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Highly Efficient Catalytic Synthesis of α-Amino Acids under Phase-Transfer Conditions with a Novel Catalyst/Substrate Pair[**]

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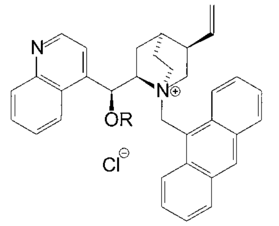
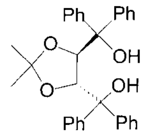
Asymmetric phase-transfer catalysis (PTC) reactions constitute one of the most challenging fields of contemporary organic synthesis.[1] Following the seminal work by O'Donnell et al.[2a] and Grabowski et al.[2b] dramatic improvements in the asymmetric efficiency of PTC reactions were achieved by introducing (9-anthracenylmethyl)cinchonidinium (**1a**, R = allyl, benzyl, H) and other cinchoninium salts as catalysts for the enantioselective alkylation of *N*-(diphenylmethylene)glycine esters with electrophiles.[2c–e] Purely synthetic, chiral, C_2-symmetrical ammonium salts were recently prepared and shown to be highly efficient in the same set of reactions.[3] Thus, preparative catalytic asymmetric syntheses of very important synthetic targets such as amino acids were developed, and enantioselectivities of up to 92-98% for the final product were achieved.[2c–e, 3]

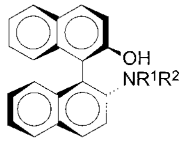


1a



TADDOL **1b**

Unfortunately, *N*-(diphenylmethylene)glycine esters are expensive, and quaternary ammonium salts are sometimes unstable under basic conditions. Hence, the search for novel types of substrates and catalysts for the asymmetric PTC synthesis of amino acids deserves further effort. Recently, we reported on the use of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **2a**) as a novel type of PTC catalyst in the alkylation of *N*-(phenylmethylene)alanine esters and thus the synthesis of α-methyl-α-amino acids with a modest *ee* of 68%.[4] Our attempts to use **2a** as a catalyst for the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters failed to give any asymmetric induction. We reasoned, however, that other types of achiral glycine derivatives capable of stronger interactions with NOBIN would be more suitable substrates.



R^1=R^2=H, **2a**, (*R*)-NOBIN
R^1=Ph, R^2=H, **2b**
R^1= R^2=Me, **2c**

Earlier, we reported on the synthesis and application of substrate **3** (see Scheme 1) in an asymmetric Michael reaction, catalyzed by (*R*,*R*)-TADDOL (**1b**), that led to 4-methylglutamic acid with a low *ee* (28%).[5] Substrate **3** seemed to be a suitable model for use in other alkylation reactions with catalyst **2a**, as there are several potential centers of substrate – catalyst interaction by formation of a hydrogen bond or a metal complex. Here we report new results on the alkylation of substrate **3** (Scheme 1) with catalysis by **2a** under phase-transfer conditions, which led to a fast (as little as 5 min), efficient synthesis of α-amino acids at ambient temperature and with *ee* values of up to 93 – 98%.

Substrate **3** was readily prepared by the templated condensation of *N*-(2-benzoylphenyl)pyridine-2-carbamide (PBP, **4**) with glycine (Gly) and $Ni(NO_3)_2$ in MeOH in the presence of MeONa (Scheme 1). Complex **3** is a red, crystalline compound, easily purified by chromatography on SiO_2 and poorly soluble in most organic solvents and water. The solubility of the complex in organic solvents such as CH_2Cl_2 or $(CH_2Cl)_2$ was greatly increased by adding **2a**.

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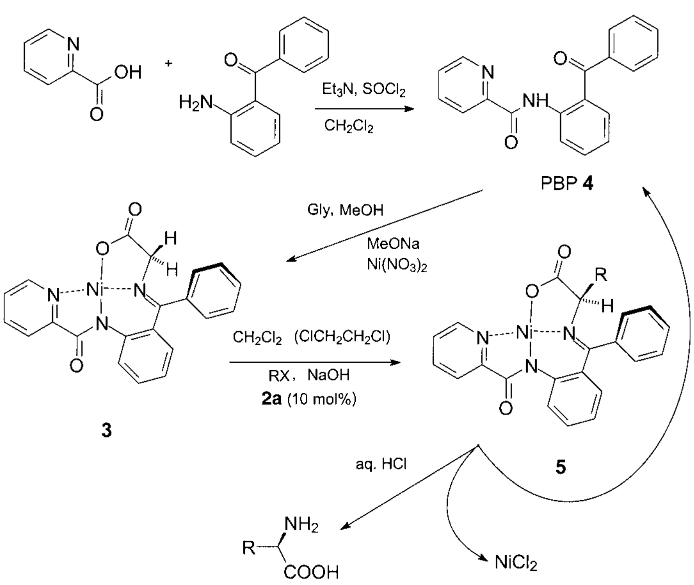

Scheme 1. Synthesis of substrate **3**, its alkylation under PTC conditions, and recovery of the target amino acids.

While no alkylation of substrate **3** was observed in the absence of a catalyst even after 5 h, addition of **2a** resulted in a remarkable change. Table 1 summarizes the experimental results of the alkylation of **3** with benzyl bromide under PTC conditions at room temperature with different catalysts and bases in various solvents, according to Scheme 1. The salient feature of this data is the superiority of unsubstituted NOBIN, in both yield and enantioselectivity, over the traditional PTC catalyst **1a** or **1b** under similar conditions (Table 1, entries 1–6). Whereas both **1a** and **1b** gave disappointingly low yields (less than 50%), even after one hour, and *ee* values of the resulting phenylalanine (Phe) in the range of 5–16% (entries 1–3), the reaction promoted by (*R*)-NOBIN (or (*S*)-NOBIN) in toluene gave the alkylated complex in a yield of 50% and Phe with an *ee* of 89% (entry 4). The reaction in CH$_2$Cl$_2$ gave (*R*)-Phe (or (*S*)-Phe) in 70% yield with 96–97% *ee* after 8 min (entries 5 and 6). As expected, increasing the polarity of the solvent lowered the *ee* of the alkylation product (entry 7), whereas (CH$_2$Cl)$_2$ served as a good substitute for CH$_2$Cl$_2$ (entries 8 and 9) that allowed the reaction to be carried out at higher temperatures (up to 70°C) without a significant drop in the product *ee* (entry 9) but with significantly increased yields.

Modification of **2a** by replacing the NH$_2$ group with NHPh (**2b**) or NMe$_2$ (**2c**) invariably decreased the efficiency of the reaction by slowing the rate and bringing the *ee* down to 3–5% (Table 1, entries 10 and 11). The *O*-benzyl derivative of **2a** was catalytically inactive.

The nature of the base is important in these reactions, as the transition from solid NaOH to KOH and then to CsOH·xH$_2$O decreased the *ee* of the reaction progressively from 96 to 16 and finally to 10 (Table 1, entries 6, 12, and 13). Using 50% aqueous NaOH was also detrimental to the *ee*, which fell from 96 to 55%, and the yield, which dropped to a meager 5% after 1 h (entries 6 and 14). Significantly, NaH was almost as efficient a base as NaOH (entries 5 and 15).

Table 2 summarizes the alkylation of substrate **3** with different alkyl halides under optimal conditions (Table 1, entry 6). All of the activated alkyl halides participated in the reaction and gave the alkylated products in good yields and with high *ee* (90–98.5%) at room temperature after 4–30 min (Table 2, entries 1–7). Unactivated alkyl halides were much less reactive, and relatively low yields of the alkylated product were obtained for the alkylation of **3** with simple alkyl iodides after short reaction times (Table 2, entries 8, 9, and 11), although the *ee* values of the recovered amino acids were still good. Longer reaction times resulted in some decrease in the *ee* of the amino acid (Table 2, entry 10). Racemization of the alkylated product during the longer time intervals might be a reason for this decline in *ee*.

The alkylated complexes **5** could be purified by chromatography or recrystallization before recovery of the amino acid. With the crystallization procedure, the *ee* of the complex or recovered amino acid was greatly improved (Table 2, entry 1). Ligand **4** was easily recovered in quantitative yield and reused to prepare **3**. The NOBIN could also be recovered from the reaction mixture by chromatography in 50% yield, though significant amounts of *O*-alkylated NOBIN were also detected in the reaction mixture.

Table 1. Asymmetric PTC alkylation of substrate **3** with benzyl bromide promoted by different catalysts and types of bases at room temperature.[a]

Entry	Solvent	Catalyst	Base	*t* [min]	Yield [%][b]	*ee* of Phe [%] (configuration)[c]
1	CH$_2$Cl$_2$	**1a**	NaOH	60	50	16 (*R*)
2	CH$_2$Cl$_2$	**1b**	NaOH	10	10	12 (*R*)
3	C$_6$H$_5$CH$_3$	**1b**	NaOH	45	10	5 (*S*)
4	C$_6$H$_5$CH$_3$	(*R*)-**2a**	NaOH	45	50	89 (*R*)
5	CH$_2$Cl$_2$	(*R*)-**2a**	NaOH	8	90	97 (*R*)
6	CH$_2$Cl$_2$	(*S*)-**2a**	NaOH	8	88	96(*S*)
7	MeCN	(*R*)-**2a**	NaOH	20	80	17 (*R*)
8	(CH$_2$Cl)$_2$	(*R*)-**2a**	NaOH	5	70	97 (*R*)
9[d]	(CH$_2$Cl)$_2$	(*R*)-**2a**	NaOH	5	86	93 (*R*)
10	CH$_2$Cl$_2$	(*R*)-**2b**	NaOH	60	10	3 (*R*)
11	CH$_2$Cl$_2$	(*R*)-**2c**	NaOH	15	15	5 (*R*)
12	CH$_2$Cl$_2$	(*R*)-**2a**	KOH	7	80	16 (*R*)
13	CH$_2$Cl$_2$	(*R*)-**2a**	CsOH·xH$_2$O	15	25	10 (*R*)
14	CH$_2$Cl$_2$	(*R*)-**2a**	50% aq. NaOH	60	5	55 (*R*)
15	CH$_2$Cl$_2$	(*R*)-**2a**	NaH	11	50	97 (*R*)

[a] Reaction conditions: concentration of **3** = 1.5–1.7 M, PhCH$_2$Br/substrate = 1.15–1.2/1, (*R*)-NOBIN/substrate = 1/10, MOH/substrate = 10/1, room temperature unless indicated otherwise, under Ar, all solvents were carefully dried. [b] Yield of the alkylated complex **5** determined after its separation from recovered **3**. [c] Determined by chiral GLC analysis of Phe recovered from the complex on chiral Chirasil-Val columns. [d] The reaction was carried out at 70°C.

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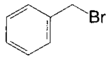
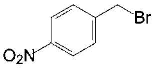
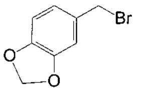
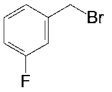
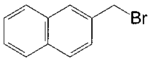
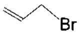
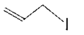
Table 2. Asymmetric PTC alkylation of substrate **3** with different alkyl halides promoted by (*R*)-NOBIN at room temperature.[a]

Entry	Alkylating agent	*t* [min]	Yield [%][b]	*ee* of (*R*)-amino acid [%][c, d]
1		8	90	97 (>99.8 %[e])
2		4	92[f]	93
3		6	70	98.5
4		7	80	94
5		6	62	98.5
6		30	68	90
7		4	75	90
8	C_2H_5I	5	2	93
9	C_2H_5I	30	15	93
10	C_2H_5I	240	35	81
11	*n*-$C_6H_{13}I$	60	10	91

[a] Reactions carried out in CH_2Cl_2, concentration of **3** was 1.5–1.7 M, RX/substrate = 1.15–1.2/1, (*R*)-NOBIN/substrate = 1/10, NaOH/substrate = 10/1–20/1, room temperature, under Ar. [b] Yield of the alkylated complex **5** estimated after its separation from unconsumed **3**. [c] Chiral GLC analysis of Phe recovered from the complex on chiral Chirasil-Val columns. [d] The enantiomerically enriched amino acids could be crystallized from 2-propanol/water to give the pure enantiomers. [e] The amino acid was recovered from the recrystallized complex. [f] 6 % of the bis-alkylated complex was detected in the reaction mixture.

Another interesting feature of catalysis by NOBIN was the observation of a very significant positive nonlinear effect, (+)-NLE,[6a] for the alkylation of **3** with BnBr (Figure 1). It is most likely that the mechanism of the reaction includes the formation of a chiral phenolate of NOBIN on the surface of the NaOH. The phenolate transfers into solution, deprotonates **3**, and the carbanion forms a chiral ion pair with NOBIN by chelating the sodium cation. Support for this concept comes from the absence of any reactivity of the *O*-Bn derivative of NOBIN and the dependence of the enantioselectivity of the reaction on the cation of the base (Table 1, entries 12–14). This chiral ion pair is then alkylated by the alkyl halides with a significant enantio-bias, similar to that of TADDOL- and NOBIN-catalyzed asymmetric alkylations of Schiff bases of alanine esters.[4] The role of the primary amino group of the ligand is crucial, since any substitution of this led to a drastic decrease in asymmetric induction (Table 1, entries 10 and 11). Likely, its role relies on interaction with Na^+ ions.[4] However, its direct interaction with Ni glycinate **3** should also be considered. Apparently, the mechanism in the case of **3** is more complex, as the alkylation of the *tert*-butyl ester of *N*-(diphenylmethylene)glycine with BnBr in CH_2Cl_2, with catalysis by (*R*)-NOBIN under the experimental conditions of Table 2, led to racemic Phe in 50 % yield after 1 h. Similarly, alkylation of Schiff bases of alanine esters with BnBr under similar conditions always led to racemic products. The less polar solvents toluene or hexane had to be employed with these substrates to obtain reasonable *ee* values of the alkylation products.[4] The (+)-NLE[6] (Figure 1) indicates that, most likely, the ionized NOBIN phenolate generates heterochiral aggregates with a lower reactivity than either homochiral aggregates or the monomeric species; and/or the heterochiral aggregates have greater stability than their homochiral counterparts. As a result, the homochiral aggregates (or the remaining monomer) with higher *ee* than that of the starting ligand will be the active species. This amplification effect is related to the reservoir effect (see the discussion in ref. [6a]).

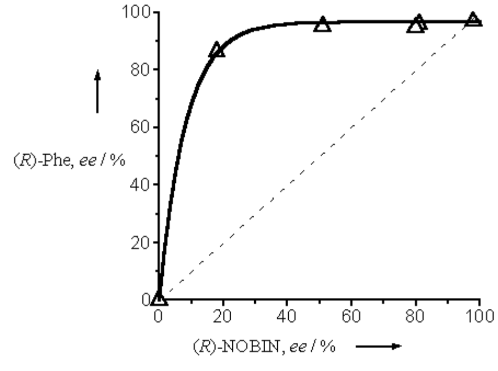


Figure 1. Positive nonlinear effect in the alkylation of **3** with BnBr, catalyzed by (*R*)-NOBIN.

In conclusion, we have developed a new substrate/catalyst pair for the efficient and simple asymmetric synthesis of a broad range of α-amino acids. The advantage of the procedure is the ease of the synthesis of the substrate **3** and availability of both enantiomeric forms of NOBIN.[7] Thus, both enantiomers of proteinogenic and nonproteinogenic amino acids become easily available in a remarkably short reaction time. The high reaction rate is particularly important for the synthesis of short-lived ^{11}C-labeled α-amino acids, a valuable class of compounds for PET diagnostics. Finally, the enantiomeric purity of synthetically derived NOBIN is not crucial for effective asymmetric induction (see Figure 1).

Experimental Section

Enantiomeric GLC analyses[8] of the amino acids were performed on a Chirasil-L-Val type phase, by using *n*-propyl esters of *N*-trifluoroacetyl derivatives of amino acids. (*R*)- and (*S*)-NOBIN were prepared as previously described.[7]

4 was prepared in 85 % yield by a straightforward condensation of picolinic acid (converted to its chloroanhydride with $SOCl_2$ in the presence of Et_3N at 0 °C) and *o*-aminobenzophenone in CH_2Cl_2 at 25 °C. M.p. 159 °C (ref. [9]: m.p. 154–156 °C). Elemental analysis (%) calcd for $C_{19}H_{14}N_2O_2$: C 75.48, H 4.67, N 9.27; found: C 75.59, H 4.68, N 9.23; IR: $\tilde{\nu}$ = 1690, 1590(amide), 1650 cm^{-1} (C=N).

3 was prepared by condensation of **4** (3.5 g, 11.6 mmol), $Ni(NO_3)_2 \cdot 6H_2O$ (6.75 g, 23.2 mmol), and glycine (1.74 g, 23.2 mmol) in MeOH (40 mL) in the presence of MeONa (4 N, 25 mL, 97.5 mmol) under reflux for 20 min and purified by crystallization from $CHCl_3$. M.p. > 280 °C (decomp) [ref. [9]: m.p. > 280 °C (decomp)], yield 91 % (4.39 g, 10.6 mmol). Elemental analysis (%) calcd for $C_{21}H_{15}N_3O_3Ni$: C 60.62, H 3.63, N 10.10; found: C 60.58, H 3.60, N 10.05; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.80$ (s, 2H, CH_2), 6.8–8.9 (m, 13H, ArH); UV (CH_2Cl_2, lgε (λ_{max})): 4.60 (354 nm); IR: $\tilde{\nu} =$ 1685, 1610 (amide), 1650 cm^{-1} (C=N).

Asymmetric alkylation of **3** under PTC conditions (described for RX = BnBr): Finely ground NaOH (2.0 g, 50 mmol), substrate **3** (2.1 g, 5 mmol), and (*R*)-NOBIN (0.14 g, 0.5 mmol) in anhydrous CH_2Cl_2 (30 mL) were stirred under Ar for 3 min at 15–20 °C. Then BnBr (1 g, 5.8 mmol) was added under Ar, and the mixture was stirred for an additional 8 min. The reaction mixture was quenched by the addition of 10 mL of aqueous AcOH and diluted with CH_2Cl_2 (30 mL). The organic layer was separated, and a small part of it was used to determine the *ee* (97% *R*) of the crude Phe (Table 1, entry 5). The residue was purified by flash chromatography on silica gel (to remove unconsumed **3**) with $CHCl_3$/acetone as eluent to give **5** (2.3 g, 4.5 mmol, 90% yield, 97% *ee* according to GLC analysis of the corresponding (*R*)-amino acid). The crude complex was crystallized from C_6H_6/acetone to give the enantiomerically pure product **5** (R = Bn; 1.9 g, 3.7 mmol, 74% yield); m.p. 276 °C, $[\alpha]_D^{25} = -3605°$ ($c = 1$, $CHCl_3$/MeOH), *ee* > 99.8% (*R*) according to GLC on the amino acid (ref. [9]: for **5** (R = Bn) with *ee* 13% (*S*): $[\alpha]_D^{25} = +370°$ ($c = 1$, $CHCl_3$/MeOH)). Elemental analysis (%) calculated for $C_{28}H_{21}N_3O_3Ni$: C 66.40, H 4.15, N 8.30; found: C 66.63, H 4.28, N 8.11; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.86$, 3.13 (ABX system, $J_{A,B} = 13.4$ Hz, 2H, CH_2), 4.36 (ABX system, $J_{A,X} = 2.9$, $J_{B,X} = 5.65$ Hz, 1H, CH), 6.80–7.90 (m, 18H, Ar); UV ($CHCl_3$, lgε (λ_{max})): 2.80 (256), 3.79 (351), 3.68 (455 nm). IR: $\tilde{\nu} = 1685$, 1615 (amide), 1660 cm^{-1} (C=N).

Recovery of amino acids, as illustrated for Phe: The crystallized complex **5** (R = Bn, 1.8 g, 3.5 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6 N HCl (5 mL) and MeOH (6 mL) for a few minutes until the red color of the solution disappeared, as described previously.[9] The solution was evaporated to dryness, water was added to the residue, and the insoluble material was filtered off, washed with water, and dried to afford **4**·HCl. The aqueous layer was adjusted to pH 8 with aqueous ammonia solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL) to remove small amounts of remaining **4**. Phe was recovered from the aqueous solution by the ion-exchange technique (DOWEX-50, H$^+$ form). (*R*)-Phe (0.40 g, yield 68%) was analyzed by chiral GLC (*ee* > 99.8%); m.p. 288–290 °C (decomp), $[\alpha]_D^{25} = +33.2$ ($c = 2$, H_2O), [ref. [10]: (*S*)-Phe $[\alpha]_D^{25} = -33.4$ ($c = 1.3$, H_2O)]. Elemental analysis (%) calcd for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48; found: C 65.36, H 6.78, N 8.44.

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Synthesis and Characterization of a Metallabenzyne**

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Interesting organometallic compounds can often be obtained by replacement of (hydro)carbon groups of organic compounds with isolobal transition metal fragments.[1] For example, the CH_2 group in $CH_2{=}CHR$ can be replaced by 16-electron transition metal fragments [L_nM] to give carbene complexes [$L_nM{=}CHR$], the CH group in $HC{\equiv}CR$ can be replaced by 15-electron transition metal fragments [L_nM] to give carbyne complexes [$L_nM{\equiv}CR$], and a CH group in benzene can be replaced by 15-electron transition metal fragments to give metallabenzenes.[2] In principle, a carbon atom in benzyne could also be replaced by 14-electron transition metal fragments to give metallabenzynes. However, such a possibility has not previously been realized. Here we describe the synthesis and characterization of the first metallabenzyne.

Treatment of [$OsCl_2(PPh_3)_3$] (**1**)[3] with an excess of $HC{\equiv}CSiMe_3$ in wet benzene produced a yellow precipitate and a brown solution. The yellow precipitate was identified as

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