>
<td>70</td>
<td>90–94 (S)</td>
</tr>
<tr>
<td>9</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>20</td>
<td>96</td>
<td>83 (S)</td>
</tr>
<tr>
<td>10</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>60</td>
<td>98</td>
<td>68 (S)</td>
</tr>
<tr>
<td>11a</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>2</td>
<td>52</td>
<td>39 (S) [88 (S)]</td>
</tr>
<tr>
<td>12</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>240</td>
<td>9</td>
<td>13 (S)</td>
</tr>
<tr>
<td>13</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>4</td>
<td>80</td>
<td>90 (R)</td>
</tr>
<tr>
<td>14</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>4</td>
<td>80</td>
<td>96 (R)</td>
</tr>
<tr>
<td>15</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>4</td>
<td>88</td>
<td>84 (S)</td>
</tr>
<tr>
<td>16</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>15</td>
<td>62</td>
<td>32 (S)</td>
</tr>
<tr>
<td>17</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37a</td>
<td>2.5</td>
<td>80</td>
<td>13 (S)</td>
</tr>
<tr>
<td>18</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37b</td>
<td>9</td>
<td>60</td>
<td>61 (S,R), 54 (S,S)</td>
</tr>
<tr>
<td>19</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37c</td>
<td>300</td>
<td>50</td>
<td>8 (S)</td>
</tr>
<tr>
<td>20</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37d</td>
<td>3</td>
<td>70</td>
<td>80 (S)</td>
</tr>
<tr>
<td>21</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37d</td>
<td>3</td>
<td>90</td>
<td>86 (R)</td>
</tr>
<tr>
<td>22</td>
<td>(R)-32b</td>
<td>NaH</td>
<td>100</td>
<td>37d</td>
<td>3</td>
<td>85</td>
<td>75 (S)</td>
</tr>
<tr>
<td>23</td>
<td>(R)-32a</td>
<td>NaH</td>
<td>100</td>
<td>37e</td>
<td>3</td>
<td>80</td>
<td>~10 (S)</td>
</tr>
<tr>
<td>24</td>
<td>(R)-32a</td>
<td>NaH</td>
<td>100</td>
<td>37e</td>
<td>60</td>
<td>85</td>
<td>~10 (R)</td>
</tr>
<tr>
<td>25</td>
<td>(R)-32a</td>
<td>NaH</td>
<td>100</td>
<td>37e</td>
<td>60</td>
<td>85</td>
<td>~10 (R)</td>
</tr>
</tbody>
</table>

*The substrate 0.07–0.1 M, at ambient temperature (unless indicated otherwise); catalyzed by 15 mol % of NOBIN, iso-NOBIN, and their derivatives in CH₂Cl₂. Run at –5 °C. Run at –78 °C. In brackets are the results obtained in toluene as solvent within 5 min; chemical yield 20%. The ratio of (S,R)/(S,S)-isomers was 7:1. The enantioselectivity shown here is lower than that reported by us in a preliminary communication. The present figure is the lowest one observed in several experiments and is likely to originate from partial racemization.*
of its mono-alkylated products. The comparison of the X-ray structures of 1 and 2 (Figures 1 and 2) clearly indicated an interaction of the methyl substituent of the alanine moiety with the adjacent phenyl group of the benzophenone fragment, causing a significant additional puckering of the chelate rings and a certain degree of rotation of the Ph relative to the coordination plane of the complex. Here, the methyl group and α-proton occupy a pseudoaxial and pseudoequatorial position, respectively. Clearly, in addition to the probable decrease in the α-CH acidity of the amino acid moiety in the mono-alkylated complexes derived from 1, further steric hindrance to the approach of the second alkylating agent also contributes to the predominant mono-alkylation of 1.

As expected, complex 3, lacking such severe intramolecular interactions, was a convenient substrate for double alkylation, allowing the synthesis of achiral R-amino acids with a quaternary carbon atom carrying two identical R-substituents (Table 2, entries 10 and 11).

Rather unexpectedly, β-naphthol was found to be a very efficient phase-transfer catalyst for the alkylation of 1, in fact even more efficient than Bu4NBr(Cl). As the pKₐ of phenol equals 18 in DMSO and those of Ni-BPB-Gly complexes of similar structure to 1 lie in the range of 17–19, the formation of a lipophilic phenolate base functioning as a PTC catalyst appears to be a plausible explanation. Most likely, the mechanism of the reaction includes the formation of the phenolate of β-naphthol on the surface of the solid NaOH. The sodium phenolate could penetrate the layers of the molecules of 1 in the crystals, thereby compensating the crystal lattice-packing forces by the lipophilic arene–arene interactions; additional interactions with the central nickel may also be involved. These effects can be assumed to work in synergy, which would result in the extraction of the otherwise insoluble 1 into CH₂Cl₂. In the next step, 1 is deprotonated to form an ion pair containing a molecule (or molecules) of naphthol, which occurs in the solution, where the subsequent alkylation takes place.

Presumably, NOBIN, iso-NOBIN, and their derivatives (31 and 32) function in the same way as β-naphthol, with the additional advantage of being chiral and capable of chelation (rather than simple coordination) of the sodium cation in the transition state of alkylation. This concept is supported by the observed difference in the enantioselectivity of the reaction as the cation of the base is changed (Table 3, entries 10–12). The chiral ionic complex of the chiral ligand, 1, and Na⁺ is then alkylated by the alkyl halide with a significant enantiofacial selection. The role of the primary amino group of the ligand is crucial, since its alkylation led to a dramatic decrease in the asymmetric induction (Table 3, entries 16 and 17). These effects strongly suggest that the NH₂ group interacts with the Na⁺ ion. However, direct interaction of the NH₂ group with the central

---

(13) Similar behavior of phenolates was reported for PTC dehydrohalogenation of alkyl halides: Makoša, M.; Chesnokov, A. Tetr. 2000, 56, 3553.
(16) We cannot exclude the presence of a molecular layer of water on the surface of the finely ground NaOH, which may have initiated the phase-transfer reaction.
Ni ion of 1 or its enolate via H-bonding cannot be ruled out. Apparently, the mechanism in the case of 1 is more complex than that in the usual PTC alkylation. Note that alkylation of tert-butyl N-(diphenylmethylene)glycinate with BnBr in CH2Cl2, catalyzed by (R)-NOBIN under the experimental conditions defined in Table 3, led to racemic phenylalanine in 50% chemical yield after 1 h. Similarly, alkylation of the Schiff bases of alanine esters with BnBr under similar conditions always led to racemic products. Less polar toluene or hexane had to be employed in the case of these substrates to obtain good enantioselectivities in the alkylations.6

The 1H NMR (Figure 7) and IR spectra of sodium NOBIN-ate, 1, and their 1:1 and 1:3 mixtures in CD2Cl2 lend further credence to the existence of special interactions of sodium NOBIN-ate with complex 1. Apparently, both compounds establish strong and rapidly reversible interactions with each other, with the aromatic protons of NOBIN situated over the Ni(II) ion, which results in a low-field shift of the signals.17 The broadening of the resonances of 1 indicates fast exchange between several species in the solution and may originate from the formation of a paramagnetic octahedral mixed complex of 1 and sodium NOBIN-ate, differing in geometry from the square-planar arrangement of ligands around the Ni ion. No significant enolate formation was observed in the mixture of sodium NOBIN-ate and 1, as indicated by the IR data and by almost no change in the UV-vis spectra of the mixture as compared to 1. As the NH2 group of free NOBIN (31a) was shown by IR not to be involved in any coordination prior to the reaction, it seems that the phenolate oxygen atom replaced the carboxyl group in the coordination sphere of Ni(II), and thus, the group became partially or fully liberated, forming a strong ionic bond with Na+. The NH2 group of NOBIN may stabilize the enolate by formation of a hydrogen bond during the next stage of the reaction. The importance of the latter bonding is evidenced by the inhibitory effect of water on the stereoselectivity of the reaction (Table 3, entry 12).

A plausible structure of the intermediate is shown in Scheme 7 for the case of sodium salt of (S)-NOBIN and 1. Although it remains to be verified whether this species does lie on the reaction coordinate, its reversible formation would help rationalize the stereocchemistry of the alkyl halide alkylation catalyzed by NOBIN. As shown in Scheme 7, the re-face of the intermediate enolate 42 is shielded by the molecule of (S)-NOBIN. The electrophilic attack should therefore preferentially occur from the si-face, giving rise to the formation of (S)-amino acids, which is consistent with the experimental observation (Tables 3 and 4).

The positive NLE (Figures 4 and 6) indicates that, most likely, the ionized NOBIN phenolate generated heterochiral aggregates with lower reactivity than either the homochiral aggregates or the monomeric species. As a result, the remaining monomer (or the homochiral aggregates) with higher ee than that of the starting ligand becomes the active species. This amplification is related to the reservoir effect (see the discussion in ref 10a). Greater self-association of racemic NOBIN-ate as compared to enantiomerically pure NOBIN-ate was clearly demonstrated in the solubility studies of 1 in the presence of the NOBIN-ates (Figure 5). An alternative mechanism would require that several homochiral NOBIN molecules take part in the transition state of the reaction, for example, one forming a mixed complex with 1 and solubilizing it, and another one removing the α-proton from the glycine moiety of the adduct. However, in light of the experimental results discussed here, the latter alternative appears unlikely.

The mechanism of the Michael addition of 1 to acrylic esters must differ from that of alkyl halide alkylation, as reversal in the sense of chirality of the products was observed. As the pKa of 1 in DMSO is close to 18–1915 and that of acetic esters is close to 30,18 the Michael addition is unlikely to generate the γ-enolate as a free species. Probably one of the functions of NOBIN is to protonate the incipient enolate simultaneously with the formation of the C–C bond. Failure to capture the intermediate γ-enolate by the alkylation with added alkyl halides or aldehydes is indicative of the absence of any free, long-lived γ-enolates on the reaction coordinate. In stereochemical terms, the concerted C–C and C–H bond formation mechanism implies that the acrylate attack occurs from the same side of the enolate where NOBIN and its acidic OH group are located, with the inevitable reversal of the direction of attack compared to the alkyl halide alkylations, as observed experimentally (Table 5).

N-Acyl derivatives of NOBIN 31f–h are much less efficient catalysts in the alkylation of 1 by alkyl halides. In fact, 31f and 31h failed to catalyze the reaction entirely. On the other hand, N-acetyl derivatives of iso-NOBIN 32b–d and 32f proved to be highly efficient catalysts for both SN2 alkylation and Michael addition with identical absolute configurations of the products obtained (when the same catalyst was used). As the electron-withdrawing groups at nitrogen (31h, 32e) greatly diminished


with the use of the chiral catalysts, and further scale-up does not present any difficulty. Combined operation. The amino acids can be prepared on a 100 g scale achiral, employing very simple and easily reproducible modes substrates for the synthesis of $R$-amino acids. 

Conclusions

The activity of the catalysts, a significant negative charge on the $N$-acyl oxygen atom appears to be a prerequisite for the catalytic activity. The rigid mutual orientation of OH and RCO groups in the transition state of the reaction by simultaneous coordination to the Ni(II) center (by the amide carbonyl) and Na$^+$ (by the phenolate). $\pi$-Stacking interaction of the aromatic moieties of the catalysts and the substrate may also contribute to the overall stabilization of the transition state. Interestingly, two rotamers A and B (Figure 8), related by a 2-fold screw axis, were observed in the crystal of acetamide $(R)$-32b, with the OH and C=O oxygens pointing in the same direction and in the opposite direction, respectively. By contrast, only one rotamer was observed in each of the crystalline amides $(S)$-32d and $(R)$-32f.

Supporting Information Available: Experimental procedures and analytical and spectral characterization data for all compounds, all NMR spectra of alkylated substrates, NMR experimental procedure for mixture of complex 1 and N-Ac-isoNOBIN 32b, IR spectra, IR experimental procedure (all PDF), and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

Figure 8. ORTEP diagrams for N-acyl iso-NOBIN derivatives $(R)$-32b, $(S)$-32d, and $(R)$-32f.

are not required for the effective asymmetric induction, as the observation of a large positive nonlinear effect indicated. The alkylation procedures are very fast and, therefore, particularly suited to the synthesis of amino acids labeled with short-lived isotopes for PET diagnostics, as the first applications of the protocol for the syntheses of $^{18}$F-labeled (S)-tyrosine and (S)-DOPA has indicated. A mechanism has been proposed to rationalize the observed effects and the stereochemical outcome. However, further experiments will be needed to shed more light on this complex problem; work toward this direction is underway in these laboratories.

Acknowledgment. The authors are grateful to Prof. D. Seebach for kindly supplying a set of TADDOLs used in the present project and to Dr. N. Ikonnikov for carrying out chiral GLC analyses of the amino acids. Financial support from a Russian Grant for Fundamental Research No. 02-03-3209, ISTC Grant No. A-356, Swiss Grant Scopes No. 7SUP062125, Descartes Prize 2001, a scholarship from DuPont during July 7, 2001—July 7, 2002 to S.R.H., a NATO Fellowship (administered by the Royal Society) to Š.V., GACR (Grant No. 203/01/D051), GAUK (Grant No. 243/20 B CH), and Ministry of Education of the Czech Republic (Project MSM 113100001) are gratefully acknowledged.

(JA035465E)