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Asymmetric Michael addition reactions of chiral Ni(II)-complex of glycine with (*N-trans*-enoyl)oxazolidines: improved reactivity and stereochemical outcome

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Abstract

Application of the (*N-trans*-enoyl)oxazolidines as Michael acceptors in the kinetically controlled additions with a Ni(II)-complex of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **1** was shown to be synthetically advantageous over the alkyl enoylates, allowing for remarkable improvement in reactivity and, in most cases, diastereoselectivity of the reactions. While the stereochemical outcome of the Michael additions of the aliphatic (*N-trans*-enoyl)oxazolidines with complex **1** depended on the steric bulk of the alkyl group on the starting oxazolidines, the diastereoselectivity of the aromatic (*N-trans*-enoyl)oxazolidines reactions was found to be controlled by the electronic properties of the aryl ring. In particular, the additions of complex **1** with (*N*-cinnamoyl)oxazolidines, bearing electron-withdrawing substituents on the phenyl ring, afforded the (2*S*,3*R*)-configured products with synthetically useful selectivity and in quantitative chemical yield, thus allowing an efficient access to sterically constrained β-substituted pyroglutamic acids and related compounds.

Recently, we reported asymmetric Michael addition reactions between a Ni(II)-complex of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **1** and a series of the β-trifluoromethyl substituted alkyl acrylates to afford the corresponding sterically constrained and trifluoromethyl-containing pyroglutamic acids in enantiomerically pure form.[1] The unique physicochemical properties of complex **1** and products of its homologation, as well as the simplicity of the experimental procedure,[2] makes the method synthetically attractive, in particular, for large scale preparations of the target amino acids. Since pyroglutamic acids can be conventionally transformed to a whole variety of amino acids such as prolines,[3] glutamines, and glutamic acids,[4] we were interested in generalizing this methodology to afford the corresponding β-alkyl and β-aryl substituted derivatives, which are extraordinary useful compounds in the de novo design of peptides with rationally modified three-dimensional structure and biological functions.[5] However, our attempts to involve β-alkyl- or β-arylacrylic esters in

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the reaction with complex **1** encountered unexpected problems of low reactivity and poor stereochemical outcome. Apparently, the successful results of the additions between **1** and trifluoromethyl containing acrylates are due to the enhanced electrophilicity and steric demands of these derivatives provided by the trifluoromethyl group.[6] To overcome the problems associated with β-alkyl- and β-arylacrylic esters we searched for other derivatives which would feature higher electrophilicity (issue of reactivity) and *s-trans* conformational homogeneity (issue of diastereoselectivity). Recently we have found that readily available and inexpensive (*N-trans*-enoyl)oxazolidines **2** have the required characteristics of the Michael acceptor allowing the corresponding additions with achiral Ni(II)-complexes of Schiff bases of glycine with *o*-[*N*-α-picolylamino]benzophenone and -acetophenone to proceed with virtually complete diastereoselectivity.[7] In this communication we report the asymmetric version of the reaction, applying Ni(II)-complex **1** as a chiral equivalent of nucleophilic glycine in the additions with various oxazolidines **2** to demonstrate the generality and synthetic efficacy of the method.

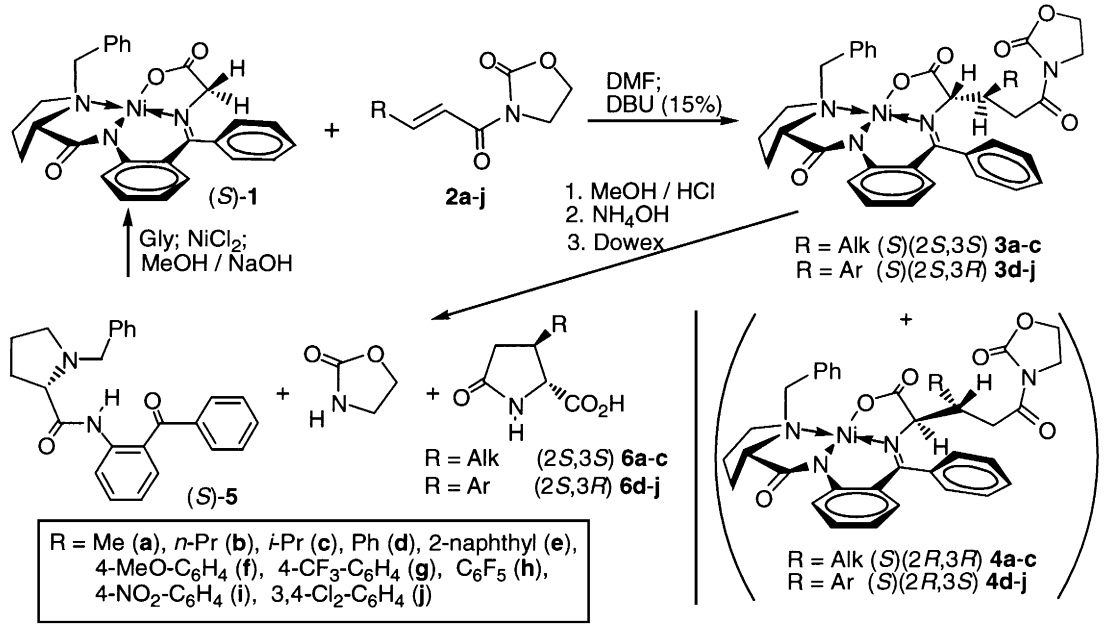
Previously we have shown that the Michael addition reaction between complex **1** and ethyl crotonate, conducted in DMF in the presence of DBU (50 mol%) for 1 h gave rise to a mixture of (2*R*,3*R*)-, (2*S*,3*S*)- and (2*S*,3*R*)-diastereomers in a ratio of 19.0:76.2:4.8, respectively, and in 78% chemical yield. In contrast, *N*-crotonyloxazolidine **2a** (Scheme 1) was found to react with complex **1** in the presence of catalytic amounts of DBU with a substantially higher reaction rate, affording quantitatively a mixture of (2*S*,3*S*)-**3a** and (2*R*,3*R*)-configured products **4a** in a ratio of 71:29, respectively (Scheme 1, Table 1, entry 1). Due to the quantitative chemical yield, this outcome is synthetically superior over the previously reported procedure,[8] as the diastereomerically pure major product (2*S*,3*S*)-**3a** could be isolated in 67% yield simply by crystallizing the resulting mixture from benzene/hexanes. Increasing the steric bulk of the alkyl group on the starting oxazolidine resulted in a reduced reaction rate of the addition of complex **1** with (*N*-hexenoyl)oxazolidine **2b**. However, the major product (2*S*,3*S*)-**3b** was obtained with slightly higher selectivity (entry 2). Having previously failed to conduct the Michael addition between complex **1** and alkyl 4-methylpentanoylate,[9] we were interested in the reaction of **1** with [*N*-(3-*iso*-propylacryloyl)]oxazolidine **2c** to provide access to 3-*iso*-propyl substituted pyroglutamic acid and its

Table 1
The reactions of **1** with **2a**–**j**[a]

entry	2	time (min)	ratio[b] 3[c]	4[c]	yield (%)
1	**a**	15	71	29	98
2	**b**	35	76	24	96
3	**c**	45	85	15	97
4	**d**	15	80	20	98
5	**e**	20	85	15	98
6	**f**	40	82	18	99
7	**g**	5	90	10	98
8	**h**	2	96	4	99
9	**i**	2	88	12	99
10	**j**	2	91	9	98

[a] All reactions conducted in DMF at ambient temperature in the presence of 15% of DBU. Ratio **1**/**2** 1/1. In all reactions complete conversion of the starting materials and no other products than **3** and **4** were observed (by ^{1}H NMR analysis). [b] Ratio of diastereomers determined by ^{1}H NMR analysis of crude reaction mixtures. [c] For absolute configuration see scheme and text.

derivatives, a particularly important sterically constraining unit in peptide design. To our satisfaction, sterically bulky oxazolidine **2c** readily reacted with complex **1** to give quantitatively a mixture of (2*S*,3*S*)-**3c** and (2*R*,3*R*)-diastereomers **4c** with a synthetically meaningful excess of the major product (entry 3). Considering the stereochemical outcome of these reactions one might conclude that oxazolidines **2a–c** feature much higher reactivities than the corresponding alkyl esters and provide better diastereoselectivity in the addition reaction with complex **1**. The absolute configuration of the diastereomeric products[10] suggests virtually complete diastereo-face selectivity on the part of oxazolidines **2a–c**, while the complex **1** (2*S*)/(2*R*)-face selectivity is relatively poor.[3]



Scheme 1.

With these results in hand, we next studied a series of the reactions between complex **1** and oxazolidines **2d–j** which bear aromatic substituents on the C,C double bond. Interestingly, the addition of phenyl-containing oxazolidine **2d** with **1** occurred with the same rate and quantitative yield as the reaction of methyl derivative **2a**, but with higher diastereoselectivity (entry 4). The main product (2*S*,3*R*)-**3d**[10,11] was isolated in 76% chemical yield simply by crystallizing the resultant mixture of diastereomers. The reaction of the more sterically bulky naphthyl-containing oxazolidine **2e** proceeded at a slightly lower rate but with better diastereoselectivity (entry 5). To investigate electronic effects of substituents on the phenyl ring of the starting oxazolidines on the stereochemical outcome of the reactions, we conducted additions of complex **1** with oxazolidines **2f** and **2g**, bearing methoxy and trifluoromethyl groups, respectively. The reaction of **2f** proceeded at a relatively slow rate, as the electron-donating methoxy group decreased the electrophilicity of the C,C double bond, but with a slightly higher stereoselectivity as compared with the results of the addition of the unsubstituted phenyl-containing derivative **2d** (entry 6). In contrast, the addition of trifluoromethyl oxazolidine **2g** occurred almost instantly and with unexpectedly high diastereoselectivity (80% de, entry 7). Drawing inspiration from these results, we conducted the addition between complex **1** and pentafluorophenyl derivative **2h**. The exothermic reaction afforded the major product (2*S*,3*R*)-**3h** with 92% ee. To examine the origin and generality of the unexpectedly high stereoselectivity observed in these additions, and bearing in mind the unique stereocontrolling ability of fluorine atoms,[7] we investigated the reactions of the oxazolidines bearing electron-withdrawing substituents other

than fluorine. To our satisfaction, the exothermic and quantitative additions of complex **1** with the 4-nitro **2i** and 3,4-dichloro derivatives **2j** featured high diastereoselectivity (entries 9 and 10) suggesting that the electron-deficiency of the phenyl ring and not the presence of fluorine atoms is the cause of the observed results. Thus, considering the stereochemical outcome of the reactions in the aromatic series, one can conclude that, as was observed in the aliphatic series, (*N*-β-arylacryloyl)oxazolidines **2d**–**j** featured perfect face-selectivity giving rise to a mixture of (2*S*,3*R*)- and (2*R*,3*S*)-configured diastereomers as a result of incomplete (2*S*)/(2*R*)-face control of the corresponding enolate derived from complex **1**.[3] However, in contrast to the aliphatic series, the stereoselectivity of the reaction of aromatic oxazolidines **2d**–**j** was found to be a function of the substituent on the phenyl ring in **2d**–**j**. Such a pronounced effect of electronic properties of the aromatic ring on the stereochemical outcome of the asymmetric reactions is quite rare and difficult to rationalize at the present stage, in particular, considering that these DBU-catalyzed additions might proceed via unchelated, non-cyclic transition states. However, one might assume that electrostatic repulsive or attractive interactions of the electron-deficient phenyl ring of **2g**–**j** with, respectively, partially positively (Ni cation) or negatively (enolate oxygen, π-stacking effects) charged sites of complex **1** could account for the observed stereochemical outcome. Molecular modelling and calculations of possible transition states, as well as additional series of the reactions, are currently in progress to further evaluate these observations.

The diastereomerically pure addition products **3a**–**j** were readily decomposed to afford the target enantiomerically pure pyroglutamic acids **4a**–**j**, along with the recovered chiral ligand (*S*)-**5** and oxazoline.[12] The former was conventionally transformed to the starting chiral Ni(II)-complex (*S*)-**1**.

In conclusion, application of (*N*-*trans*-enoyl)oxazolidines **2** as Michael acceptors in kinetically controlled additions with Ni(II)-complex **1** allowed for remarkable improvement in reactivity and, in most cases, diastereoselectivity of the reactions. While in the aliphatic series the stereochemical outcome was found to be a function of the steric bulk of the alkyl group on the starting oxazolidines **2**, in the aromatic series electronic properties of substituents on the phenyl ring of **2** were shown to control the diastereomeric ratio of the products, suggesting quite intriguing transition states involved. Synthetically attractive characteristics of the method, such as (i) room temperature reactions, (ii) quantitative chemical yields and (iii) simple work-up and isolation of the target products, should render it a useful alternative to literature methods, in particular for preparing the corresponding aromatic amino acid analogues with electron-withdrawing substituents.

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