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A unique case of face diastereoselectivity in the Michael addition reactions between Ni(II)-complexes of glycine and chiral 3-(*E*-enoyl)-1,3-oxazolidin-2-ones†

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Abstract

The origin of virtually complete face diastereoselectivity in the organic base-catalyzed, room temperature Michael addition reactions between Ni(II)-complexes of Schiff bases of glycine and chiral 3-(*E*-enoyl)-4-substituted-1,3-oxazolidin-2-ones was shown to stem from the unusual mode of steric interactions in determining the corresponding transition state.

Keywords: amino acids; asymmetric synthesis; Michael additions; nickel(II) complex; oxazolidin-2-ones.

Recently, we discovered that chiral 3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **1a** (Fig. 1) in the presence of DBU easily react with Ni(II)-complexes of glycine Schiff bases such as **2a**,**b** and

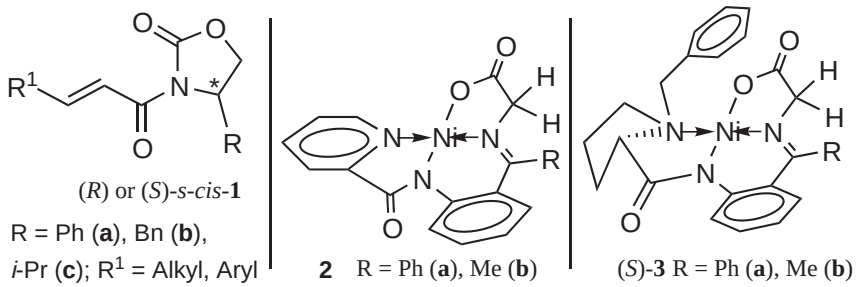

Figure 1.

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† We are particularly pleased and honored to dedicate this paper to Professor Harry Wasserman on the occasion of his 80th birthday! His years of excellence in chemistry, leadership, and wise council have been an inspiration, and we thank him for all his warmth and kindness.

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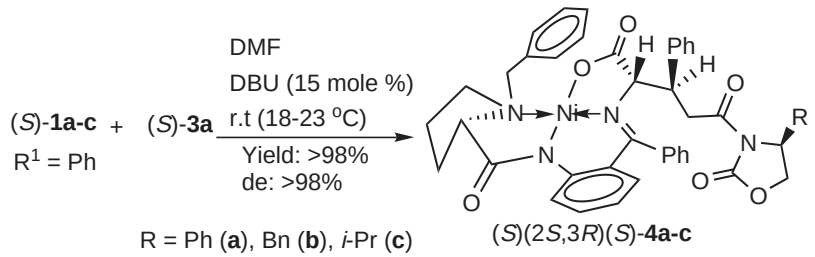
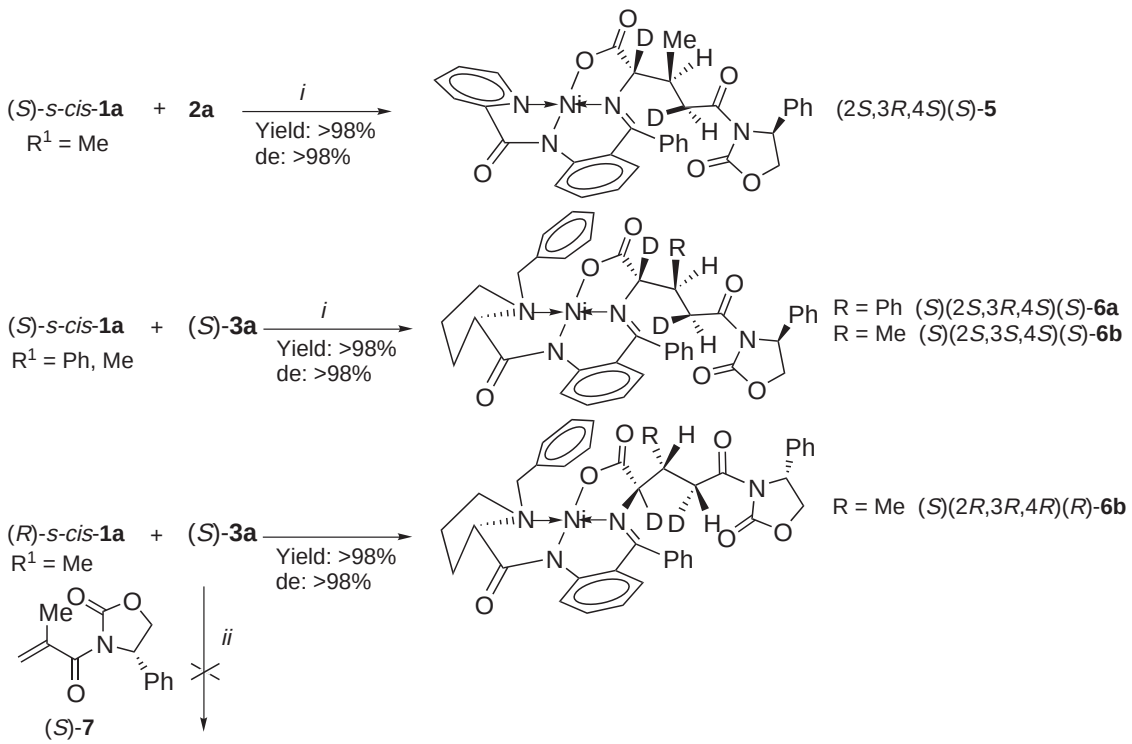
3a,**b** giving rise to single diastereomeric products in quantitative chemical yield.[1] A striking feature of these reactions, as compared with previously reported methods,[2] are that they proceed: (1) at *room temperature*; (2) in the presence of *catalytic amounts of non-chelating organic base*, and (3) afford the corresponding products with *virtually complete diastereoselectivity*. In this communication we report new and unexpected results on the reactions under study which extend their generality and synthetic value, and provide us with a sufficient amount of data to deduce a unique origin of the diastereoselectivity observed.

The most important conclusion one could draw from the previous results is the overwhelming stereocontrolling power of the chiral oxazolidin-2-ones **1a**, which were used as Michael acceptors in our studies.[1c,d] We have demonstrated that the extraordinary high diastereoselectivity of the additions between oxazolidin-2-ones **1a**, and complexes **2a**,**b** and **3a**,**b** (Fig. 1) is not influenced either by the substituent R on the C,C double bond of the oxazolidin-2-ones **1a**, nor by the ketimine substituent R (Me, Ph) of the Ni(II)-complexes **2a**,**b** and **3a**,**b**. Regardless of the electronic or steric nature of these substituents the reactions proceeded with virtually complete diastereoselectivity.[1c,d] Furthermore, in the additions of **1a** with chiral complexes **3a**,**b** the stereocontrolling power of the former was shown to overwhelm completely the stereochemical preferences of **3a**,**b** giving rise to the corresponding products, with the absolute configuration dictated solely by the chirality of oxazolidin-2-ones **1a**.[1c] Our choice of 3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **1a** as Michael acceptors was stimulated by the results we reported several years ago on a general application of 4-phenyl-1,3-oxazolidin-2-one, as a superior chiral auxiliary,[3] and the more recent data reported by Williams et al.[4] who demonstrated that the phenyl-containing 3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **1a** are much more efficient, as compared with the more frequently used 4-benzyl-1,3-oxazolidin-2-one derivatives, in controlling the facial diastereoselectivity in the corresponding conjugate additions of C-nucleophiles. Based on these results we assumed that application of chiral 1,3-oxazolidin-2-ones, other than 4-phenyl derivatives, as Michael acceptors in the additions with glycine complexes **2a**,**b** and **3a**,**b**, would result in a variable stereoselectivity depending on the nature of the substituent at the C-4 stereogenic center of the chiral oxazolidin-2-one. Therefore, we studied the addition reactions between chiral complex **3a** and cinnamic acid-derived chiral oxazolidine-2-ones **1b**,**c** ($R^1 = Ph$) (Fig. 1, Scheme 1) containing benzyl and *i*-propyl groups, respectively, which were conducted under our standard conditions: DMF, 15 mol% DBU, rt. In contrast to our expectations, the reactions proceeded with virtually complete stereoselectivity affording as the sole diastereomeric products **4b**,**c** of (2*S*,3*R*) absolute configuration. The only noticeable effect of the substituents was the reaction rate. The addition of the *i*-propyl-containing **1c** was completed in 80 min, while the reaction of the benzyl derivative **1b** was markedly faster (40 min).



Scheme 1.

However, both reactions were substantially slower than the 18 min required for the addition of the phenyl derivative **1a** with complex **3a**. This could be reasonably accounted for by considering the steric bulk and electronic effects of the substituents (Ph, Bn, *i*-Pr) on the electrophilicity of the C,C double bond in **1a**–**c**. Two conclusions can be drawn from these results. First, the method becomes more general since in principal any commercially available C-4 substituted oxazolidin-2-one can be used as a chiral auxiliary to provide virtually complete stereochemical control in Michael addition reactions. Second, the substituent at C-4 in **1a**–**c** does not directly control the face diastereoselectivity of the C,C double bond,[5] but plays the role of a topographical feature controlling the access to one or the other side of the whole molecule depending on the substituent's position, up or down, relative to the plane of **1a**–**c**. If this conclusion is correct, one could expect high levels of stereoselectivity in γ-protonation/deuteration of the corresponding intermediate adducts. To check this out, we conducted reactions of achiral **2a** and chiral **3a** glycine complexes with (*S*)- and (*R*)-configured crotonyl and cinnamyl derived 4-phenyl-1,3-oxazolidin-2-ones **1a** in the presence of *i*-PrOD using our standard conditions (Fig. 1, Scheme 2). The results exceeded our expectations; in all reactions studied we isolated as the sole reaction products **5** and **6** with virtually complete stereoselectivity at the newly formed γ-stereogenic center of the glutamic acid residue.[7] These results offer a unique opportunity for preparing stereochemically defined, selectively γ-isotopically labeled glutamic/pyroglutamic acids, compounds of critical importance in biological/enzymatic studies. Another synthetic opportunity one could envision would be highly diastereoselective synthesis of 4-substituted glutamic/pyroglutamic acids. To this end, we prepared 3-methacryloyl-4-phenyl-1,3-oxazolidin-2-one **7** and



Scheme 2. Key: (i) DMF/*i*-PrOD; DBU (15 mol%); rt (18–23°C). (ii) DMF; DBU (15 mol%); rt (18–23%)

studied its reaction with the chiral **3a** glycine complex. Previously we demonstrated that the addition between crotonyl derived chiral oxazolidin-2-one **1a** ($R^1 = Me$) and glycine complex **3a**, under our standard reaction conditions (DMF, 15 mol% DBU, rt), proceeded at a very high reaction rate (5 min) furnishing a single diastereomeric product in quantitative chemical yield.[1c] In sharp contrast, the addition of methacryloyl-derived oxazolidin-2-one **7** with complex **3a**, conducted under the same reaction conditions, did not proceed at all. The dramatic affect of the methyl's position on the C,C double bond of the starting Michael acceptor (α-Me versus β-Me) on the reactivity in the additions with complex **3a** was totally unexpected. The same outcome, no reaction, was obtained in the additions of achiral complexes **2a**,**b** with oxazolidin-2-one **7**. While these results were synthetically disappointing they gave us an important insight into the mechanism of the reactions. These data show that the transition state involved in the additions of crotonyl derived chiral oxazolidin-2-one **1a** ($R^1 = Me$) and glycine complexes **2** and **3** cannot be attained in the case of methacryloyl derived oxazolidin-2-one **7** additions.

Three possible transition states **A**, **B** and **C** (Fig. 2), with the approach geometry *like*, can be constructed to fit the observed stereochemical outcome of the addition reactions. Considering these three, one finds that only transition state (TS) **C** can account for the all the synthetic details we encountered in this study. First of all in the TS **C** the Michael acceptor's carbonyl and the enolate oxygen are in close proximity to each other so the reaction can occur with the required minimum charge separation, that cannot be realized in the TS **A** and **B**. Second, considering steric non-bonding interactions, the TS **C** might be regarded as more favorable as compared with **A** and **B** in which the oxazolidinone molecule experiences severe non-bonding steric repulsive interactions with the Ni-complex (TS **B**). Next, the TS **C** also accounts for the unusually high diastereoselectivity of the deuteration at the gamma position of the glutamic acid residue. In the TS **C** one face of the Michael acceptor molecule, and thus the corresponding intermediate adduct, is completely blocked by the Ni-complex plane leaving the opposite face as the only way for deuteration. The striking difference in the reactivity between β- and α-substituted oxazolidin-2-ones **1a** and **7** can also be easily accounted for considering the TS **C**. In the case where the R^1 group is methyl, it points directly into the Ni atom and thus, the TS **C** could not be realized. The central question of this study, the stereocontrolling role of the C-4 substituent of the chiral oxazolidinone ring can be fully rationalized using TS **C**. In the TS C, which represents the interaction between chiral/achiral Ni(II)-complex and (*R*)-configured Michael acceptors, the substituent R^2 at C-4 of the chiral oxazolidinone ring is pointing up, away from any possible steric interactions with the rest of substituents on both the Ni(II)-complex and the Michael acceptor. In this position the substituent R^2 does not control directly the facial diastereoselectivity of the Michael acceptor's C,C double bond via a stereodiscrimination

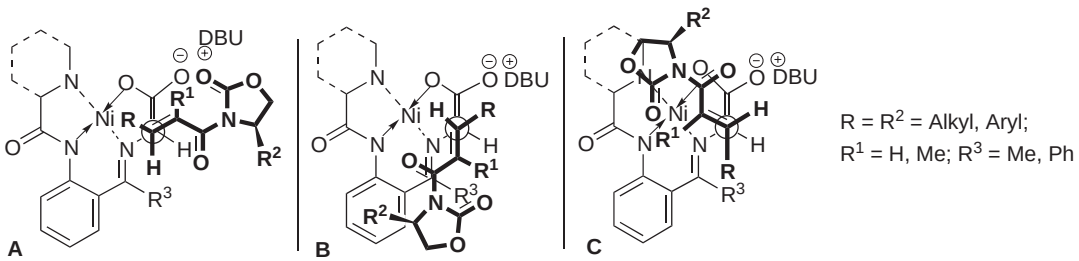


Figure 2.

process but, as mentioned above, works as a topographical feature, making a difference in accessibility of the Michael acceptor plane sides by the plane of the Ni(II)-complex. Thus, in the case when the Michael acceptor is of opposite (*S*)-configuration, the TS **C** cannot be formed, as the phenyl pointed down will interfere with the approaching Ni(II)-complex plane. Instead, the (*S*)-configured Michael acceptor will allow the Ni-complex to approach the opposite Michael acceptor's side to form a similar TS leading to the products with (2*S*,3*S*) (R = *n*-alkyl) absolute configuration.

In summary, our results demonstrate that the mode of controlling face diastereoselectivity, realized in the reactions under study, is a much more powerful way to achieve stereocontrol in asymmetric reactions, as compared with the usual stereo-discrimination process involving interactions between a stereocontrolling element with other substituents on the reacting molecules. For instance, an obvious advantage, as evident from the present study, is the virtually complete stereochemical outcome, and the extraordinary generality of the reactions as a result of the fact that neither the steric nor electronic nature of the substituent R^3 on the starting Ni(II)-complex, or substituents R and R^2 on the Michael acceptor, are involved in determining the stereochemical fate of the reaction. In this regard, it is interesting that the exceptional stereoselectivities of enzymes, receptors and other biological acceptors also utilize this mode of stereocontrol!

Acknowledgements

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5. Recently an Italian group studied the addition reactions between chiral 4-benzyl- or -isopropyl-containing 3-(*E*-enoyl)-1,3-oxazolidin-2-ones and various N-nucleophiles in the presence of *sym*-collidine at room temperature (see Ref. 6), conditions which are very similar to those used in our Michael additions. Their results clearly demonstrated that the substituent, Bn or isopropyl, on the chiral oxazolidin-2-ones, does not control the face diastereoselectivity of the corresponding additions.
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7. Apart from chemically and stereochemically complete deuteration in the γ-position, over 80% deuteration in the α-position was also observed; see Scheme 2.