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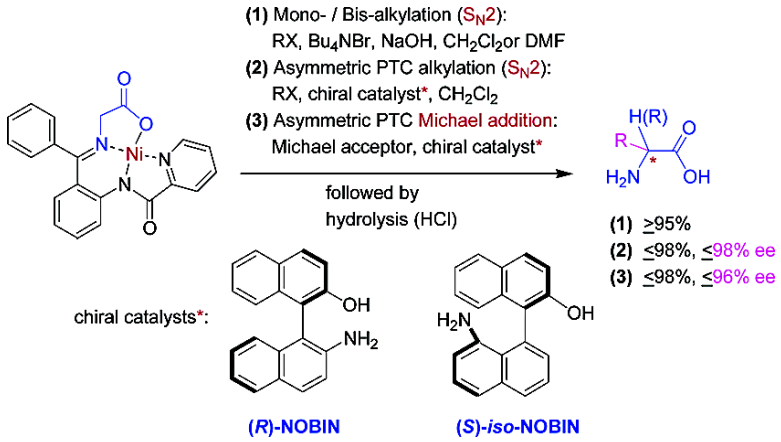
*J. Am. Chem. Soc.*, **2003**, 125 (42), 12860-12871• DOI: 10.1021/ja035465e • Publication Date (Web): 30 September 2003



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

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***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 *o*-aminobenzophenone or picolinic acid and methyl *o*-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 *β*-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 α-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 a complex between 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 α-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 α-amino acids with a tertiary α-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 alkylations with cinchona alkaloid derivatives as chiral phase-transfer catalysts (PTC), dramatic improvements have been achieved.[3] Purely synthetic, chiral $C_2$ symmetrical ammonium salts have recently been prepared and shown to be highly efficient in the same set of reactions.[4] Nevertheless,

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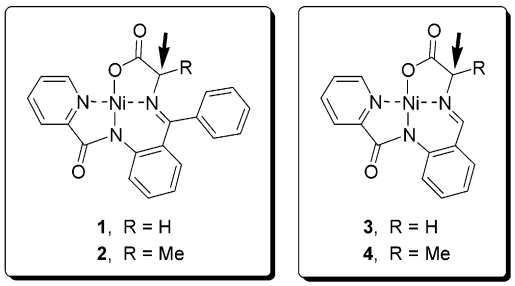
(1) (a) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238−264. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (e) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585. (f) Diaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (g) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron*: *Asymmetry* **2000,** *11*, 645.


**10.1021/ja035465e CCC: $25.00** 

***Chart 1.*** Ketimine and Aldimine Ni(II) Complexes

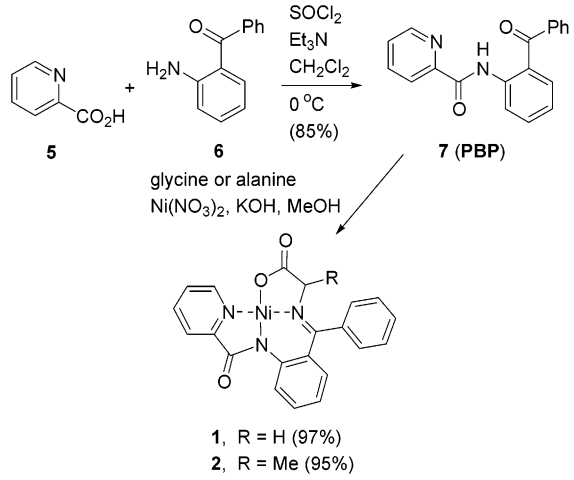



despite the recent progress in the catalytic asymmetric synthesis of α-amino acids,[5] asymmetric PTC alkylation of glycine or alanine derivatives still represents the simplest and most straightforward route to a variety of enantiomerically enriched α-amino acids.

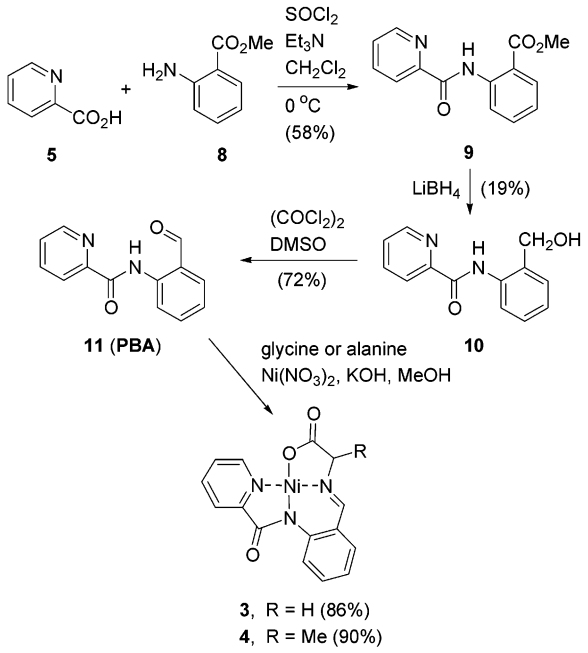
Previously, we have reported on the synthesis and application of the square-planar nickel(II) complex **1** (Chart 1) in asymmetric Michael reaction, catalyzed by (*R*,*R*)-TADDOL [(*4R*,*5R*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol)], which led to 4-methylglutamic acid with low enantioselectivity (28% ee).[6a] 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 α-methyl-α-amino acids with modest enantioselectivity (68% ee).[6b]

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 α-monosubstituted α-amino acids or α,α-disubstituted α-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 α,α-disubstituted α-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.[7]

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




***Scheme 2.*** Synthesis of Ni(II) Complexes **3** and **4**




## 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 MeONa in methanol (Schemes 1 and 2). The red-colored, crystalline, diamagnetic complexes **1** and **3** can be purified by chromatography or crystallization from $CHCl_3$. Racemic complexes **2** and **4** were obtained in the same way, using (±)-alanine instead of glycine. The ketone precursor **7** (PBP) was obtained by condensation of the in situ-generated chloride of α-picolinic acid (**5**) with *o*-aminobenzophenone (**6**),

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(4) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (c) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551.

(5) (a) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790 and references therein. (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (c) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762 and references therein.

(6) (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Smirnov, V. V.; Chesnokov, A. A. *Mendeleev Commun.* **1997**, 137. (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Singh, I.; Parmar, V. S.; Vyskočil, Š.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041.

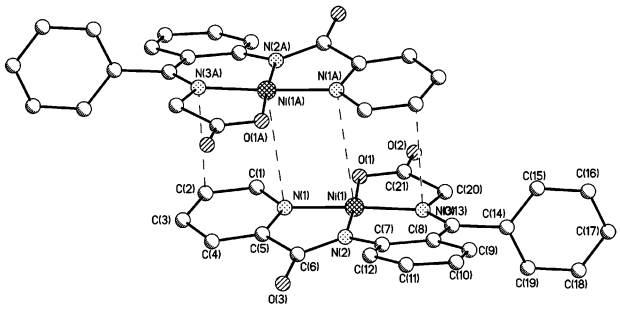



***Figure 1.*** Scheme illustrating the formation of the heterochiral dimers in the crystal of **1**.

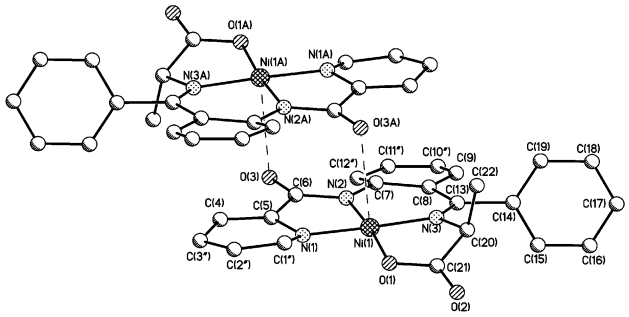



***Figure 2.*** Scheme illustrating the formation of the heterochiral dimers in the crystal of (±)-**2**. The other position of the disordered ligand is omitted for clarity.

as reported in our preliminary communication;[7a] an improved procedure is described in the Experimental Section of the Supporting Information. The aldehyde precursor **11** was synthesized as follows: condensation of the in situ-generated chloride of α-picolinic acid (**5**) with methyl *o*-anthranilate (**8**) afforded amide **9**, which was reduced with $LiBH_4$ to give alcohol **10**. Swern oxidation of the latter alcohol provided the required aldehyde **11**.

The X-ray structure of **1** and (±)-**2** (Figures 1 and 2, Table 1) suggests that the complexes are neutral, with the two positive charges at the central Ni ion neutralized by two negative charges ($CON^-$ and $COO^-$) of the tetradentate ligand. The ligand is slightly puckered with two enantiomeric conformations of two molecules of **1** and (±)-**2** in the crystal cell, restoring the overall racemic crystal arrangement. The principal bond lengths and angles in complexes **1** and (±)-**2** are close to each other and are typical for this type of compound (see Table 1). The slight variation of the bond lengths in the ligand in **1** and (±)-**2** cannot be rationalized as the consequence of the presence of the methyl group at C(20) or the influence of crystal packing and seems to originate from a systematic bias introduced by the disorder in (±)-**2**.

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).

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

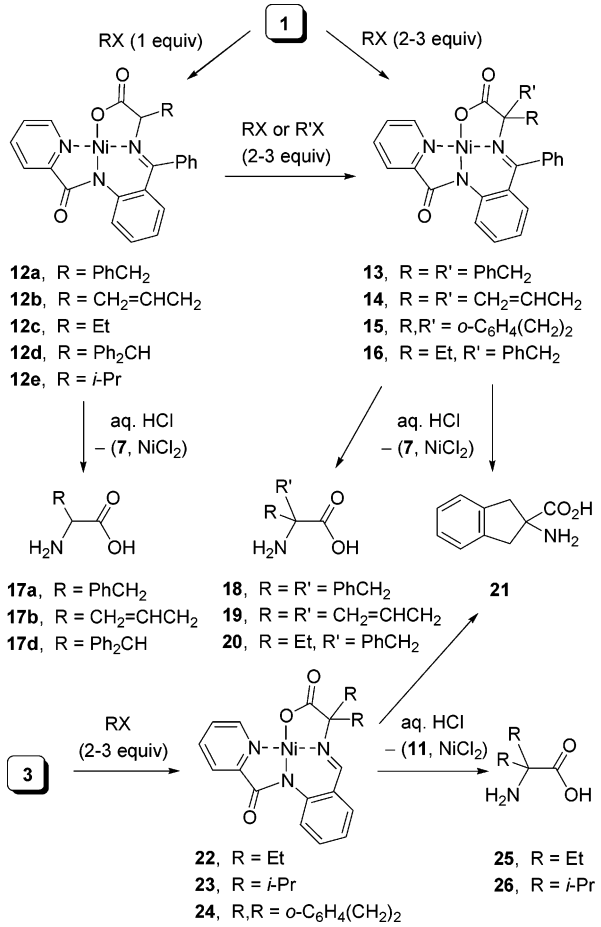
| | (bond/angles) | |
|---|---|---|
| atoms | **1** | **2** |
| Ni(1)−O(1) | 1.851(2) | 1.857(2) |
| Ni(1)−N(1) | 1.876(3) | 1.881(3) |
| Ni(1)−N(2) | 1.861(3) | 1.874(3) |
| Ni(1)−N(3) | 1.843(2) | 1.846(3) |
| O(1)−C(21) | 1.289(4) | 1.299(4) |
| O(2)−C(21) | 1.231(4) | 1.217(4) |
| O(3)−C(6) | 1.220(4) | 1.217(4) |
| N(1)−C(1) | 1.333(4) | 1.353(8) |
| N(1)−C(5) | 1.352(4) | 1.323(4) |
| N(2)−C(6) | 1.381(4) | 1.370(4) |
| N(2)−C(7) | 1.395(4) | 1.402(5) |
| N(3)−C(13) | 1.292(4) | 1.297(4) |
| N(3)−C(20) | 1.486(4) | 1.486(4) |
| O(1)−Ni(1)−N(1) | 90.8(1) | 90.7(1) |
| O(1)−Ni(1)−N(2) | 176.7(1) | 173.3(1) |
| O(1)−Ni(1)−N(3) | 87.6(1) | 87.1(1) |
| N(1)−Ni(1)−N(2) | 86.0(1) | 86.1(1) |
| N(1)−Ni(1)−N(3) | 176.0(1) | 175.4(2) |
| N(2)−Ni(1)−N(3) | 95.6(1) | 96.5(1) |

**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 $Bu_4NBr$, $Bu_4NCl$, or β-naphthol as PTC catalysts in $CH_2Cl_2$ 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 $NiCl_2$ and the amino acid were easily isolated by ion exchange chromatography. The results of the alkylations are summarized in Table 2.

At a 1:1 molar ratio of the alkylating agent to the substrate, the monoalkylation of the ketimine complex **1** proceeded quantitatively both in $CH_2Cl_2$ 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 alkylating agents, such as benzyl and allyl bromide (Table 2, entries 6 and 7) in DMF. α,α′-Dibromo-*o*-xylene can be employed to give cleanly the corresponding

(7) Preliminary data on the asymmetric alkylation of **1** under PTC conditions, catalyzed by NOBIN, have been reported by us earlier: (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S.; North, M.; Vyskočil, Š.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1948. (b) Vyskočil, Š.; Meca, L.; Tišlerová, I.; Císařová, I.; Polášek, M.; Harutyunyan, S.; Belokon, Y. N.; Stead, R. M. J.; Farrugia, L.; Kočovský, P. *Chem.−Eur. J.* **2002**, *8*, 4633.

***Scheme 3.*** Alkylation of Ni(II) Complexes **1** and **3**[a]




[a] For catalysts, conditions, and results, see Table 2.

complex of 2-amino-2′-carboxy-indane **15** (Table 2, entry 8) from which the amino acid **21** can be released. Notably, the alkylation of a chirally modified O'Donnell substrate with this alkyl halide was reported as being accompanied by simultaneous N-alkylation of the nitrogen atom of the glycine moiety, giving rise to the corresponding heterocyclic derivative of amino acid.[8]

A procedure for the stepwise bis-alkylation of **1** was elaborated, starting with mono-alkylation of **1** with an alkyl bromide under PTC conditions in $CH_2Cl_2$, followed by a second alkylation with another activated alkyl halide in DMF. In this way, alkylation of **1** with EtBr, followed by the alkylation of the resulting mono-alkylated complex with benzyl bromide, gave α-ethylphenylalanine **20** after the decomposition of the bis-alkylated complex (Table 2, entry 9).

The glycine moiety of the aldimine complex **3** is much less sterically hindered, and only bis-alkylated complexes were formed selectively under PTC in $CH_2Cl_2$ or DMF even at a 1:1 ratio of the alkylating agent to the substrate. The increase of the latter ratio to 2.5 led to the formation of the bis-alkylated complexes in quantitative yields (Table 2, entries 10 and 11). Even the sterically hindered *iso*-propyl iodide reacted readily to give the corresponding bis-alkylated complex (Table 2, entry 11), from which α,α-diisopropylglycine **26** was released in a very good chemical yield.[9]

The Ni chelation serves as a means of protection for both the amino and carboxyl groups of the amino acid moiety so 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 α-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 $CH_2Cl_2$ (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 $CH_2Cl_2$ 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 $(CH_2)_2Cl_2$ served as a good substitute for $CH_2Cl_2$ (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 $CsOH\cdot H_2O$ 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 $NH_2$ group with $NMe_2$ (**31d**) or NHPh (**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*-acyl-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

(8) Guillena, G.; Najera, C. *J. Org. Chem.* **2000**, *65*, 7310.

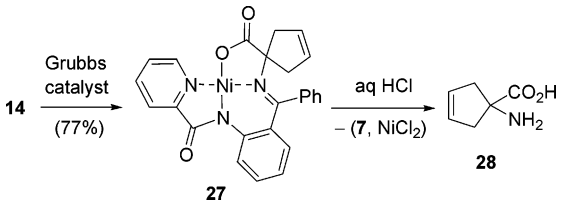
(9) The Schiff base derived from benzaldehyde and *i*-propyl glycinate gave no products of bis-*C*-alkylation under the same conditions; only a mixture of the mono-alkylated product, i.e., ValO-*i*-Pr Schiff base, and unidentified material was detected by $^1H$ NMR in the reaction mixture.

***Table 2.*** Mono- and Bis-alkylation of Ni(II) Complexes **1** and **3** with Alkyl Halides (Scheme 3)[a]

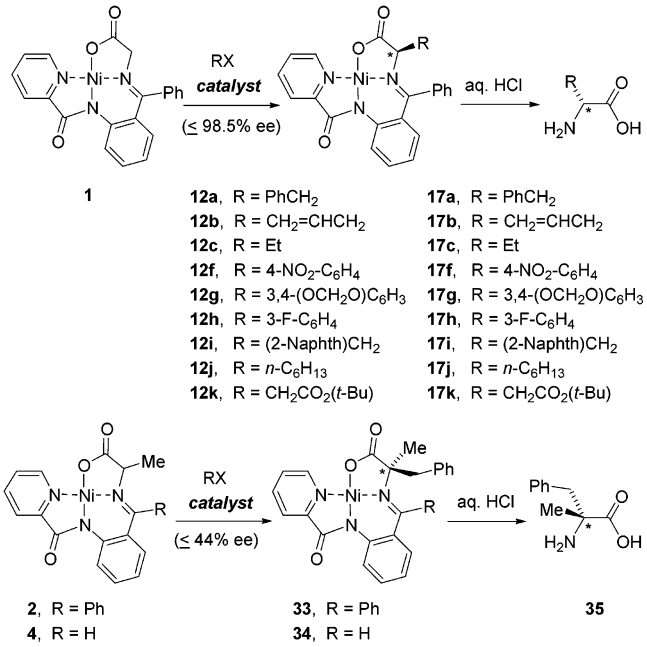
| entry | substrate | alkyl halide[b] | solvent/base | catalyst[c] (10–15%) | time (h) | mono-alkylation[d] | bis-alkylation[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1** | $PhCH_2Br$ | $CH_2Cl_2$/NaOH | TEBA−Br | 1 | >95 | |
| 2 | **1** | AllylBr | $CH_2Cl_2$/NaOH | TBAB | 1 | >95 | |
| 3 | **1** | EtI | $CH_2Cl_2$/NaOH | TEBA−Br | 15 | >95 | |
| 4 | **1** | $Ph_2CHCl$ | DMF/NaOH[a] | | 0.5 | >83 | |
| 5 | **1** | *i*-PrI (3 equiv) | DMF/NaH | | 1 | >95 | |
| 6 | **1** | $PhCH_2Br$ (2 equiv) | DMF/NaOH | | 1 | | 81 |
| 7 | **1** | AllylBr (3 equiv) | DMF/NaH | | 1 | | 59 |
| 8 | **1** | *o*-$C_6H_4(CH_2Br)_2$ (1equiv) | DMF/NaH | | 1 | | 32[e] |
| 9 | **1** | (1) EtI | $CH_2Cl_2$/NaOH | TEBA−Br | 15 | >95 | |
| | | (2) $PhCH_2Br$ | DMF/NaOH | | 0.5 | | >95 |
| 10 | **3** | EtI (2.5 equiv) | DMF/NaOH[f] | | 0.5 | | >95 |
| 11 | **3** | *i*-PrI (3 equiv) | DMF/NaH | | 1 | | 70 |
| 12 | **3** | *o*-$C_6H_4(CH_2Br)_2$ (1equiv) | DMF/NaOH | | 1 | | 48[e] |

[a] The substrate 0.1−0.4 M. [b] Unless indicated otherwise, 1.1 equiv. Methyl iodide and other substituted benzyl bromides could also be used successfully. [c] β-Naphthol (entries 1−5) could also be used as catalysts. [d] The chemical yields of the products were calculated on the initial **1** or **3** and determined by weighing the separated complexes before their decomposition. [e] The initial substrates were recovered from the reaction mixture in 30−40% yields. [f] NaH can also be used as a base in the reaction.

***Scheme 4.*** Grubbs Cyclization of **14**



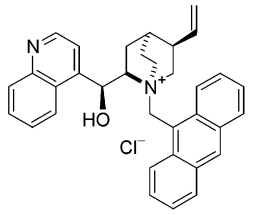

***Scheme 5.*** Asymmetric Alkylation of Ni(II) Complexes **1**, **2**, and **4**[a]



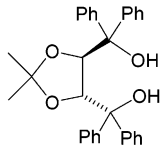

[a] For catalysts, conditions, and results, see Tables 3 and 4.

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).

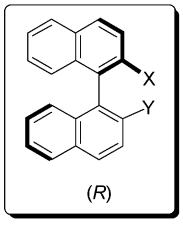
***Chart 2.*** Chiral Phase Transfer Catalysts[a]

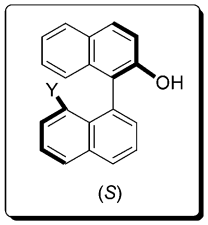



**29**




**30** (**TADDOL**)




**31a**, X = OH, Y = $NH_2$ (**NOBIN**)
**31b**, X = OH, Y = OH (**BINOL**)
**31c**, X = $NH_2$, Y = $NH_2$
**31d**, X = OH, Y = $NMe_2$
**31e**, X = OH, Y = NHPh
**31f**, X = OH, Y = NHCHO
**31g**, X = OH, Y = NHCOMe
**31h**, X = OH, Y = $NHCOCF_3$
**31i**, X = OH, Y = $NHCO_2$(*t*-Bu)

**32a**, Y = $NH_2$ (***iso*-NOBIN**)
**32b**, Y = NHCOMe
**32c**, Y = NHCO(*i*-Pr)
**32d**, Y = NHCO(*t*-Bu)
**32e**, Y = $NHSO_2C_6H_4Me$
**32f**, Y = NHCOAd
**32g**, Y = Br

[a] Both enantiomers were available for **31a**, **31b**, and **32a**; Ad = 1-adamantyl.

Table 4 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 4, 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 4, 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 4, 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 4, entry 10). The introduction of electron-withdrawing groups into the side chain of the amino acid moiety

***Table 3.*** Asymmetric PTC Alkylation of Ni(II) Complexes **1**, **2**, and **4** with Benzyl Bromide Promoted by Different Catalysts and Types of Bases at Room Temperature (Scheme 5)[a]

| entry | Ni(II) complex | solvent | catalyst | base | time (min) | yield[b] (%) | ee of Phe (%) (configuration)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **1** | $CH_2Cl_2$ | **29** | NaOH | 60 | 50 | 16 (*R*) |
| 2 | **1** | $CH_2Cl_2$ | **30** | NaOH | 10 | 10 | 12 (*R*) |
| 3 | **1** | $C_6H_5CH_3$ | **30** | NaOH | 45 | 10 | 5 (*S*) |
| 4 | **1** | $C_6H_5CH_3$ | (*R*)-**31a** | NaOH | 45 | 50 | 89 (*R*) |
| 5 | **1** | $CH_2Cl_2$ | (*R*)-**31a** | NaOH | 8 | 90 | 97 (*R*) |
| 6 | **1** | $CH_2Cl_2$ | (*S*)-**31a** | NaOH | 8 | 88 | 96 (*S*) |
| 7 | **1** | MeCN | (*R*)-**31a** | NaOH | 20 | 80 | 17 (*R*) |
| 8 | **1** | $(CH_2)_2Cl_2$ | (*R*)-**31a** | NaOH | 5 | 70 | 97 (*R*) |
| 9[d] | **1** | $(CH_2)_2Cl_2$ | (*R*)-**31a** | NaOH | 5 | 86 | 93 (*R*) |
| 10 | **1** | $CH_2Cl_2$ | (*R*)-**31a** | KOH | 7 | 80 | 16 (*R*) |
| 11 | **1** | $CH_2Cl_2$ | (*R*)-**31a** | $CsOH \times H_2O$ | 15 | 25 | 10 (*R*) |
| 12 | **1** | $CH_2Cl_2$ | (*R*)-**31a** | 50% aq NaOH | 60 | 5 | 55 (*R*) |
| 13 | **1** | $CH_2Cl_2$ | (*R*)-**31a** | NaH | 11 | 50 | 97 (*R*) |
| 14 | **1** | $CH_2Cl_2$ | (*S*)-**31b** | NaOH | 60 | 14 | 17 (*S*) |
| 15 | **1** | $CH_2Cl_2$ | (*R*)-**31c** | NaOH | 30 | 16 | 18 (*S*) |
| 16 | **1** | $CH_2Cl_2$ | (*R*)-**31d** | NaOH | 15 | 15 | 5 (*R*) |
| 17 | **1** | $CH_2Cl_2$ | (*R*)-**31e** | NaOH | 60 | 10 | 3 (*R*) |
| 18 | **1** | $CH_2Cl_2$ | (*R*)-**31f** | NaOH | 35 | traces | not determined |
| 19 | **1** | $CH_2Cl_2$ | (*R*)-**31g** | NaOH | 30 | 30 | 28 (*S*) |
| 20 | **1** | $CH_2Cl_2$ | (*R*)-**31h** | NaOH | 20 | traces | not determined |
| 21 | **1** | $CH_2Cl_2$ | (*S*)-**32a** | NaOH | 13 | 36 | 87.5 (*S*) |
| 22 | **1** | $CH_2Cl_2$ | (*R*)-**32b** | NaOH | 6 | 90 | 71 (*S*) |
| 23 | **1** | $CH_2Cl_2$ | (*S*)-**32c** | NaOH | 7 | 60 | 90 (*R*) |
| 24 | **1** | $CH_2Cl_2$ | (*S*)-**32d** | NaOH | 9 | 70 | 92 (*R*) |
| 25 | **1** | $CH_2Cl_2$ | (*S*)-**32e** | NaOH | 30 | traces | not determined |
| 26 | **2** | $CH_2Cl_2$ | (*R*)-**31a** | NaOH | 1200 | 90 | 44 (*R*) |
| 27 | **4** | $CH_2Cl_2$ | (*R*)-**31a** | NaOH | 40 | 92 | 20 (*R*) |

[a] Reaction conditions: concentration of the substrate (**1**, **2**, or **4**): 0.17−2.0 M; ratio of the $PhCH_2Br$/substrate, 1.2:1; catalyst/substrate, 1:10; MOH/substrate, 10:1; room temperature unless indicated otherwise; under Ar, all solvents were carefully dried. [b] Chemical yield of the alkylated complex determined after its separation from unreacted substrate. [c] Determined for phenylalanine recovered from the complex by chiral GLC analysis on chiral Chirasil-Val columns. [d] The reaction was carried out at 70 °C.

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 4, entry 1). Enantiomeric purity of the amino acid moiety can be roughly assessed by measuring the optical rotation of the complexes before crystallization, as the specific rotation of enantiomerically pure samples were only marginally influenced by the structure of its side chain. Furthermore, the same principles apply to the CD spectra of the complexes: Figure 3 illustrates the positive Cotton effects for the complexes of amino acids of (*S*)-configuration and negative effects for the (*R*)-amino acid complexes. Despite different structures of the side chains of the amino acid moieties (phenylalanine and glutamic acid), the CD curves were almost mirror images. Thus, the absolute configuration of any amino acid moiety can be easily assigned by checking the sign of the Cotton effect of the corresponding Ni complex.

As in the case of racemic synthesis, the amino acids and PBP (**7**) could be easily recovered in a quantitative yield and PBP (**7**) reused to prepare complex **1**. NOBIN (**31a**) could also be partly recovered from the reaction mixture by chromatography (usually in less than 20% yield), though significant amounts of alkylated NOBIN derivatives of unidentified structure were also detected in the reaction mixture. Fortunately, the latter byproducts were not catalytically active in the reaction, as shown by control experiments.

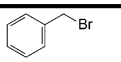
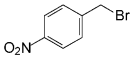
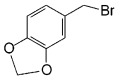
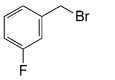
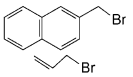
Another interesting feature of the NOBIN catalysis was the observation of a significant positive nonlinear effect (NLE)[10] for the alkylation of **1** with BnBr (Figure 4). In practical terms, this means that even the catalyst of 30% ee is sufficient to bring about the same level of asymmetric induction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

The solubility of **1** in $CH_2Cl_2$ [or $(CH_2)_2Cl_2$] 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 $S_N2$ 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.

(10) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int., Ed.* **1998**, *37*, 2922. (b) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532.

***Table 4.*** Asymmetric PTC Alkylation of Ni(II) Complex **1** with Alkyl Halides Promoted by (*R*)-NOBIN (**31a**) at Room Temperature (Scheme 5)[a]

| entry | alkylating agent | time (min) | yield (%)[b] | ee of (*R*)-amino acids (%)[c] |
|---|---|---|---|---|
| 1 |  | 8 | 90 | 97 (>99.8%[d]) |
| 2 |  | 4 | 92[e] | 93 |
| 3 |  | 6 | 70 | 98.5 |
| 4 |  | 7 | 80 | 94 |
| 5 |  | 6 | 62 | 98.5 |
| 6 | | 30 | 68 | 90 |
| 7 | | 4 | 75 | 90 |
| 8 | | 5 | 2 | 93 |
| 9 | | 30 | 15 (70[f]) | 93 |
| 10 | | 240 | 35 | 81 |
| 11 | *n*-$C_6H_{13}I$ | 60 | 10 | 91 |
| 12 | $BrCH_2COOtBu$ | 4 | 22 | 49 |
| 13 | $BrCH_2COOtBu$ | 8 | 53 | 40 |
| 14 | $BrCH_2COOtBu$ | 20 | 98 | 25 |

[a] Reaction conditions: the reactions were carried out in $CH_2Cl_2$; concentration of **1** was 0.17−2.0 M; ratio of the RX/substrate, 1.2:1; (*R*)-NOBIN/substrate, 1:10; NaOH/substrate, 10−20:1; room temperature; under Ar. [b] Chemical yields of the alkylated complex were estimated after the product separation from unreacted **1**. [c] Determined by chiral GLC analysis on chiral Chirasil-Val columns for the amino acid released from the crude complex. In several instances, the amino acids thus obtained were subsequently recrystallized from an *i*-PrOH−water mixture to give an enantiopure product. [d] The amino acid was released from a recrystallized complex. [e] The bis-alkylated complex (6%) was detected in the reaction mixture. [f] Fifty percent of **31a** was used as catalyst.

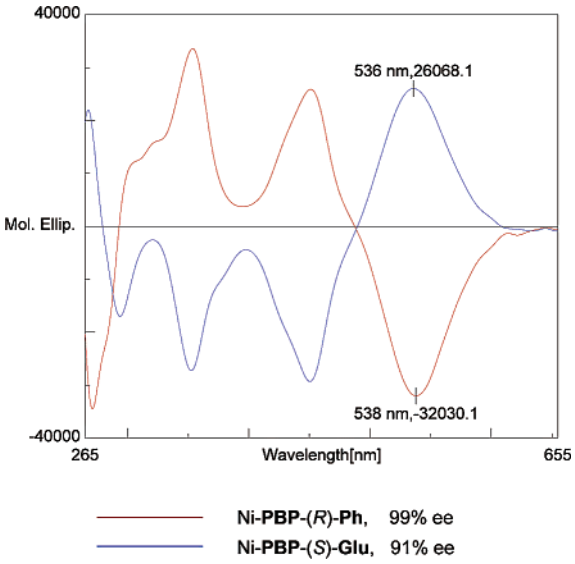



***Figure 3.*** CD curves of Ni−PBP−(*R*)-Phe (99% ee), negative Cotton effect at 538 nm, and that of Ni−PBP−(*S*)-Glu (91% ee), positive Cotton effect at 536 nm.

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 $CH_2Cl_2$ 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

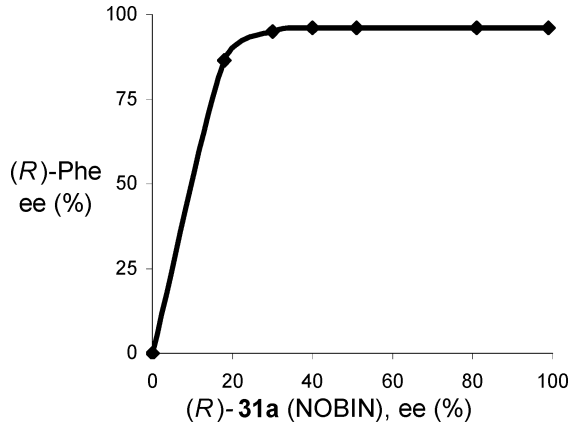



***Figure 4.*** Positive nonlinear effect in the alkylation of **1** with BnBr catalyzed by (*R*)-NOBIN.

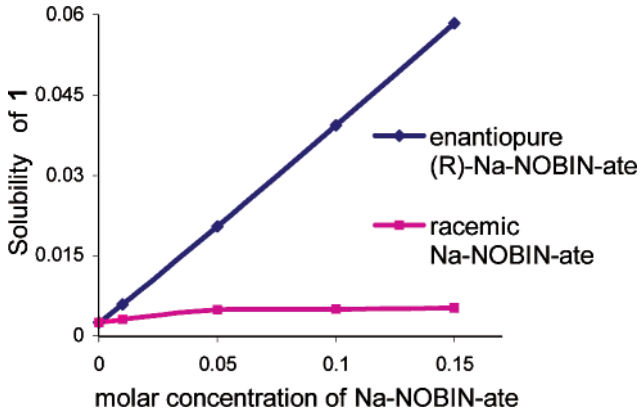



***Figure 5.*** Increase in the solubility of **1** in $(CH_2)_2Cl_2$ affected by sodium (*R*)-NOBIN-ate and racemic NOBIN-ate.

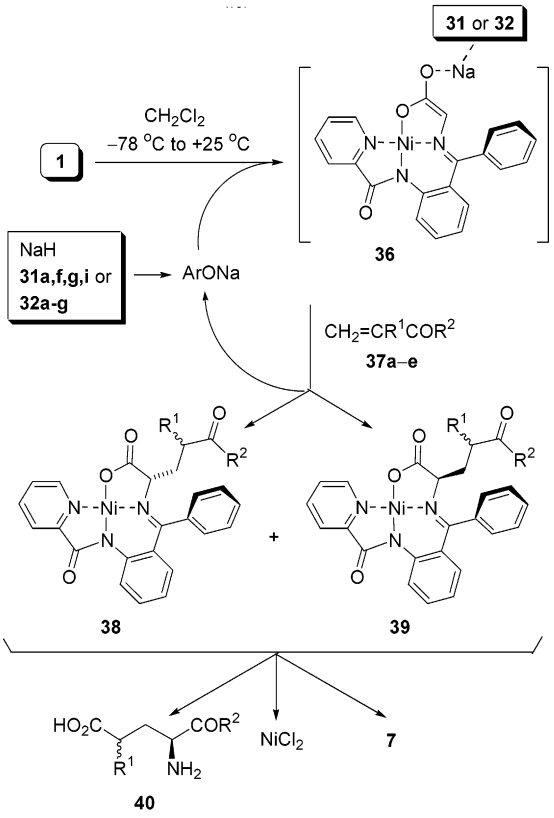
acids obtained by decomposition of the latter complexes was determined by chiral GLC. While PBP (**7**) was easily recovered in most cases, the recovery of the catalysts was attempted only in the case of **32b** (70% yield); its reuse did not lead to any noticeable loss of the ability to effect asymmetric 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 alkylations catalyzed by **31a** (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[a]




**37–39:** **a**, $R^1$ = H, $R^2$ = OMe; **b**, $R^1$ = $CH_3$, $R^2$ = OMe; **c**, $R^1$ = H, $R^2$ = H; **d**, $R^1$ = H, $R^2$ = $C_5H_{10}N$; **e**, $R^1$ = H, $R^2$ = $NH_2$

**40:** **a**, $R^1$ = H, $R^2$ = OH; **b**, $R^1$ = $CH_3$, $R^2$ = OH; **c**, $R^1$ = H, $R^2$ = H; **d**, $R^1$ = H, $R^2$ = $C_5H_{10}N$; **e**, $R^1$ = H, $R^2$ = $NH_2$

[a] 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).

**$^1$H 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 $^1$H NMR spectra of both **1** and sodium NOBIN-ate in $CD_2Cl_2$ 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 $CCl_4$ exhibits one band for $\nu$(OH) at 3527 $cm^{-1}$ and two bands ($\nu_{as}$ and $\nu_s$) at 3482 $cm^{-1}$ and at 3394 $cm^{-1}$ for the $NH_2$ group. The NH stretches have the same values as those for $\beta$-naphthylamine whereas the $\nu$(OH) is 81 $cm^{-1}$ lower compared to that for $\beta$-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 $\nu$(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 $\beta$-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 naphthalene $\pi$-systems.[11] 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).

(11) Iogansen, A. V. *Spectrochim. Acta, Part A* **1999**, *55*, 1585.

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

| entry | Ni(II) complex | catalyst | base (mol %) | acrylic acid derivative | time (min) | yield (%) | ee of amino acids (configuration) |
|---|---|---|---|---|---|---|---|
| 1 | **1** | (*R*)-**31a** | NaH (10) | **37a** | 3 | 40 | 26 (*S*) |
| 2[b] | **1** | (*R*)-**31a** | NaH (10) | **37a** | 30 | 15 | 33 (*S*) |
| 3[c] | **1** | (*R*)-**31a** | NaH (10) | **37a** | 600 | 5 | 45 (*S*) |
| 4 | **1** | (*R*)-**31f** | NaH (100) | **37a** | 6 | 65 | 2 (*R*) |
| 5 | **1** | (*R*)-**31g** | NaH (100) | **37a** | 3 | 50 | 55 (*S*) |
| 6 | **1** | (*R*)-**31i** | NaH (100) | **37a** | 2 | 70 | 30 (*S*) |
| 7 | **1** | (*R*)-**32a** | NaH (100) | **37a** | 3 | 50 | 13 (*S*) |
| 8 | **1** | (*R*)-**32b** | NaH (100) | **37a** | 2 | 70 | 90−94 (*S*) |
| 9 | **1** | (*R*)-**32b** | NaH (100) | **37a** | 20 | 96 | 83 (*S*) |
| 10 | **1** | (*R*)-**32b** | NaH (100) | **37a** | 60 | 98 | 68 (*S*) |
| 11[d] | **4** | (*R*)-**32b** | NaH (100) | **37a** | 2 | 52 | 39 (*S*) [88 (*S*)][d] |
| 12 | **2** | (*R*)-**32b** | NaH (100) | **37a** | 240 | 9 | 13 (*S*) |
| 13 | **1** | (*S*)-**32c** | NaH (100) | **37a** | 4 | 80 | 90 (*R*) |
| 14 | **1** | (*S*)-**32d** | NaH (100) | **37a** | 4 | 80 | 96 (*R*) |
| 15 | **1** | (*R*)-**32e** | NaH (100) | **37a** | 40 | 75 | 8 (*S*) |
| 16 | **1** | (*R*)-**32f** | NaH (100) | **37a** | 4 | 88 | 84 (*S*) |
| 17 | **4** | (*R*)-**32f** | NaH (100) | **37a** | 15 | 62 | 32 (*S*) |
| 18 | **1** | (*S*)-**32g** | NaH (100) | **37a** | 2.5 | 80 | 13 (*S*) |
| 19 | **1** | (*R*)-**32b** | NaH (100) | **37b** | 9 | 60 | 61 (*S*,*R*), 54 (*S*,*S*)[e] |
| 20 | **1** | (*R*)-**32b** | NaH (100) | **37c** | 300 | 50 | 0 |
| 21 | **1** | (*R*)-**32b** | NaOH (100) | **37d** | 3 | 70 | 80 (*S*) |
| 22 | **1** | (*S*)-**32d** | NaOH (100) | **37d** | 3 | 90 | 86 (*R*) |
| 23 | **1** | (*R*)-**32f** | NaOH (100) | **37d** | 3 | 85 | 75 (*S*) |
| 24 | **1** | (*R*)-**31a** | NaOH (100) | **37d** | 3 | 80 | ∼10 (*S*) |
| 25 | **1** | (*R*)-**32a** | NaOH (100) | **37e** | 60 | 85 | ∼10 (*R*) |

[a] 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 $CH_2Cl_2$. [b] Run at −5 °C. [c] Run at −78 °C. [d] In brackets are the results obtained in toluene as solvent within 5 min; chemical yield 20%. [e] 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.[7b] The present figure is the lowest one observed in several experiments and is likely to originate from partial racemization.

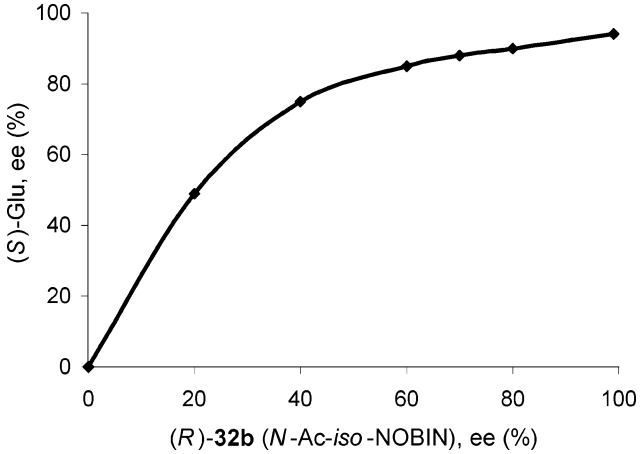



***Figure 6.*** Positive nonlinear effect in the Michael addition of acrylic ester **37a** to **1** catalyzed by (*R*)-8-acetamido-2′-hydroxy-1,1′-binaphthyl (**32b**).

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 $\nu_{asym}$ of the carboxyl group ($\nu_{sym}$ of the carboxyl group is observed at 1329 $cm^{-1}$). The difference between $\nu_{asym}$ and $\nu_{sym}$ modes is 346 $cm^{-1}$, which is typical for monodentate coordination of the ionized carboxylic group with metal cations.[12]

The IR spectra of the mixtures of free NOBIN and **1** in dichloroethane or dichloromethane in a wide range of ratios of complex **1** to NOBIN did not provide evidence for any interaction between the two compounds.

The spectra of mixtures of sodium NOBIN-ate and **1** at various ratios were recorded in dichloroethane and compared to the spectra of the initial substances. In the range of CO stretches, the intensity of $\nu_{asym}$ 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 $CD_2Cl_2$ 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 $NH_2$ group of NOBIN-ate and any fragment of complex **1**. (2) The frequency of the $\nu_{asym}$ 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 $CH_2$ group at 2927 and 2855 $cm^{-1}$ were still observed in the spectrum of the mixture, indicating that the $CH_2$ 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═N 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

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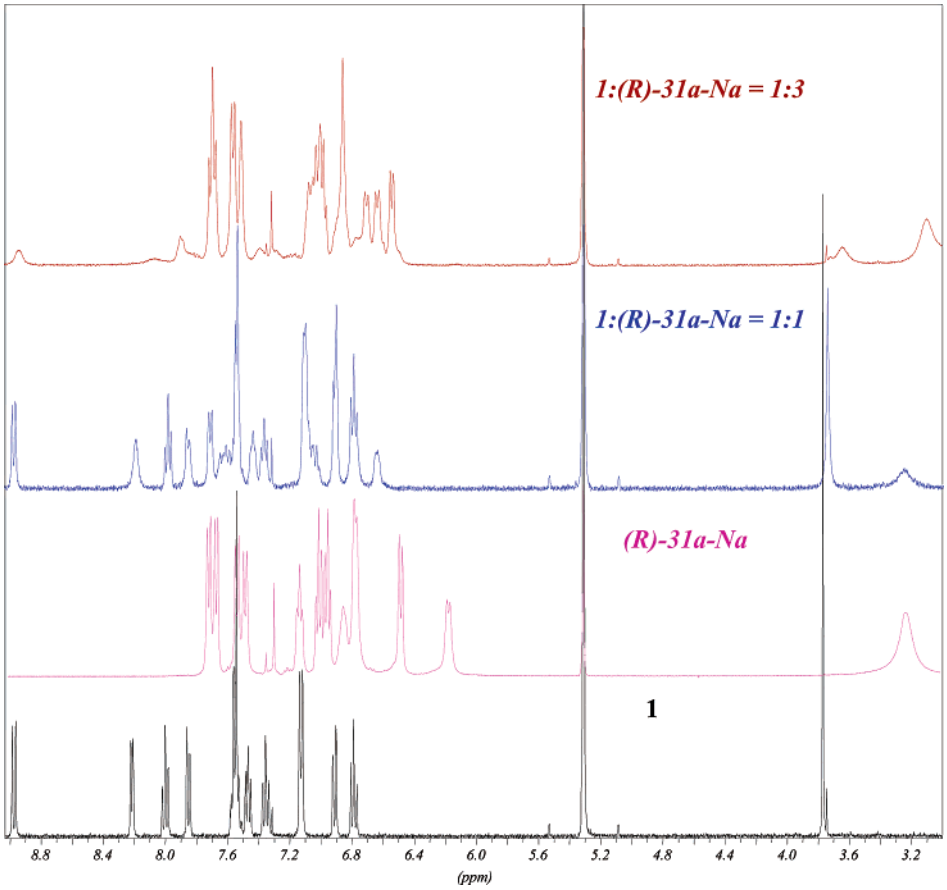



***Figure 7.*** $^1$H NMR spectra of **1**, sodium salt of NOBIN, and mixtures of both at ratios 1:1 and 1:3 (from the bottom to the top).

of its mono-alkylated products.[2b] 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 α-amino acids with a quaternary carbon atom carrying two identical α-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 $Bu_4NBr(Cl)$.[13] As the p$K_a$ of phenol equals 18 in DMSO[14] and those of Ni−BPB-Gly complexes of similar structure to **1** lie in the range of 17−19,[15] 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.[16] 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 $CH_2Cl_2$. 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 $NH_2$ group interacts with the $Na^+$ ion. However, direct interaction of the $NH_2$ group with the central

(13) Similar behavior of phenolates was reported for PTC dehydrohalogenation of alkyl halides: Mąkosza, M.; Chesnokov, A. *Tetrahedron* **2000**, *56*, 3553.
(14) Bordwell, F. G.; Liu, W.-Z. *J. Am. Chem. Soc.* **1996**, *118*, 10819.
(15) Terekhova, M. I.; Belokon, Y. N.; Maleev, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Belikov, V. M.; Petrov, E. S. *Bull Acad. Sci. USSR, Div. Chem. Sci.* (Engl. Transl.) **1986**, *35*, 824; *Izv. Akad. Nauk, Ser. Khim.* **1986**, 905.

(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.

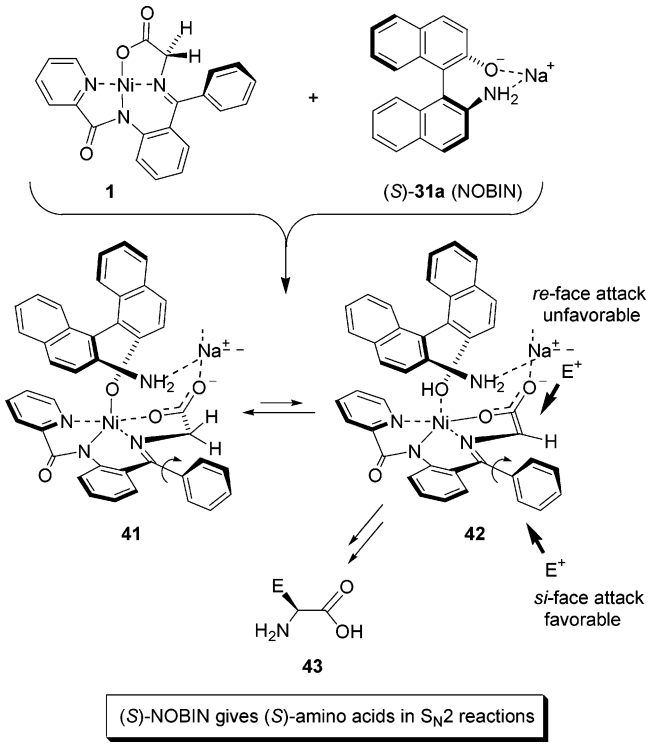
Ni ion of **1** or its enolate via H-bonding cannot be ruled out. Apparently, the mechanism in the case of **1** is more complex than that in the usual PTC alkylation. Note that alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate with BnBr in $CH_2Cl_2$, catalyzed by (*R*)-NOBIN under the experimental 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 $^1$H NMR (Figure 7) and IR spectra of sodium NOBIN-ate, **1**, and their 1:1 and 1:3 mixtures in $CD_2Cl_2$ 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 $NH_2$ 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 $NH_2$ 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 stereochemistry 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

***Scheme 7.*** Proposed Mechanism for the Asymmetric Alkylation of **1**




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 p$K_a$ of **1** in DMSO is close to 18−19[15] and that of acetic esters is close to 30,[18] the Michael addition is unlikely to generate the $\gamma$-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 $\gamma$-enolate by the alkylation with added alkyl halides or aldehydes is indicative of the absence of any free, long-lived $\gamma$-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*-acyl derivatives of *iso*-NOBIN **32b**−**d** and **32f** proved to be highly efficient catalysts for both $S_N2$ 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

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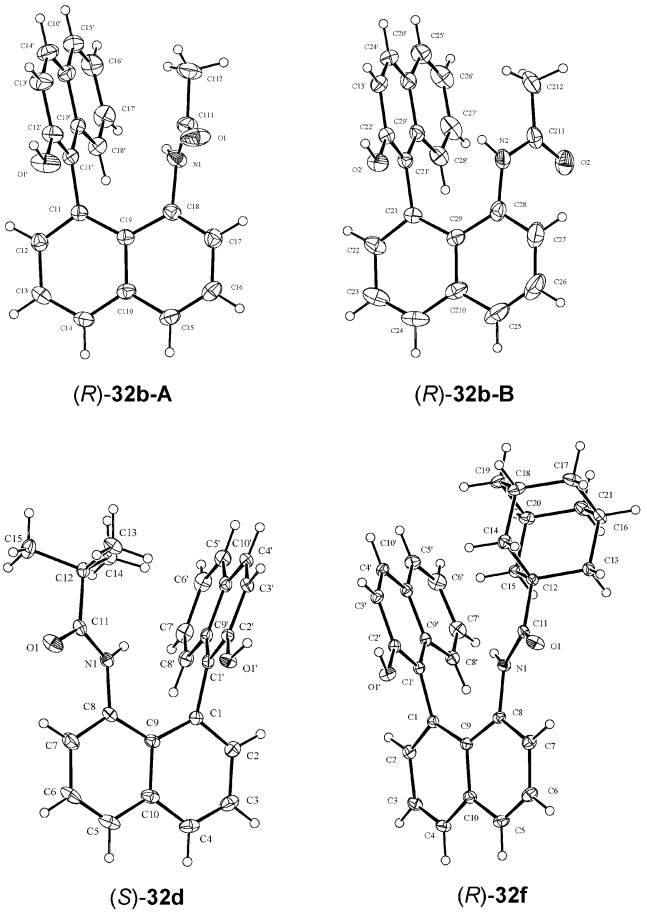


***Figure 8.*** ORTEP diagrams for *N*-acyl *iso*-NOBIN derivatives (*R*)-**32b**, (*S*)-**32d**, and (*R*)-**32f**.

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 **32b**−**f** (Figure 8) might facilitate efficient interactions with the enolate of **1** 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 and in the opposite direction, respectively. By contrast, only one rotamer was observed in each of the crystalline amides (*S*)-**32d** and (*R*)-**32f**.

## Conclusions

We have developed a new series of efficient nucleophilic substrates for the synthesis of α-amino acids, both chiral and achiral, employing very simple and easily reproducible modes of operation. The amino acids can be prepared on a 100 g scale and further scale-up does not present any difficulty. Combined with the use of the chiral catalysts, (*S*)- and (*R*)-NOBIN,[19] (*S*)- and (*R*)-*iso*-NOBIN,[7b] and their derivatives (**31** and **32**), this method opens a convenient synthetic route to the enantiomerically pure α-amino acids of both configurations. The additional bonus of this protocol is that the enantiomerically pure catalysts 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.[20]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. 7SUPJ062125, 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., GAČR (Grant No. 203/01/D051), GAUK (Grant No. 243/20B CH), and Ministry of Education of the Czech Republic (Project MSM 113100001) are gratefully acknowledged.

**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-*iso*-NOBIN **32b**, IR spectra, IR experimental procedure (all PDF), and crystallografic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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