Screening of Optically Active Nickel Initiators for Enantioasymmetric Polymerization of γ-Benzyl Glutamate-*N*-Carboxyanhydride

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The incorporation of only L-amino acids into DNA-encoded proteins imparts a great biological significance to the chirality of amino acids. This importance also translates to compounds synthesized from amino acid components. As with all chiral materials, it is typically more difficult to synthesize amino acids as pure enantiomers rather than as racemic mixtures. One method of utilizing the racemate is to kinetically resolve it into optically pure product and unreacted enantiomer.[1] We have explored the polymerization of α-amino acid-*N*-carboxyanhydrides (NCAs) to form block copolypeptides for applications as biomedical materials.[2] In such materials, the absolute configuration of the amino acid monomers is crucial for both structural development and biological activity.[3] To utilize synthetic, racemic amino acids in these materials, we pursued the use of optically active initiators to develop enantioasymmetric polymerizations. We now report the use of chiral pyridinyl oxazoline ligands in nickel initiators to enantioasymmetrically polymerize γ-benzyl-glutamate NCA.

Enantioasymmetric ring-opening polymerizations have been developed for many chiral cyclic monomers such as epoxides and episulfides.[4] There also have been attempts to prepare optically active polypeptides from racemic NCA mixtures. Interest in this area has arisen from the pharmaceutical value of the optically active products as well as possible relevance to the origins of handedness in biological macromolecules.[5] Some of the different chiral initiators used to induce asymmetry in NCA polymerizations include optically active amines[6] and polypeptides,[7] organoaluminum complexes,[8] and chiral nickel carboxylates.[9] These initiators generally displayed moderate-to-poor efficiencies and gave complex polymerizations whose propagation steps were poorly understood. All systems gave broad molecular weight distributions and poor control of polymer molecular weights and displayed reasonable enantioselectivities only at very low conversions of monomer.

We have developed nickel initiators that allow the controlled polymerization of NCAs.[2] Using this methodology, polypeptides can be prepared with defined chain lengths and with narrow molecular weight distributions. A key feature of this system is that all polymer formation occurs with identical nickel-containing reactive species. The straightforward nature of this system provides a superior starting point for the development of an enantioasymmetric polymerization system compared to previous methods used to polymerize NCAs. In particular, asymmetric initiators can be prepared by direct substitution of the achiral 2′,2′-bipyridyl (bpy) ligand in our nickel system with a suitable optically active ligand (Figure 1).

The choice of a suitable chiral ligand required some consideration. Most common chiral ligands are bidentate, since the chelate structure provides both a rigid environment as well as asymmetry around the metal.[1] A large number of chiral chelating ligands are based on bisarylphosphines,[10] which unfortunately form ineffective initiators when complexed with nickel due to their poor donating ability, as we have previously shown for PPh_3.[2] For this reason, we focused our attention on *N*-donor ligands that are similar in character to bpy, which forms a very efficient initiator.[11] We initially explored diimine and bisoxazoline ligands (e.g., **1**−**4**) (Figure 2), which have been used extensively in metal-mediated asymmetric aziridinations,[12] Diels−Alder reactions,[13] and olefin polymerizations.[14] These ligands were found to bind only weakly to zerovalent nickel and were thus also generally ineffective in generating active NCA polymerization initiators. To increase coordinating ability, we decided to study hybrid ligands consisting of pyridine coupled with either a chiral imine or oxazoline group (Figure 3).

To test the efficiency of such ligands, we prepared achiral **5** and evaluated its ability to form an active initiator. When **5** was mixed with $Ni(COD)_2$ in tetrahydrofuran (THF), a stable blue complex, **5**Ni(COD), was formed. This compound displayed NCA polymerization activity that was virtually identical to that of bpyNi-

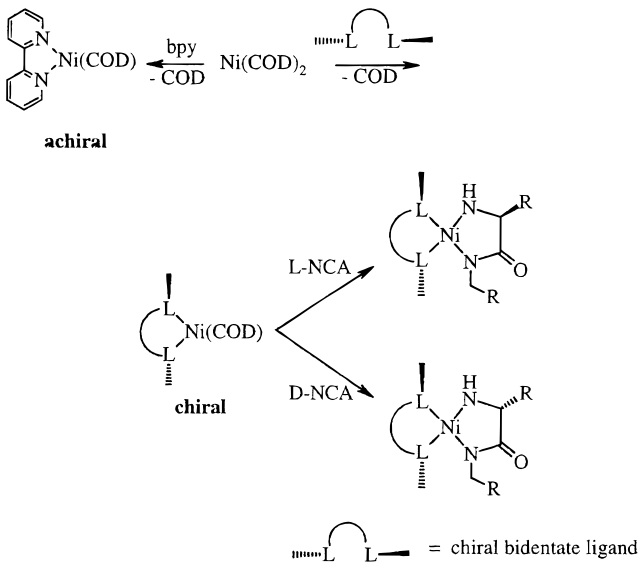

Figure 1. Strategy for formation of chiral nickel NCA polymerization initiators.

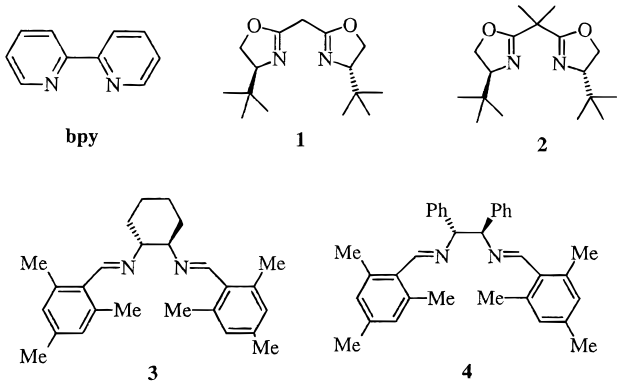

Figure 2. Bpy and chiral bisoxazoline and diimine ligands screened in this study.

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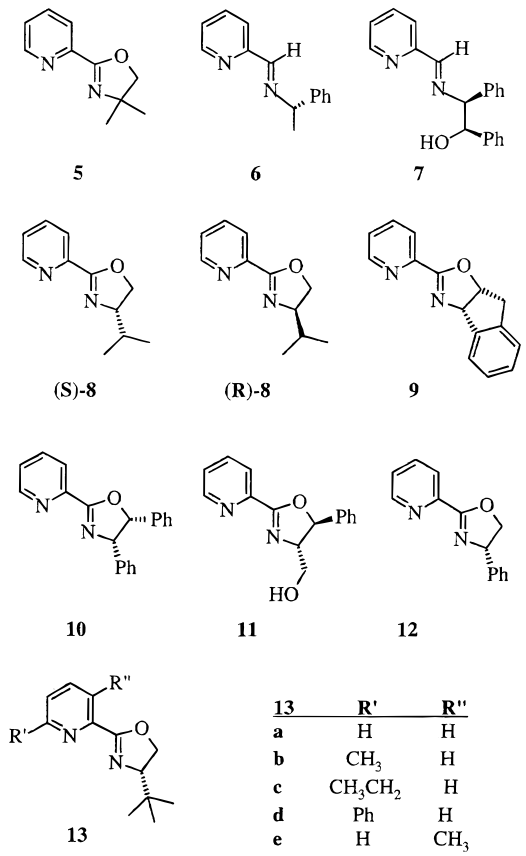
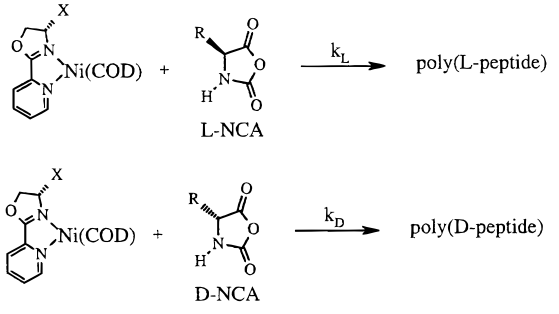


13	R'	R''
a	H	H
b	CH_3	H
c	CH_3CH_2	H
d	Ph	H
e	H	CH_3

Figure 3. Pyridinyl-imine and pyridinyl-oxazoline ligands used to prepare chiral nickel initiators.

(COD), demonstrating that pyridinyl oxazoline ligands can form active initiators.[15] On the basis of this success, we prepared a number of optically active pyridinyloxazolines and their corresponding Ni(COD) complexes (Figure 3). These initiators also supported the controlled polymerization of Glu NCA.[15] In evaluating these complexes, we initially decided to screen their abilities to separately homopolymerize L- and D-Glu NCA, rather than studying the enantioasymmetric polymerization of racemic Glu NCA (eq 1). It was assumed that k_D/k_L



(1)

would be a good crude measure of initiator enantioselectivity. We studied the polymerization of Glu NCA since this monomer forms a soluble polymer which is readily characterized[16] and since this monomer was used for most previous studies on asymmetric NCA polymerization.[7−9]

In polymerizations of L- and D-Glu NCA, it was found that **6**Ni(COD) and **7**Ni(COD) initiators gave no control of polymer molecular weight and gave very low enantioselectivities. These pyridinyl-imine ligands were not able to bind strongly to nickel and were abandoned in favor of the pyridinyl-oxazolines. Initial studies on the **(S)-8**Ni(COD) initiator with Glu NCA in THF showed that this initiator gave both controlled polymerization and a k_D/k_L ratio of 1.4(0.1) (Table 1). Since the antipodal initiator **(R)-8**Ni(COD) gave an equal but opposite selectivity [k_L/k_D = 1.3(0.1)], it was apparent that the chirality of the ligated metal complex was responsible for the observed selectivities. The free ligands **(S)-8** and **(R)-8**, in absence of nickel, were inefficient initiators that gave negligible polymer formation over the course of a nickel-initiated polymerization. It is worth noting that with the chiral initiators the polymerization rates for both D- and L-monomers are markedly slower than in polymerizations with achiral initiators (Table 1). This result is not entirely surprising since increasing the steric bulk around the metal center should slow polymer formation, especially since the polymer chain itself also crowds the metal center.

Table 1. Kinetic Data for Polymerization of L- and D-Glu NCA Using LNi(COD) Initiators[a]

ligand	k_{obs}^D ($\times 10^4$ s^{-1})	k_{obs}^L ($\times 10^4$ s^{-1})	k_{obs}^D/k_{obs}^L
5	5.0	5.0	1.0
(*S*)-8	2.3	1.6	1.4
(*R*)-8	2.1	2.8	0.7
9	2.3	2.1	1.1
10	3.0	1.7	1.8
11	4.2	3.4	1.2
12	3.8	2.4	1.6
13a	1.3	0.25	5.2
13b	0.033	0.083	0.4
13c	0.033	0.067	0.5
13d	0.01	0.033	0.3
13e	1.2	0.8	1.5

[a] All polymerizations were run at 20 °C in THF with [Ni] = 3.2 mM.

By varying the size or nature of the substituents on the oxazoline ring, we were able to alter initiator properties. Disubstitution of the oxazoline, as in ligands **9**−**11**, gave no substantial increases in selectivities (Table 1). As seen with initiators derived from these ligands, substitution at the 5 position of the oxazoline had little effect on selectivity (e.g., compare the results from use of ligands **10** and **12**). However, use of ligand **13a**, which contains the bulky *tert*-butyl group on the oxazoline ring, increased k_D/k_L to 5.2(0.1) (Table 1). The additional steric bulk in **13a**, relative to that of **8**, resulted in a dramatic increase in selectivity. It is evident that the selectivity of these initiators is highly sensitive to substitution on the 4 position of the oxazoline ring.

When **13a**Ni(COD) was used to polymerize racemic Glu NCA, a 17% enantiomeric excess of the D-antipode was found in the stereocopolymer formed at 16% conversion. As would be expected by changes in monomer concentrations, the enantiomeric excess of the D-antipode in the copolymer decreased as the polymerization proceeded (Figure 4). It would be desirable to isolate and analyze the copolymer formed at very low conversion (<5%), so that the true asymmetric selectivity of this initiator could be measured when the concentrations of both D- and L-antipodes are equal. However, since these are living polymerizations, only oligomers were produced at low monomer conversions and it was not experimentally feasible to separate these from the residual monomer. Despite this, we have confirmed that the kinetic selectivity for the D-antipode displayed by **13a**Ni(COD) in homopolymerizations was also displayed in polymerizations of the racemate.

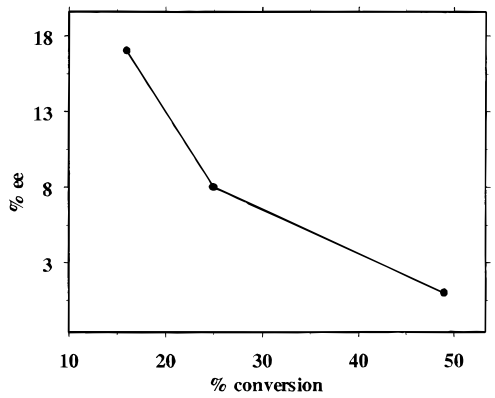


Figure 4. Enantiomeric excess of D-benzylglutamate in the polymer formed from polymerization of racemic Glu NCA as a function of monomer conversion using **13a**Ni(COD) initiator.

Encouraged by the selectivity shown by initiator **13a**Ni(COD), we next synthesized ligands **13b**−**e**, derivatives of **13a** containing substituents on the pyridine ring (Figure 3). It was thought that the additional substituents on **13b**−**d** would add to the steric congestion at the metal, resulting in greater selectivity. Likewise, the methyl in **13e** was expected to interact with the oxazoline ring to limit its possible rotations relative to the pyridine ring. The initiator **13e**Ni(COD) gave a low selectivity relative to **13a**Ni(COD), possibly because the oxazoline was forced to rotate out of a preferred orientation for interaction with the metal center. Surprisingly, the initiators prepared from ligands **13b**−**d** gave selectivities opposite to that of all other (*S*)-configuration initiators, with L-Glu NCA polymerizing faster than D-Glu NCA [k_L/k_D = 2.5(0.1) − 3.3(0.1)]. Uncertainty relating to the exact geometry around the active nickel center (e.g., 4, 5, or 6 coordinate) makes predictions regarding these results highly speculative. However, it can be seen that enantioselectivity is strongly influenced by subtle changes in the ligand environment around the metal. By examining the effects of ligand modifications such as these, we plan to learn more about the nature of the active nickel species so that enantioselectivity can be predictably adjusted.

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Supporting Information Available: Details of polymerizations, kinetic analyses and syntheses for all new ligands (11 pages). See any current masthead page for ordering and Internet access instructions.

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