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New generation of nucleophilic glycine equivalents

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Abstract—A new generation of nucleophilic glycine equivalents, designed to contain a functional framework, that allows control over the physical properties as well as the reactivity, is described. The reactivity of these nucleophilic glycine equivalents have been compared to previously described examples with the application of various transformations such as alkyl halide alkylations, Michael additions, and aldol condensations.

Among the most practical and generalized approaches for preparing amino acids is the homologation of nucleophilic glycine equivalents (NGEs). Analysis of the relevant literature, dealing with the asymmetric homologation approach, revealed two general approaches. The first involves the design of properly protected NGEs that incorporate an element of chirality into their framework. This approach has enjoyed a great deal of creativity producing dozens of various chiral NGEs. The second approach revolves around the alkylation of the *tert*-butyl glycinate benzophenone Schiff base **1** (Fig. 1) under phase transfers conditions (PTC) using a catalytic amount of chiral quaternary ammonium salt.[1] Most of the work in this area has concentrated on the development of new catalysts, which recently culminated with the discovery of *N*-spiro C_2-symmetric quaternary ammonium salts.[2] By contrast, fewer studies have been made to improve on the structure of Schiff base **1** until recently.[3] Recently, we have synthesized picolinic acid/*o*-aminoacetophenone derived glycine Schiff base **2a** (Fig. 1) and demonstrated its potential as a NGE for asymmetric, organic base-catalyzed Michael addition reactions.[4] On the other hand the *o*-aminobenzophenone derivative **2b**, described by Belokon' et al,[5] has proven to be an excellent NGE for the practical large-scale preparation of *sym*-α,α-dialkyl amino acids.[5,6] Although Schiff bases **2a**,**b** possess advantages over **1**, such as stability and predictable formation of the (*E*)-enolates, their synthetic value is greatly limited by poor solubility in most organic solvents.

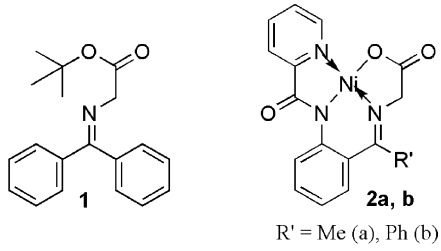

Figure 1.

We report herein a new generation of NGEs **3a**–**c** (Scheme 1), which can be easily prepared on the kilogram scale from ligands **4a**–**c**, glycine and a source of Ni(II). Ligands **4a**–**c** in turn, are easily available in high chemical yields starting from the acid bromide **5**, a dialkylamine and either *o*-aminobenzophenone or *o*-aminoacetophenone.[7]

The major concern with this design was the potential problem with chemoselectivity, as one may envision that both of the glycine moieties in **3a**–**c** may be alkylated, especially under the harshly basic conditions necessary to perform *bis*-alkylations (Scheme 1). However, it was exciting to find that in the presence of sodium *t*-butoxide in DMF, alkyl halides such as benzyl, cinnamyl, and allyl bromides alkylated the methylene moiety of the glycine Schiff base exclusively. These reactions proceeded to completion, at room temperature, to afford the corresponding α,α-disubstituted α-amino acid

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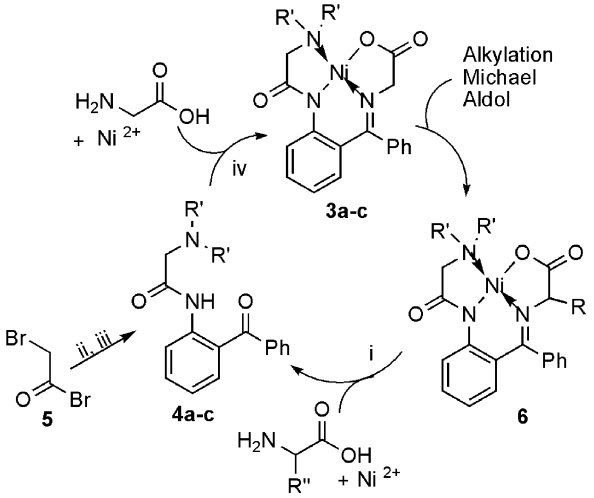


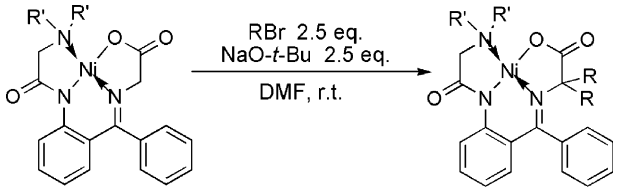
Scheme 1. Reagents and conditions: (i) 3 N HCl, 60 °C; (ii) *o*-aminobenzophenone, K_2CO_3, acetonitrile, rt; (iii) NHR'_2, K_2CO_3, acetonitrile, 60 °C; (iv) KOH, MeOH, 60 °C; (a) R′ = Bu; (b) R'_2 = piperidyl; (c) R′ = Bn.

containing products **7a–c**; **8a**; **9a** in high yields, >92% from **3a** to **3c** (Table 1). The products **7a–c**; **8a**; **9a** were found to be extremely clean, eliminating any need for purification before their disassembly.

With the chemoselectivity issue no longer a concern, it seemed as if a side-by-side comparison of the NGEs **1**, **2a**,**b**, and **3a–c** was in order. Therefore, PTC benzylations were performed in 30% aqueous NaOH/CH_2Cl_2 with *N*-(*n*-Pr)$_4$Br as the catalyst (Table 2). It was found that compound **3b** was more reactive than **2b**, however less reactive than **1**. Although, **2b** and **3b** gave rise to the corresponding products **11b**, **12b** in virtually quantitative yield, Schiff base **1** underwent partial hydrolysis, significantly lowering the yield of **10**.

The most interesting results were obtained from of the PTC homologation of complex **3a** with benzyl bromide and various chiral quaternary ammonium salts. Initial attempts to benzylate complex **3a** with the use of cinchonidine derived catalysts (15 mol %)[8] proved disheartening as they resulted in racemic products. However,

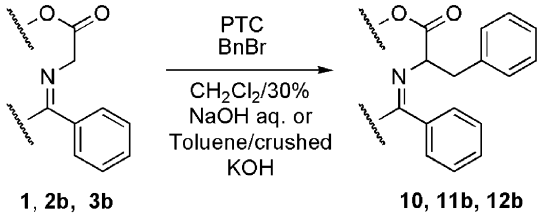
Table 1.



Entry	R′	R	Time (min)	Product	Conversion[a] **3/7**	Yield[b] (%)
1	Bn (**3c**)	Bn	15	**7c**	>99	90
2	Piperidyl (**3b**)	Bn	15	**7b**	>99	91
3	Bu (**3a**)	Bn	15	**7a**	>99	93
4	Bu (**3a**)	Allyl	15	**8a**	>99	92
5	Bu (**3a**)	Cinnamyl	15	**9a**	>99	88

[a] Determined by NMR analysis of the crude reaction mixtures.
[b] Isolated yield of the crude product.

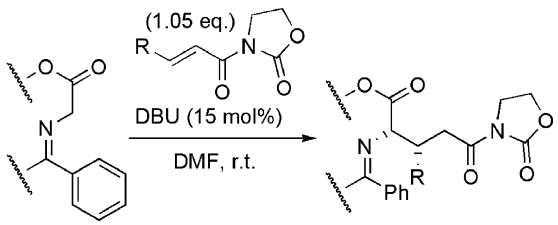
Table 2.



Entry	Sub.	Solvent	Base	Time (h)	Product	Ratio[a] reac/prod	Yield[b] (%) **10**, **11b**, **12b**
1[c]	**3b**	CH_2Cl_2	NaOH aq	1	**12b**	<1/>99	>99
2	**2b**	CH_2Cl_2	NaOH aq	1.5	**11b**	<1/>99	>99
3	**1**	CH_2Cl_2	NaOH aq	0.5	**10**	<1/>99	86

[a] Determined by NMR analysis of the crude reaction mixtures.
[b] Isolated yield of the crude product.
[c] For reactions with chiral PTCs the solvent was toluene and the base as well as the temperature were varied.

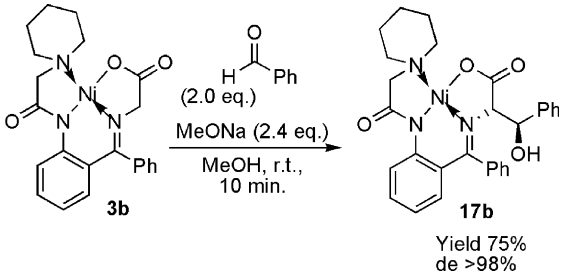
Table 3.



Entry	Sub.	R	Time	Product	Conversion[a] reac/prod	Yield[b] (%) **13**, **14b**, **15b**, **16b**	de
1	**3b**	Ph	4 min	**15b**	<1/>99	>99	>98
2	**3b**	*n*-Pr	20 min	**16b**	<1/>99	90	>98
3	**2b**	Ph	50 min	**14b**	<1/>99	>99	>98
4[c]	**3b**	Ph	18.5 h	**15b**	<5/>95	>95	>90
5[c]	**1**	Ph	18.5 h	**13**	>70	>70	—[d]

[a] Determined by NMR analysis of the crude reaction mixtures.
[b] Isolated yield of the crude product.
[c] Reaction conducted in CH_2Cl_2 in the presence of DBU (1.15 equiv).
[d] Three products obtained in a ratio of 72:12:10.

reactions catalyzed by the *N*-spiro C_2-symmetric quaternary ammonium salt (1 mol %),[9] provided the corresponding amino acid derivative in high optical purity in a biphasic system of toluene and crushed potassium hydroxide, at 0 °C. Although the 92% ee obtained from the reaction is impressive, it was interesting to note that the true stereochemical outcome of the catalyzed reaction is being concealed by the presence of a noncatalytic pathway that provides 8% yield of racemic products. Therefore suggesting, virtually complete control of the stereochemical outcome may be realized by eliminating the noncatalytic pathway.[10]



Scheme 2.

In order to expand the comparison of reactivities, Michael additions between the three Schiff base derived glycine equivalents and 3-substituted acryloyloxazolidin-2-one derivatives were evaluated (Table 3). Again compound **3b** reacted at a much higher rate than **2b**, however both provided the appropriate products in nearly quantitative yield and virtually complete diastereoselectivity.[11] In contrast, the Michael addition of Schiff base **1** failed to advance to completion and provided at least three of the four possible diastereomers in a 7.2:1.2:1.0 ratio.

Finally to emphasize the truly versatile nature of the compounds **3b**, an aldol reaction was conducted, under conditions not compatible with either of the other Schiff bases **1** or **2a**,**b**, due to low solubility **2a**,**b** or instability of **1** (Scheme 2). However, allowing **3b** and an aldehyde, such as benzaldehyde, to react in the presence of sodium methoxide, in methanol provided the corresponding (2*S**,3*R**) β-hydroxy-α-amino acid in 98% de.[12]

In summary, a new generation of nucleophilic glycine equivalents has been introduced With several points of flexibility incorporated into this design, considerable control over the reactivity and physical properties, solubility in particular, of these NGEs can be realized by the proper choice of the corresponding *o*-aminobenzophenone or *o*-aminoacetophenone and dialkylamine. Moreover, the structural flexibility included in this design allows for the connection between the stoicheometric and catalytic approaches to the asymmetric synthesis of amino acids, as the application of various C_2-symmetrical dialkylamines can provide for an internal source of chirality. With respect to efficiency, compounds **3a**–**c** are very inexpensive,[13] and can be stored at room temperature in an open atmosphere while retaining high chemical reactivity. The homologation of NGEs **3a**–**c** can be conducted under homogeneous or PTC conditions via alkyl halide alkylations, Michael and aldol addition reactions affording the corresponding products in high chemical yields and enantio- or diastereoselectivity. These products can also be easily isolated and disassembled to release the target amino acids along with quantitative recovery and reuse of the ligands **4a**–**c**.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.050.

References and notes

1. For seminal publication, see: (a) O'Donnell, M.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; (b) For recent review, see: O'Donnell, M. *Acc. Chem. Res.* **2004**, *37*, 506.
2. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519; (b) Lygo, B.; Allbutt, B.; James, R. S. *Tetrahedron Lett.* **2003**, *44*, 5629.
3. While compound **1** features excellent solubility in most of the organic solvents, it has relatively high CH acidity, and the products derived from it can be purified by chromatography, their hydrolytic instability can lead to eroded yields. Moreover, the acyclic nature of these substrates, which leads to the possibility of either *Z*- or *E*-enolate geometry, can make the interpretation of the stereochemical outcome of reactions and the rational design of catalysts difficult.
4. (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747; (b) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984.
5. Belokon, Y. N.; Bespalova, N. B.; Churkina, T. D.; Cisarova, I.; Ezernitskaya, M. G.; Harutyunyan, S. R.; Hrdina, R.; Kagan, H. B.; Kocovsky, P.; Kochetkov, K. A.; Larionov, O. V.; Lyssenko, K. A.; North, M.; Polasek, M.; Peregudov, A. S.; Prisyazhnyulk, V. V.; Vyskocil, S. *J. Am. Chem. Soc.* **2003**, *125*, 12860.
6. (a) Ellis, T. K.; Martin, C. H.; Tsai, G. M.; Ueki, H.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 6208; (b) Ellis, T. K.; Hochla, V. M.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 4973.
7. The Supplementary data is available online with the paper in ScienceDirect. The Supplementary data includes spectral characterization data for all new compounds as well as representative experimental procedures and catalyst structures.
8. *N*-(9-Anthracenylmethyl)-cinchonidinium chloride, and *O*-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide were used.
9. (*S*,*S*)-3,4,5-Trifluorophenyl-NAS bromide, for structure see Ref. 4.
10. Although preliminary studies suggest that increasing the lipophilicity of the complexes decreases the extent of the noncatalytic pathway, the stereochemistry and the stereochemical rational are still under investigation.
11. Based on extensive stereochemical data involving Michael addition reactions between the picolinic acid derived NGEs **2a**,**b** and oxazolidinone derived Michael acceptors, the relative configuration of the products are assigned (2*R**,3*R**) for complex **16b** and (2*R**,3*S**) for complexes **14b** and **15b**. The stereochemistries of the three observed diastereomers from the Michael addition reaction of the Schiff base **1** were not determined.
12. Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Tararov, V. I.; Savel'eva, T. F.; Churkina, T. D.; Ikonnikov, N. S.; Kochetkov, K. A.; Orlova, S. A.; Pysarevsky, A. P.; Struchkov, Y. T.; Raevsky, N. I.; Belokon, Y. N. *Tetrahedron: Asymmetry* **1995**, *7*, 1741.
13. Compounds **3a**–**j** may be synthesized from $0.65 to $0.80 per gram, depending on the price of the dialkylamine employed.