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Improved Synthesis of Proline-Derived Ni(II) Complexes of Glycine: Versatile Chiral Equivalents of Nucleophilic Glycine for General Asymmetric Synthesis of α-Amino Acids

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Abstract: A synthetically practical and operationally convenient method for preparing (*S*)-2-[*N*-(*N*′-benzylprolyl)-amino]benzophenone (BPBP) and hitherto unknown (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]-4-methylbenzophenone (4-Me-BPBP), (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]-5-nitrobenzophenone (5-NO_2−BPBP), and their corresponding Ni(II) complexes with glycine [GlyNi(II)BPBP], a widely used chiral equivalent of nucleophilic glycine, and new analogues [GlyNi(II)-4-Me-BPBP] and [GlyNi(II)-5- NO_2-BPBP] is described. The key step of the method is the synthetically efficient amid bond formation between the corresponding *o*-aminobenzophenones, featuring significant steric shielding and low nucleophilicity of the amino functionality as well as sterically constrained (*S*)-*N*-benzylproline (BP).

Asymmetric synthesis of α-amino acids[1,2] via homologation of chiral equivalents of electrophilic[1−3] or nucleophilic[1,2,4] glycine is methodologically the most straightforward, practical and so far the most reliable[5] approach for preparing various amino acids, in particular, structurally complex and sterically constrained derivatives.[4,6] Among the vast variety of chiral equivalents of glycine developed to date,[1−4,6] the Ni(II) complex of glycine Schiff base with (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]benzophenone [(BPBP)-**1a**] and GlyNi(II)BPBP-**2a** (Scheme 1), introduced by Bolokon' et al.,[7] has several unique features. The Ni(II) complex **2a** is the only chiral equivalent of glycine to offer a stereochemically reliable and efficient (>95% de) homologation via alkyl halide alkylation, aldol, and Michael addition reactions under operationally convenient conditions, i.e., without recourse to inert atmosphere, rigorously dried and degassed solvents, and low temperature. Furthermore, the glycine equivalent **2a** features attractive physicochemical characteristics such as high crystallinity and solubility in certain organic solvents leading to a convenient purification of the homologation products and high volume yields. Practical synthesis of various α-amino acids using the glycine equivalent **2a**, including fluorine-, phosphorus-, and sulfur-containing analogues as well as isotopically labeled derivatives, is well-documented by Belokon's group,[8] our group,[9] and other groups.[10]

Unfortunately, practitioners in academic and industrial research laboratories have been discouraged from forming a wider synthetic appreciation and application of the chiral glycine equivalent **2a** for preparing various tailor-made α-amino acids[8−10] due to the unreasonably high commercial price[11] and inefficient literature procedures[12] for its preparation. In this paper, we report a full and detailed account of the synthesis of complex **2a** as well as its hitherto unknown derivatives **2b**,**c**, recently developed by our laboratories. The method presented here involves application of inexpensive reagents and operationally convenient conditions, therefore allowing the synthetically efficient and large-scale preparation of ligands **1a**−**c** and complexes **2a**−**c**.

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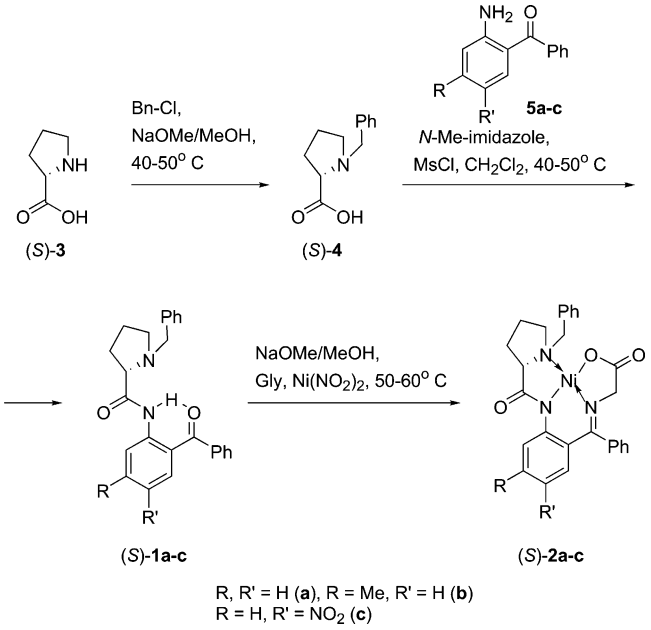
SCHEME 1



The published route for preparation of complex **2a**, starting from enantiomerically pure (*S*)- or (*R*)-proline (Pro) (**3**), reported by Bolokon' et al.,[12] employed cheap reagents, such as KOH, for preparation of *N*-benzylproline **4** (BP) (Scheme 1), and $SOCl_2$ for the activation of **4**, to react with *o*-aminobenzophenone **5a**. While this procedure, in our hands, generated the target compounds **4**, **1a**, and finally **2a**, many of its features made it ultimately unattractive for large-scale preparation, for example, the problems associated with the control of pH, merely using indicating paper, for preparing BP-**4**. In addition, further transformation to the ligand **1a**, employing excess $SOCl_2$, led to variable and generally low chemical yields. Moreover, formation of numerous byproducts on the stage of amidation of *o*-aminobenzophenone **5a** and incomplete transformation to ligand **1a** necessitated laborious purification of **1a** prior to its use for preparing complex **2a**. Furthermore, the published procedure employs an almost 50% excess of BP-**4** on the amidation stage rendering the method economically unattractive, especially for preparing the target compounds starting from rather expensive (*R*)-Pro-**3**. The above listed problems, associated with the control of pH, in the synthesis of BP-**4**, as well as the amidation stage, had to be resolved.

We have achieved an improved synthesis of BP-**4**, as depicted in Scheme 1. Application of the commercially available and cheap NaOMe as a base and MeOH as solvent in the reaction of Pro-**3** with benzyl chloride was found to lead to clean and efficient mono-benzylation of **3** affording BP-**4** with a reproducible >85% chemical yield. Since the commercial NaOMe, in contrast to KOH, does not contain unknown amounts of water or carbonates, the calculated amount of concentrated HCl was reliably used in order to quench the reaction mixture. According to the optical rotation and ^{1}H NMR data of the crude product, thus prepared (*S*)-BP-**4** was found to be >95% pure and therefore was used without further purification for preparing ligand **1a**.

With an improved route to BP-**4** in hand, we were in position to turn our attention to its condensation with *o*-aminobenzophenones **5a**−**c**. Amidation of carboxylic acids in general, especially the formation of a peptide bond, has been an area of intense research and is well documented.[13,14] On the other hand, examples of the synthesis of amides using sterically hindered acids and

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TABLE 1. Amidation of (*S*)-*N*-Benzylproline 4 with *o*-Aminobenzophenones 5a−c via the Intermediate Mixed Anhydride Formation[a]

entry	amine **5a**,**b**	conditions: base (equiv)	conditions: acid-Cl	ratio[b] **5a**,**b**/**1a**,**b**	yield[c] (%) **1a**,**b**
1	**a**	TEA (2.0)	TsCl	65/35	ND
2	**a**	TEA (2.0)/DMAP (0.2)	TsCl	41/59	ND
3	**a**	TEA (2.0)/DMAP (1.0)	TsCl	8/92	88.5
4	**a**	DMAP (3.0)	TsCl	<5/95	93.0
5	**a**	TEA (2.0)/MeIm (1.0)	TsCl	11/89	ND
6	**a**	MeIm (3.0)	TsCl	8/92	90.0
7	**a**	MeIm (2.2)	TsCl	8/92	90.5
8	**a**	MeIm (2.2)	MsCl	<5/95	93.5
9	**b**	MeIm (2.2)	MsCl	<5/95	94.0
10	**c**	MeIm (2.2)	MsCl	20/80	77.0

[a] All reactions were run in commercial-grade dichloromethane; (**4**/**5a**−**c** = 1.1/1). [b] Determined by NMR (300 MHz) analysis of the crude reaction mixtures. [c] Isolated yield of pure products based on **5**.

sterically hindered or low-nucleophilic amines are quite rare in the literature.[14] In particular, synthesis of the target ligand **1a**, derived from sterically constrained BP-**4** and *o*-aminobenzophenones **5a**−**c**, possessing both undesirable features of steric hindrance and low nucleophilicity of the amino group, cannot be performed with synthetically useful yields by straightforward application of the literature methods.[14] Of the literature methods, activation of the carboxylic function by in situ formation of the corresponding mixed carboxylic−sulfonic or −carbonic anhydrides[14d−g] was shown to be the most effective for reactions with sterically hindered or low-nucleophilic amines. However, the first amidation attempt of BP-**4** with benzophenone **5a** in a solution of dichloromethane, using *p*-tolylsufonyl chloride (TsCl), to generate the corresponding mixed anhydride, and triethylamine (TEA), as a base, gave a rather disappointing result. The reaction proceeded sluggishly giving rise to a mixture of the target **1a** and starting amine **5a** in ratio of 65/35 (Table 1, entry 1). To improve the conversion of **5a** to **1a**, we decided to use 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as a catalyst, since it has a known powerful effect on many reactions including acylations on nitrogen.[15] Using a catalytic amount of DMAP along with TEA, we obtained a noticeable increase in the conversion of starting **5a** (entry 2). After several attempts, we found that the use of a stoichiometric amount of DMAP resulted in a dramatic improvement of the ratio affording the target **1a** in a synthetically useful yield (Table 1, entry 3). Further attempts to improve the ratio by running the reaction at higher temperature (dichloroethane was used as a solvent) resulted in a decreased conversion, suggesting that the corresponding mixed anhydride might be unstable at high temperature. On the other hand, application of DMAP as a base, instead of TEA, as well as an additive allowed us to further increase the conversion of **5a** and isolated yield of the target ligand **1a** (entry 4).

We assumed that, though successful, the application of a stoichiometric amount of relatively expensive DMAP would render the method economically unattractive, in particular the large-scale preparations. Therefore, we directed our efforts to find a cheap but effective additive to be used in the place of DMAP. *N*-Methylimidazole (MeIm), which is substantially cheaper than DMAP, was shown to play a similar catalytic role to DMAP in acylations on nitrogen.[15] To our satisfaction, the reaction conducted using MeIm (1 equiv) along with TEA (2 equiv) gave results comparable with those of the DMAP-assisted reaction (entry 5 vs 3). Taking into account that the best conversion of the starting amine **5a** was achieved when we used DMAP as a catalyst and a base (entry 4), we conducted the analogous reaction using 3 equiv of MeIm. The result obtained was slightly lower compared with that of DMAP-assisted reaction (entry 6 vs 4). However, it was in the range of a synthetically useful outcome. In a successive series of experiments, gradually decreasing the amount of MeIm, we found that at least 2.2 equiv of MeIm were necessary to reliably reproduce >90% conversion of amine **5a** to ligand **1a** (entry 7). Finally, we conducted a series of experiments using various analogues of TsCl to improve the chemical and/or economical outcome of this key amidation step. As a result, we found that the application of methansulfonyl chloride (MsCl) in place of TsCl allowed for a noticeable improvement of the method. Thus, the use of MsCl, which is cheaper and easier to handle compared to TsCl, afforded a synthetically useful conversion of amine **5a** to the target ligand **1a** which was isolated in 93.5% yield (entry 8). Under the same reaction conditions the methyl-containing benzophenone **5b** was used to prepare a new ligand **1b**, which was isolated in a chemical yield similar to **1a** (entry 9). In contrast, the application of the nitro-containing derivative **5c** resulted in a noticeably lower conversion (entry 10), apparently due to the strong electron-withdrawing effect of the nitro group in direct conjugation with the amino function. Nevertheless the ligand **1c** was isolated in a synthetically useful chemical yield.

The purification of ligands **1a**−**c** from the residual amounts of **5a**−**c** and some byproducts merits additional comments. According to the Bolokon' procedure,[12] the ligand **1a** can be purified by crystallization of the crude product from ethanol. While this procedure generated relatively pure samples of **1a**, we found this crystallization protocol rather unpractical, as the recovery of the ligand **1a**, in a series of experiments was generally below 75%. Considering some other options to isolate the target ligand **1a** in the highest possible chemical yield, we ruled out the use of expensive silica gel column chromatography because it is inappropriate for the large scale preparations. After several attempts, using differences in physicochemical properties of **1a** and **5a**, we found that precipitation of the target **1a**, as the hydrochloric salt from a solution of the reaction mixture in acetone offers a simple, efficient and operatively convenient procedure.

The corresponding Ni(II) complexes **2a**−**c** were prepared from ligands **1a**−**c** under previously reported conditions.[12]

In the ^{1}H NMR spectra of complexes **2a**−**c**, the protons of the glycine methylene moiety were found to be sensi-

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tive to the effect of the substituent. Thus, the chemical shift of the protons of the glycine methylene group in **2c** were found to be shifted downfield (3.79 ppm) and in **1b** shifted upfield (3.70 ppm), as compared with that of the unsubstituted complex **2a** (3.73 ppm). These data suggested that the glycine methylene moiety in **2c** is more, and in **2b** is less CH acidic as compared with the complex **2a**. This observation provides ground for the rational design of this type of complexes with controlled reactivity of the glycine methylene group.

In summary, an efficient, large-scale method for preparing BP and hitherto unknown ligands 4-Me-BPBP, 5-NO_2-BPBP, and their corresponding Ni(II) complexes with glycine has been developed. The key step of the method is formation of the mixed anhydrides derived from *N*-benzylproline and methanesulfonyl chloride.

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Supporting Information Available: General experimental procedures and ^1H and ^{13}C spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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