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ORIGINAL ARTICLE

Using the same organocatalyst for asymmetric synthesis of both enantiomers of glutamic acid-derived Ni(II) complexes via 1,4-additions of achiral glycine and dehydroalanine Schiff base Ni(II) complexes

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Abstract (*S*)- and (*R*)-BIMBOL were efficient PT catalysts of asymmetric Michael addition of prochiral Ni–PBP–Gly (**1**) to acrylic esters and malonic esters to Ni–PBP–Δ-Ala (**2**) correspondingly. The salient feature of the catalysis is opposite configurations of Glu prepared via the two paths with BIMBOL of the same configuration and a perspective novel catalytic procedure for the synthesis of Gla derivatives.

Keywords γ-Carboxyglutamic acid · Glutamic acid · Asymmetric organocatalysis · Michael addition

Abbreviation

PBP	*N*-(2-benzoylphenyl)pyridine-2-carboxamide
Ni–PBP–Gly (**1**)	Ni(II) complex of a Schiff base of glycine with PBP
Ni–PBP–Δ-Ala (**2**)	Ni(II) complex of Schiff base of dehydroalanine with PBP
MOM	Methoxymethylene group
DCE	Dichloroethane
DCM	Dichloromethane
HMDSLi	Lithium hexamethyldisilaside
Gly	Glycine
Glu	Glutamic acid
Gla	γ-Carboxyglutamic acid
PTC	Phase transfer catalysis
TADDOL	(2,2′-Dimethyl-1,3-dioxolan-4,5-diyl)bis(diphenylmethanol)
NOBIN	2′-Amino-[1,1′-binaphthalen]-2-ol
iso-NOBIN	8′-Amino-[1,1′-binaphthalen]-2-ol
BINOL	[1,1′-Binaphthalene]-2,2’-diol
BIMBOL	3,3′-Bis(hydroxydiphenylmethyl)-[1,1′-binaphthalene]-2,2′-diol
ee	Enantiomeric excess
dr	Diastereomers ratio

Introduction

Enantiomerically pure (*S*)-Glu and its derivatives are very important physiologically active compounds (Huffman and Scelly 1963; Smith et al. 2011). Although Glu itself is produced microbiologically and is a cheap industrial commodity (Huffman and Scelly 1963), its enantiomerically pure derivatives, in particular Gla, are not easily available. This was a reason why the methods of asymmetric synthesis of Glu and its derivatives were sought. Presently, several synthetic protocols have been elaborated based on both stoichiometric (Williams 1989; Duthaler 1994; Cativiela and de DÍaz Villegas 1998; Ma 2003) and catalytic versions (Maruoka and Ooi 2003; Corey et al. 1998; Vyskočil et al. 2002; Belokon et al. 2003; Lygo et al. 2001; Nájera and Sansano 2007; Tsubogo et al. 2010; Kobayashi and

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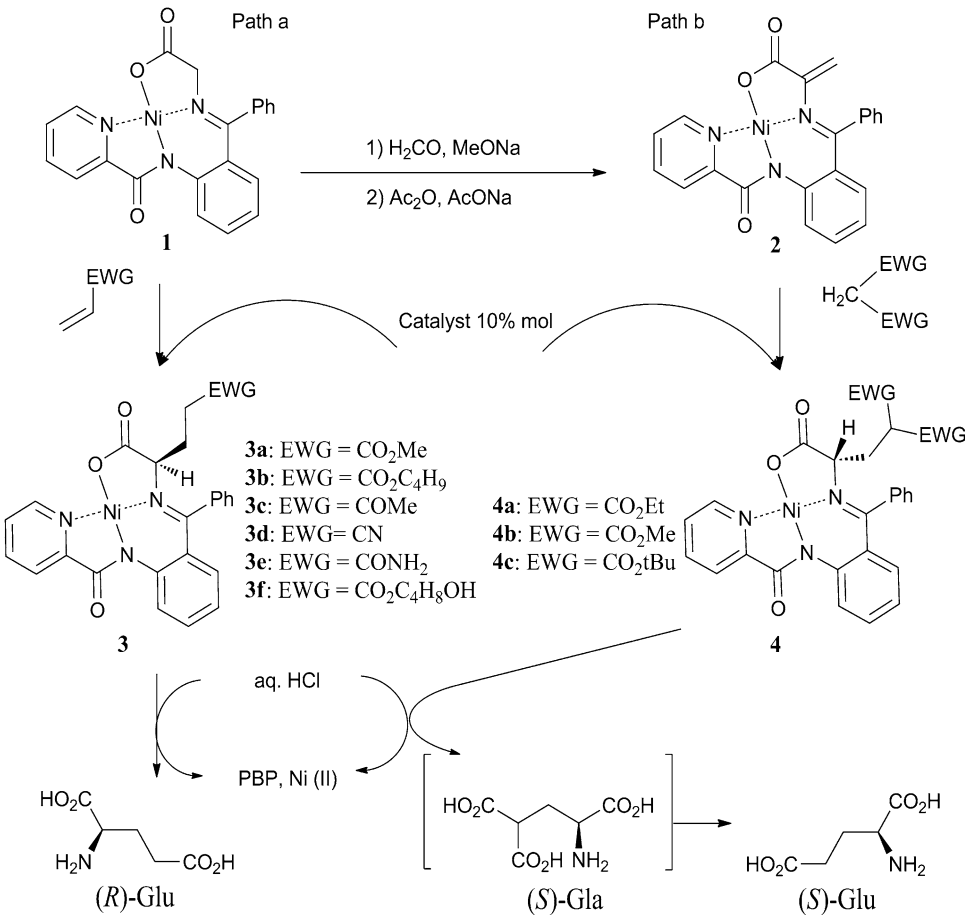
Yamashita 2011) of Michael additions of chiral or achiral activated Gly derivatives to acrylic acid derivatives. In particular, some of us developed an asymmetric procedure of Michael addition of an achiral Ni–PBP–Gly complex (**1**) to acrylic esters, (Scheme 1) catalyzed by (*R* or *S*)-NOBIN (Vyskočil et al. 2002) and (*R* or *S*)-*iso*-NOBIN (Belokon et al. 2003). Another synthetic path to Glu includes Michael addition of malonic esters to Ni–PBP–Δ-Ala (**2**) (Scheme 1) catalyzed by (*R*, *R*)-TADDOL earlier developed by some of us (Belokon et al. 2004). The stereodetermining stage of path (a) is the C–C bond formation, whereas that of path (b) is the asymmetric protonation of the transient carbanionic species. The latter type of asymmetric catalytic reactions is becoming a popular subject of research (Pracejus et al. 1977; Kumar et al. 1991; Emori et al. 1998; Fehr 1996; Yanagisawa and Yamamoto 1999; Yanagisawa et al. 2000; Muñoz-Muñiz and Juaristi 2003; Nishimura et al. 2001; Cheon and Yamamoto 2008; Navarre et al. 2008), in particular, as applied to amino acid syntheses (Tsubogo et al. 2010; Kobayashi and Yamashita 2011; Belokon et al. 2004; Leow et al. 2008)

Recently, we elaborated a chiral salt of (*R* or *S*)-BIMBOL (Wang et al. 2007) (see Chart 1) as an efficient multifunctional catalyst of enantioselective addition of some CH-acids to cyclohex-2-enone and nitrostyrene (Belokon et al. 2011). We envisaged that the application of the catalytic system to the reactions of Scheme 1 could lead to a novel synthetic protocol for the preparation of both Glu and Gla.

Herein, we found that (*S*)- or (*R*)-BIMBOL were efficient PT catalysts of both reactions, yielding enantiomerically enriched Glu via both paths. The salient feature of the catalysis is opposite configurations of Glu prepared via the two paths with BIMBOL of the same configuration and a perspective novel catalytic procedure for the synthesis of Gla.

Results and discussion

Complexes **1** and **2** were prepared as earlier described (Vyskočil et al. 2002; Belokon et al. 2004). The structure of **1** was also established and discussed earlier (Vyskočil et al. 2002). The X-ray structure of **2** (Fig. 1) suggests that the complex is neutral with the two positive charges at the central Ni atom neutralized by two negative charges of the tetradentate PBP ligand. Bond lengths and angles (see Table in experimental section in supporting information)



Scheme 1 Catalytic asymmetric synthesis of Glu and Gla

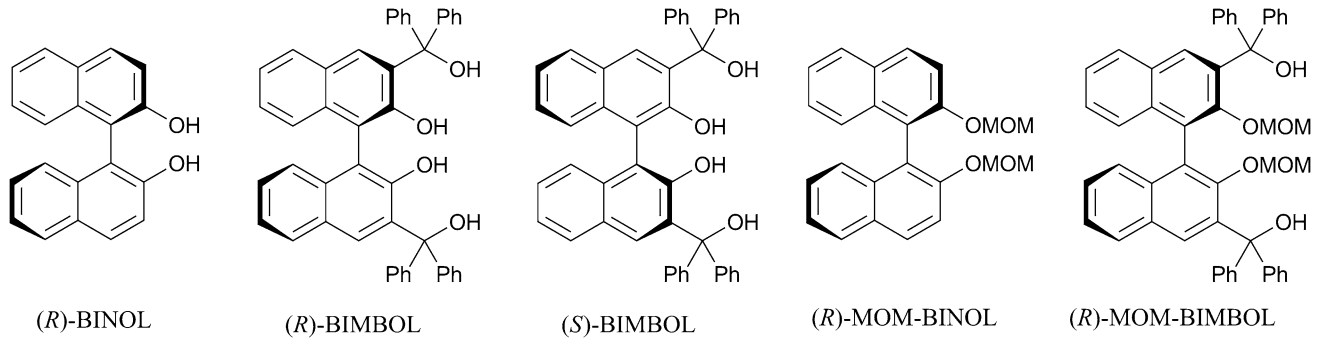


Chart 1

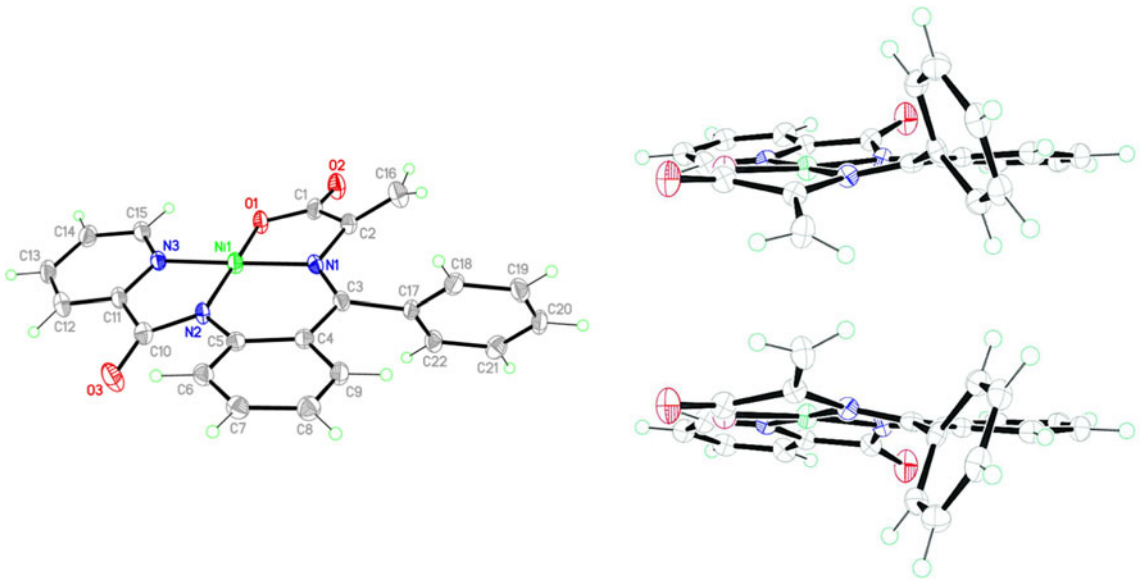


Fig. 1 X-ray structure of **2** with two enantiomeric conformations of the complex in crystals

are similar to those observed for the complexes of that type (Vyskočil et al. 2002).

The salient feature of the complex is chiral puckering of the ligand with two enantiomeric conformations of the amino acid moieties δ and λ (Fig. 1, right section, top and bottom correspondingly), restoring racemic crystal arrangement in the crystal cell. As a result of the puckering, the plane of the phenyl substituent at the C=N bond is skewed relative to the expected perpendicular position relative to the plane of the bond and equals 107°. Such an arrangement means shielding of the C=C bond of the dehydroalanine moiety either from the *re* or *si*-side. A similar situation existed for **1** where it was the glycine moiety that was chirally shielded, as earlier discussed (Belokon et al. 2003). Evidently, any chiral catalyst capable of fixing either chiral conformations of the substrate in the transition state of the reaction would be an effective asymmetry inducing agent.

Figure 2 illustrates the changes that occur in the ^{1}H NMR spectra of both (*S*)-BIMBOL (spectrum A) and **2** (spectrum B) in $CDCl_3$ when mixed at a 1:1 ratio (spectrum C). The most salient features of the spectra are the significant shifts of the resonances of both OH protons of BIMBOL (4.74 and 6.70 ppm) to lower fields (5.08 and 6.89 ppm, respectively) in the **2**/BIMBOL mixture. Simultaneously, a proton of the pyridine moiety of **2** (at C12, Fig. 1) was shifted to stronger fields (from 8.25 to 8.15 ppm). The observation can be rationalized, assuming formation of H-bonded complex of BIMBOL and **2**. Most likely, both substances were connected by the BIMBOL phenol OH group hydrogen bonding with O3 oxygen atom of **2**.

The ability to stabilize a chiral conformation of **2** by BIMBOL was confirmed by running the CD spectra of the mixture (Fig. 3). The appearance of a positive Cotton effect at 548 nm unequivocally supports our notion of

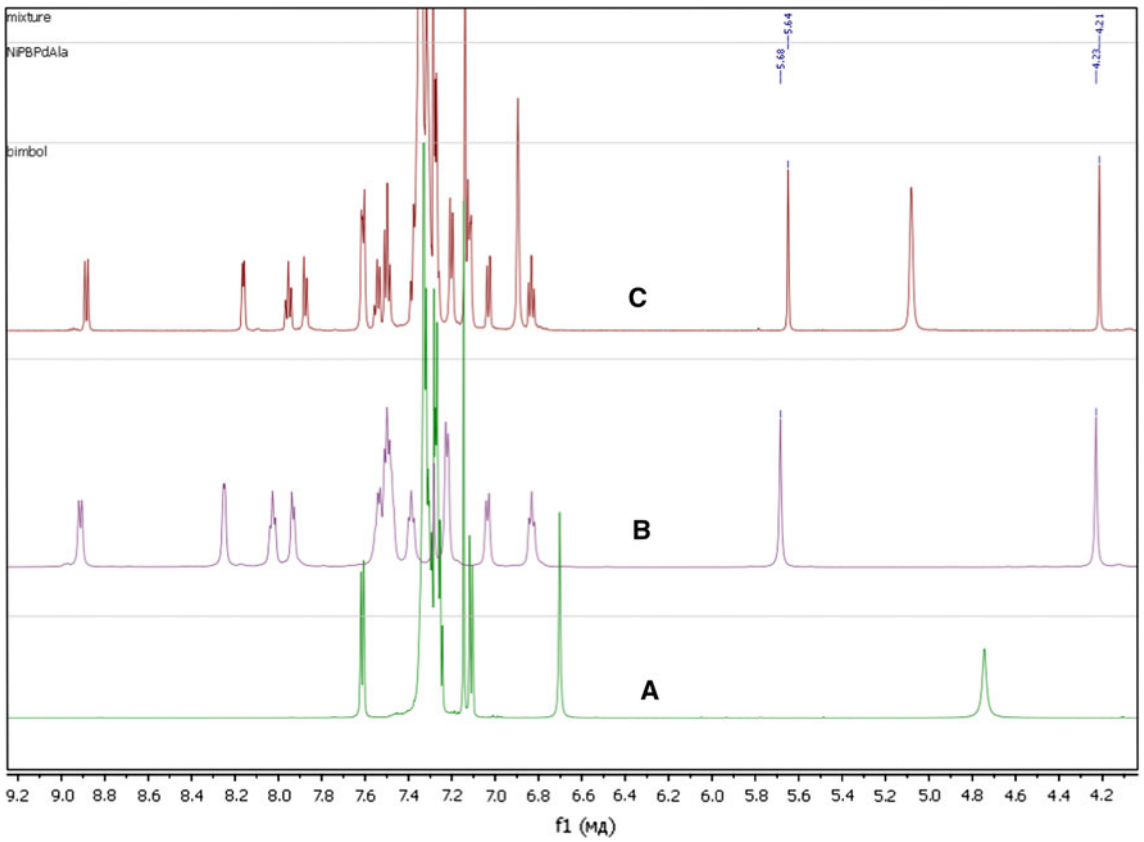


Fig. 2 ^{1}H NMR spectra of (*S*)-BIMBOL, **2** and a mixture of both at a 1:1 ratio. (from *bottom* to the *top*)

BIMBOL ability to shift the equilibrium between the two enantiomeric conformations of **2**. This represented another case of Pfeiffer effect (Pfeiffer and Quell 1931; Kirshner et al. 1968). The CD spectra of enantiomerically enriched complexes **3** (Belokon et al. 2003) indicated that the positive effect at 536 nm corresponded to (*S*)-**3**, which had the λ-conformation of the amino acid chelate ring. According to X-ray data, the similar complexes of alanine had the same type of chiral puckering (Belokon et al. 2003) as **2**. Thus, other closely related chiral complexes, such as **3**, can be used as a model to compare their Cotton effects with those of **2**. Evidently, one can assume that (*S*)-BIMBOL stabilized a conformational enantiomer with λ-conformation of the dehydroalanine moiety in **2** (Fig. 1, right, bottom structure). Undoubtedly, the strongly basic negatively charged carbanions generated from either **1** or **2** will be more strongly coordinated by BIMBOL and their conformational preferences might be different. However, the Pfeiffer effect observed in the case of a mixture of **2** and (*S*)-BIMBOL serves as a proof of principle experiments, supporting our general concept.

The Michael addition of **1** to methyl acrylate (Scheme 1) was carried out in DCM at ambient temperature with NaH as a base and with 10% mol of one of the catalysts presented in the Chart 1 (Table 1, runs 1–4).

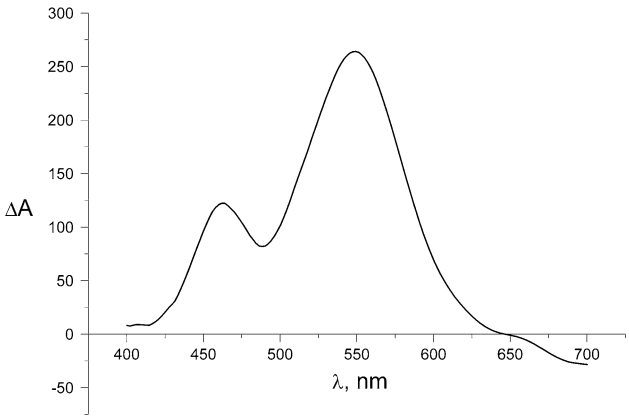


Fig. 3 CD spectra of a 1:1 mixture of (*S*)-BIMBOL and **2** (Fig. 2 shows the ^{1}H spectra of the mixture)

The reaction was stopped after 5 min with aqueous acetic acid and the yield of the Michael adduct estimated by ^{1}H NMR. The ee of product was assessed using the optical rotation of the forming complex, as described earlier (Belokon et al. 2003). The values were corroborated by chiral GLC analysis of the amino acid recovered from the complex (Table 2, run 9). The results are summarized in Table 1.

Evidently, BIMBOL was the most efficient of the series of catalysts, affording 60% chemical yield of the product (Table 1, run 4), whereas the chemical yields were only 10–15% in cases of (*R*)-BINOL, (*R*)-MOM-BINOL or (*R*)-MOM-BIMBOL (Table 1, runs 1–3). Some asymmetric induction was also detected for the BIMBOL catalysis that was completely absent in other cases.

To improve the catalytic performance of BIMBOL, a series of alkali metal bases was tested under the same catalytic conditions. The results are summarized in Table 2.

Under the conditions, no bis-alkylation products were detected in the reaction mixture. The reason for this has been already discussed in our previous paper on **1** alkylation (Belokon et al. 2003) and, generally, is similar to the reasoning for rationalizing similar behavior of glycine ester benzophenone imines, as discussed by O'Donnell (O'Donnell et al. 1988). In short, the first alkylation results in greater puckering of the chelated amino acid moiety in **3**, as compared to the initial **1** (because of the interaction of the alkyl group in **3** with the phenyl substituent at the C=N bond). A consequence of it was greater pseudo-equatorial orientation of the amino acid α-proton in **3**, as compared to those of **1**. This results in diminished acidity of **3** relative to **1** due to the stereoelectronic effects. Thus, it is the initial **1** and not **3** that produced a sufficient amount of reactive transient carbanions under the same alkalinity of the reactive solution. Eventually, this led to the reaction being effectively stopped at the mono-alkylation step.

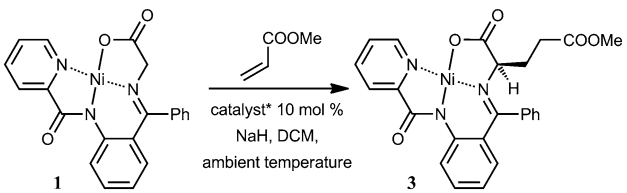
The data summarized in Table 2 support the notion of the paramount importance of the alkali metal ion of the base on the efficiency of the catalysis.

The performance of the catalytic system increased in the order Li < Rb < Na < K (Table 2, runs 3–5, 6, 9, 11). Use of PhOLi and ^{n}BuLi produced low efficiency catalysts with only 40–50% chemical yield of the Michael adduct and a meager 1–3% ee after 15 min (Table 2, runs 3, 4). Both ee and the chemical yields were improved on switching to HMDSLi and NaH (Table 2, runs 5, 6). Even better asymmetric induction was achieved with ^{t}BuOK and KOH (Table 2, runs 8, 9 and 14, 15). The maximum ee was 68% with 10% mol of BIMBOL and one equivalent of KOH (Table 2, run 14). Further fourfold decrease in the amount of the catalyst resulted in diminished ee of the product (Table 2, runs 9, 12, 13). Even more dramatically, the sense of chirality was reversed when Li or Na cations were substituted with K cation (Table 2, runs 5 and 6, as compared to 8–10, 12–15). Evidently, both cations and anions of the base were involved in the stereochemical arrangement of the transition state of the C–C bond formation.

The additions of other activated olefins to **1** were conducted under the optimal conditions of run 14 of Table 2. The data are summarized in Table 3.

The addition of **1** to other acrylic esters resulted in somewhat lower enantioselectivity as compared to methyl acrylate (Table 2, run 14 and Table 3, runs 1, 2). **1** was added to methylvinylketone also under the same conditions (Table 3, runs 3–5). However, the process was accompanied by racemization of the final product. The notion was supported by the greater enantiomeric purity of the product in case of smaller concentrations of the base (Table 3, runs 3–5). The effect could be rationalized by assuming faster C–C bond formation relative to the racemization of the final adduct. Thus, at smaller concentrations of the base, it was easier to detect greater amounts of the unracemized adduct even at great conversions of **1**. The phenomena was already observed and discussed in the case of NOBIN-catalyzed addition of **1** to acrylic esters (Belokon et al. 2003). The same tendency was observed in case of **1** addition to acrylonitrile

Table 1 Catalyst structure–activity relationship study in the addition of **1** to acrylate[a]



Run	Catalysts	Yield (%)	ee (%)[b]
1	(*R*)-BINOL	10	0
2	(*R*)-MOM-BINOL	10	0
3	(*R*)-MOM-BIMBOL	15	0
4	(*R*)-BIMBOL	60	14 (*R*)

[a] Reaction conditions: catalyst (7.2×10^{-6} mol), **1** (7.2×10^{-5} mol), methyl acrylate (4.32×10^{-4} mol), NaH (7.2×10^{-5} mol), 1 mL of DCM, 5 min at ambient temperature under Ar

[b] Determined by the optical rotation of the final complex; product configuration in parentheses

Table 2 BIMBOL catalyzed asymmetric addition of **1** to methyl acrylate[a]

Run	Base (eq[b])	Catalyst (% mol[b])	Yield (%)	ee (%)[c]
1	^{t}BuOK (1)	No catalyst	70	0
2	KOH (1)	No catalyst	60	0
3[d]	PhOLi (2)	(*R*)-BIMBOL (10)	50	3 (*R*)
4[d]	^{n}BuLi (0.2)	(*R*)-BIMBOL (10)	40	0
5	HMDSLi (1)	(*R*)-BIMBOL (10)	80	35 (*R*)
6	NaH (2)	(*R*)-BIMBOL (10)	98	31 (*R*)
7[e]	NaOH (0.5)	(*S*)-BIMBOL (10)	95	2 (*S*)
8	^{t}BuOK (1)	(*R*)-BIMBOL (10)	99	47 (*S*)
9	^{t}BuOK (0.5)	(*S*)-BIMBOL (10)	99	60 (60[f]) (*R*)
10	^{t}BuOK (0.2)	(*S*)-BIMBOL (10)	60	45 (*R*)
11	RbOH(1)	(*R*)-BIMBOL (10)	80	2 (*S*)
12	^{t}BuOK (0.5)	(*S*)-BIMBOL (5)	90	46 (*R*)
13	^{t}BuOK (0.5)	(*S*)-BIMBOL (2.5)	90	41 (*R*)
14	KOH (1)	(*S*)-BIMBOL (10)	99	68 (*R*)
15	KOH (0.5)	(*S*)-BIMBOL (10)	99	60 (*R*)
16[g]	NaOH (0.5)	(*S*)-BIMBOL (10)	99	11 (*S*)

[a] For the reaction conditions see the footnote to Table 1, unless indicated otherwise

[b] Equivalents of the base or mol percent of the catalyst relative to **1**

[c] Product ee was determined by the optical rotation of the final complex, unless indicated otherwise; product configuration in parentheses

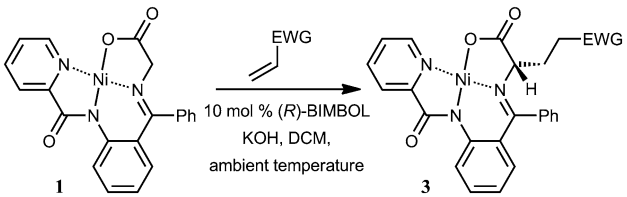
[d] The reaction was conducted for 15 min

[e] The reaction was conducted for 50 min

[f] Determined by chiral GLC analysis on chiral *Chirasil-Val* columns for the amino acid released from the crude complex

[g] The reaction was carried out at 80°C in DCE

Table 3 (*R*)-BIMBOL-catalyzed asymmetric addition of **1** to different acrylates[a]

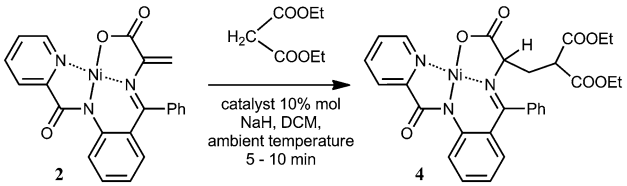


Run	EWG	KOH (eq)[b]	Time (min)	Yield (%)	ee (%)
1	–COOMe	1	5	99	68 (*S*)
2	$-COOC_4H_9$	1	60	90	49 (*S*)
3	–COMe	1	8	95	3 (*S*)
4		0.5	7	95	34 (*S*)
5		0.25	90	95	44 (*S*)
6	–CN	1	30	80	1 (*S*)
		0.5	30	85	7 (*S*)
		0.25	120	25	10 (*S*)
7	$-CONH_2$	1	20	95	0
8	$-COOC_4H_8OH$	1	10	95	0

[a] For the reaction conditions, see the footnote to Table 1, unless indicated otherwise

[b] Relative to **1**

Table 4 Catalyst structure–activity relationship study in the case of malonate addition to **2**[a]



Run	Catalyst	Yield (%)[b]	ee (%)[c]
1	None	95	–
2	(*R*)-BINOL	>95	6 (*R*)
3	(*R*)-MOM-BIMBOL	>95	0
4	(*S*)-BIMBOL	>95	23 (*S*)

[a] The reaction conditions: 10% mol of the catalysts (5.8×10^{-6} mol), 1 mL of DCM, 5.8×10^{-5} mol of **2**, 1.16×10^{-5} mol of malonate, 1 eq of NaH (relative to **2**), 5–10 min at an ambient temperature under Ar

[b] Esimated by ^{1}H NMR

[c] Estimated by the specific rotation at 589 nm of the recovered final adduct. The correctness of the determination was in some cases supported by the analysis of glutamic acid recovered from the adduct; product configuration in parentheses

Table 5 (*S*)-BIMBOL-catalyzed asymmetric addition of malonic ester to **2**[a]

Run	Base (eq)[b]	Solvent	*T* (°C)	Yield (%)	ee (%)[c]
1	BuLi (0.1)	DCE	80	99	30 (*S*)
2	BuLi (0.4)	DCE	80	99	17 (*S*)
3	LiOH (0.5)	DCE	80	99	35 (*S*)
4	NaH (0.5)	DCM	20–25	99	37 (*S*)
5	NaOH (0.5)	DCM	20–25	99	63 (*S*)
6	NaOH (0.5)	DCE	80	99	35 (*S*)
7	KOH (0.5)	DCM	20–25	99	65 (*S*)
8	RbOH (0.7)	DCM	20–25	99	13 (*S*)
9	$CsOH \times H_2O$ (0.5)	DCM	20–25	99	41 (*S*)
10[e]	KOH (0.5)	CH_2Cl_2	−20	15	20 (*S*)
11	KOH (0.5)	Toluene	80	99	64 (*S*)
12	KOH (0.5)	DCE	80	99	76 (*S*)
13	KOH (0.25)	DCM	25	99	62/62[d] (*S*)
14[f]	Mono-K salt of BIMBOL (0.1)	DCE	80	99	70 (*S*)
15[f]	Tetra-K salt of BIMBOL (0.1)	DCE	80	99	80 (*S*)

[a] For the reaction conditions see the footnote to Table 4, unless indicated otherwise

[b] Relative to **2**

[c] Estimated by the angle of rotation at 589 nm of the recovered final adduct. The correctness of the determination was in some cases supported by the analysis of glutamic acid recovered from the adduct (see run 13); product configuration in parentheses

[d] Determined by chiral GLC analysis of the final glutamic acid recovered from the complex

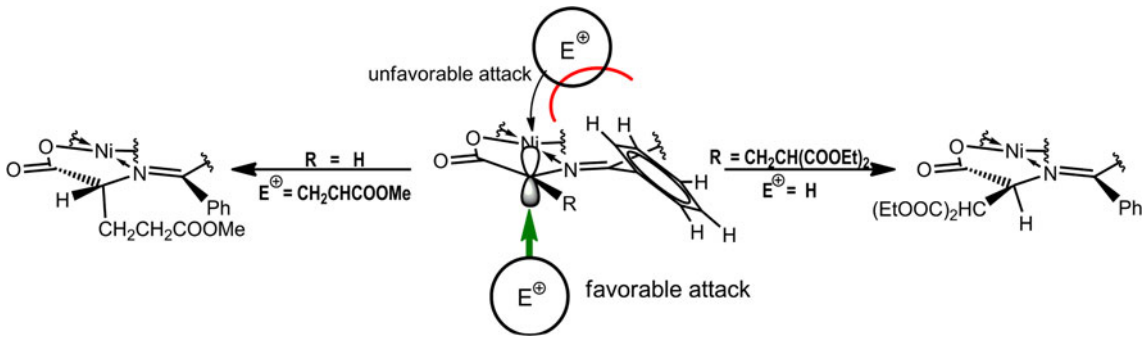
[e] The reaction was run for 8 h

[f] The catalyst was prepared by the reaction of metallic potassium with (*S*)-BIMBOL

(Table 3, run 6). Probably, greater electron withdrawing properties of CN group, increasing the racemization rate of the adduct, led to a very low ee in case of acrylonitrile addition reactions (Table 3, run 6). Acrylamide also added to **1**, but the final product was racemic (Table 3, run 7). Surprisingly, **1** added to δ-hydroxybutyl acrylate without any asymmetric induction (Table 3, run 8).

The addition of malonic ester to **2** was promoted by NaH in DCM at an ambient temperature even without any chiral catalyst added (Table 4, run 1).

There were practically no asymmetric inductions observed when 10% mol of (*R*)-BINOL or (*R*)-MOM-BIMBOL was added (Table 4, runs 2, 3). Noticeable ee was detected when (*S*)-BIMBOL was employed under the conditions.



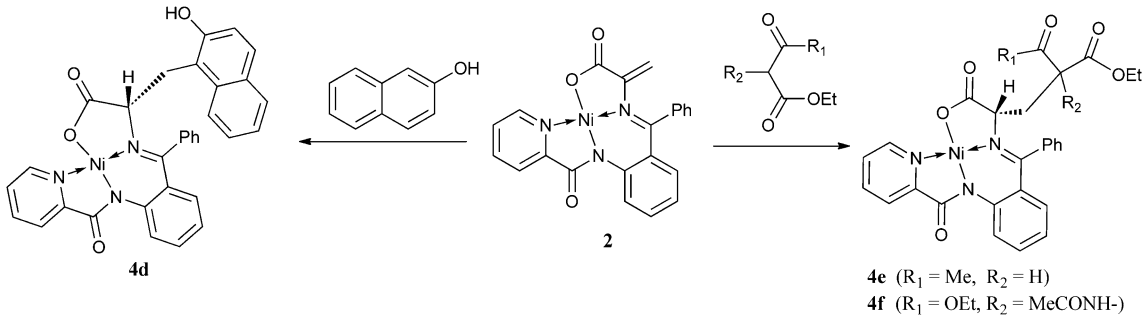
Scheme 2 Stereochemical model rationalizing opposite configurations of the adducts formed in case of **1** and **2**, as catalyzed by BIMBOL of the same configuration

Table 6 (*S*)-BIMBOL-catalyzed asymmetric addition of different CH-acids to **2**[a]

Run	CH-acids	Time (min.)	Yield (%)	ee (%)[b]
1	$CH_2(COO^tBu)_2$	45	90	45 (*S*)
2	$CH_2(COOEt)_2$	7	>95	76 (*S*)
3	$CH_2(COOMe)_2$	7	>95	83 (*S*)
4	Diethyl 2-acetamidomalonate	7	>95	(dr 1/9) 61 (*S*)
5	$MeCOCH_2COOEt$	7	>95	(dr 1/4) 88 (*S*)
6	Naphthalen-2-ol	80	85	0

[a] The reaction conditions: 1 mL of DCE, temperature 80°C, 0.058 mmol of **2**, CH-acids 2 eq (relative to 2), KOH 0.5 eq (relative to **2**), 10% mol of a catalyst (*S*)-BIMBOL

[b] Estimated by the angle of rotation at 589 nm of the recovered final adduct; product configuration in parentheses



Scheme 3 Catalytic asymmetric synthesis of derivatives of glutamic acid and 2-hydroxynaphthalen-1-yl-alanine

The data summarized in Table 5 indicate that potassium-derived bases gave the best induction in case of (*S*)-BIMBOL-catalyzed reaction (Table 5, runs 1–9, 11–15). The temperature increase from −20 to 25°C and 80°C led to greater ee of the product, the complex of Gla (Table 5, runs 7, 10, 11, 12). The best results were obtained with mono- and tetra-potassium salts of (*S*)-BIMBOL (Table 5, runs 14, 15).

The recovery of a protected version of Gla from closely related chiral BPB copper complexes has been recently described (Smith et al. 2011) and was not pursued in this work.

The salient feature of the condensation was independence of the sense of the asymmetric induction on the metal cation of the alkali base used (compare Table 2 and 5). In addition, in the presence of KOH (*S*)-BIMBOL catalyzed the addition of **1** to acrylates furnishing the complex of (*R*)-Glu (Table 2, runs 9, 10, 12–15), whereas the addition of malonic ester to **2**, catalyzed by (*S*)-BIMBOL, gave complexes of (*S*)-Gla (Table 5, runs 7, 10–14), after hydrolysis of which (*S*)-Glu was recovered (Scheme 1).

The observation can be rationalized, applying the stereochemical model depicted in Scheme 2.

Hypothetically, chiral BIMBOL might stabilize similar chiral conformations (see a model chiral conformation of **2** in Fig. 1 and Scheme 2) of the carbanions, derived either from **1** by the abstraction of its α-proton by KOH or from **2**

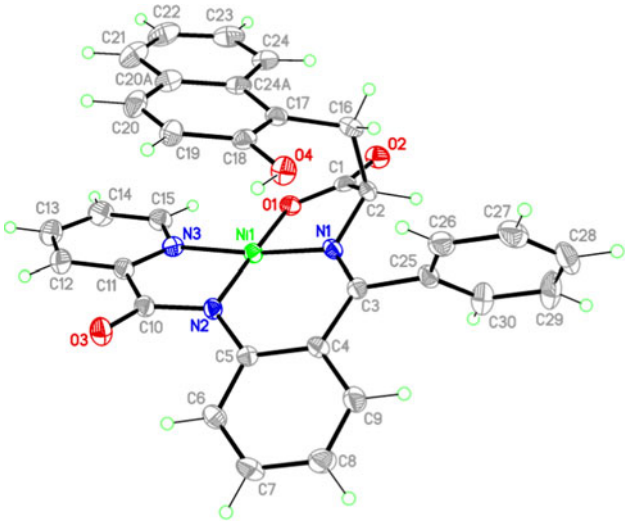


Fig. 4 X-ray structure of **4d**

by the addition of the potassium malonate salt. Thus, the same *si*-side (or *re*-side) of both transient carbanions will be shielded by the phenyl substituent. It would correspond to opposite configurations in case of the addition and protonation (most likely by BIMBOL) in spite of the same preference of the attack because of the resulted priorities of the groups in the final chiral compounds. It would imply the (*S*)-configuration of the adduct in case of protonation, leading to Gla complex, and (*R*)-configuration of Glu in case of the Michael addition of **1** to acrylate (as depicted in Scheme 2) or vice versa, depending on which carbanion conformation was stabilized.

Naphthalen-2-ol added to **2** by its α-carbon atom (Fig. 4), as shown by the X-ray structure analysis of the adduct **4d**. Unfortunately, the product was racemic (Table 6, run 6).

Other nucleophiles also added to **2** under the optimal conditions in the presence of KOH (see Schemes 1, 3). The results are summarized in Table 6. The values of ee of the adduct was inversely dependent on the size of the malonic ester (Table 6, runs 1–3), increasing from *t*-butyl malonate (45%) to ethyl (76%) and methyl malonates (83%). Diethyl 2-acetamidomalonate was also active giving 61% ee of the adduct (Table 6, run 4). Ethyl acetylacetate was also active with 88% ee and dr 1/4 of the product (Table 6, run 5).

Conclusion

BIMBOL proved to be an efficient catalyst of asymmetric synthesis of glutamic acid and its derivatives via Michael addition of achiral glycine Ni-complexes to acrylic esters under PTC conditions. It was efficient as a catalyst of asymmetric protonation of the intermediate carbanions formed by the addition of CH-acids to Ni-dehydroalanine complexes under PTC conditions. We hope to further modify the BIMBOL molecule to improve its performance, and work to this end is ongoing in our laboratory.

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