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Efficient Stereoselective Syntheses of Cyclic Amino Acids via Michael-Induced Ring-Closing Reactions†

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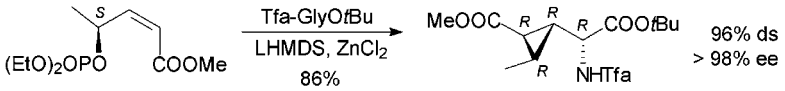
ABSTRACT



Zn-chelated glycine ester enolates are highly efficient nucleophiles for the synthesis of *trans*-methoxycarbonylcyclopropyl- and cyclobutylglycines by domino sequences of Michael additions and subsequent ring closures. They react to give the anti isomers with high yields and excellent diastereoselectivities.

Cyclic amino acids such as carboxycyclopropylglycines have attracted interest due to their remarkable biological activity. They can be regarded as conformationally fixed analogues of the natural amino acid glutamate. It has been shown that these amino acids can interact very strongly and selectively with the metabotropic glutamate receptors in the mammalian central nervous systems.[1] Therefore, the interest in the stereoselective synthesis has increased considerably in recent years. Besides approaches to introduce the amino acid functionality via Strecker reaction,[2] several routes have been developed to construct the cyclopropyl unit, e.g., by metal-catalyzed cyclopropanations or carbene addition reactions.[1a,3] Joucla et al. were the first to report an approach based on the MIRC (Michael-induced ring closure) concept[4] to the desired cyclopropylic compounds by using lithium enolates of O'Donnell's phenylimino glycine esters[5] as nucleophiles.[6] These glycine synthons react with a wide range of acceptor-substituted unsaturated systems such as nitro compounds, sulfones, and esters.[7] Besides the imines, the Schöllkopf bislactime ethers can be used for an asymmetric approach of that kind.[8] Kanemasa et al. used enolates of sarcosine esters and amides and observed selective anti or syn product formation, depending on the protecting groups used.[9] An efficient synthesis of the syn product was also described by using enolates of *N*,*N*-dibenzylglycinate.[10] The ring-enlarged cyclobutyl analogues can be obtained via an anti-selective [2 + 2] cycloaddition.[11]

In our group, metal-chelated glycine ester enolates play a dominant role in the stereoselective synthesis of α-amino

† Dedicated to prof. M. T. Reetz on the occasion of his 60th birthday.

(1) (a) Shimamoto, K.; Ohfune, Y. *J. Med. Chem.* **1996**, *39*, 407 and refs cited herein. (b) Shimamoto, K.; Ohfune, Y. *Synlett* **1993**, 919. (c) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Wright, R. A.; Johnson, B. G.; Schoepp, D. D. *J. Med. Chem.* **1998**, *41*, 346. (d) Pellicciari, R.; Costantino, G. *Curr. Opin. Chem. Biol.* **1999**, *3*, 433.

(2) (a) Landor, S. R.; Landor, P. D.; Kalli, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2921. (b) Pajouhesh, H.; Chen, J.; Pajouhesh, S. H. *Tetrahedron: Asymmetry* **2000**, *11*, 4537.

(3) (a) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chanda, R. J. *J. Org. Chem.* **1988**, *53*, 1947. (b) Pellicciari, R.; Natalini, B.; Marinozzi, M.; Monahan, J. B.; Snyder, J. P. *Tetrahedron Lett.* **1990**, *31*, 139. (c) El Abdioui, K.; Martinez, J.; Viallefont, P.; Vidal, Y. *Bull. Soc. Chim. Belg.* **1997**, *106*, 425. (d) Rifé, J.; Ortuño, R. M.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 8958. (e) Godula, K.; Donaldson, W. A. *Tetrahedron Lett.* **2001**, *42*, 153. (f) Mohapatra, D. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1851. (g) Pajouhesh, H.; Curry, K.; Pajouhesh, H.; Meresht, M. H.; Patrick, B. *Tetrahedron: Asymmetry* **2003**, *14*, 593.

(4) (a) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609. (b) Prempree, P.; Radviroongit, S.; Thebtaranonth, Y. *J. Org. Chem.* **1983**, *48*, 3553.

(5) Review: M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3.

(6) Joucla, M.; El Goumzili, M.; Fouchet, B. *Tetrahedron Lett.* **1986**, *27*, 1677.

(7) Zindel, J.; de Meijere, A. *Synthesis*, **1994**, 190.

(8) Mazón, A.; Pedregal, C.; Prowse, W. *Tetrahedron*, **1999**, *55*, 7057.

(9) (a) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411. (b) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875. (c) Kanemasa, S.; Nomura, M.; Taguchi, Y. *Chem. Lett.* **1992**, 1801.

(10) Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377.

(11) Tsujishima, H.; Nakatani, K.; Shimamoto, K.; Shigeri, Y.; Yumoto, N.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 1193.

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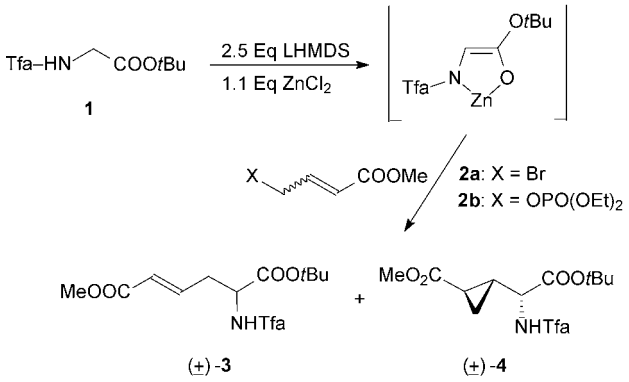
acids.[12] Therefore, we wanted to apply these nucleophiles also to domino reactions such as conjugate additions and subsequent cyclizations.

Due to very promising results in the field of the palladium-catalyzed allylic alkylations,[13] we used the chelated zinc enolate of trifluoroacetyl (Tfa)-protected glycine ester **1** as a nucleophile and commercially available methyl 4-bromo-but-2(*E*)-enoate **2a** as a first acceptor (Scheme 1). The

Scheme 1. Reactions of Chelated Enolates with Functionalized Michael Acceptors

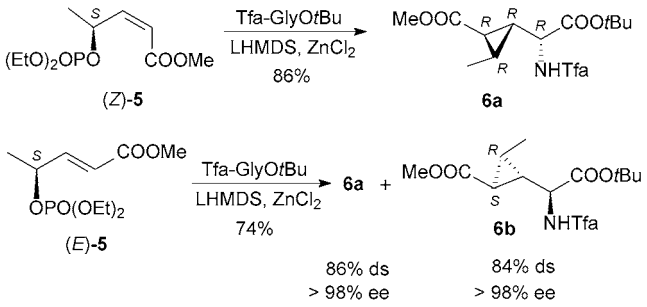


acceptor	yield [%] 3	4	ds *anti:syn*
(*E*)-**2a**	16	36	92: 8
(*E*)-**2b**	–	59	79:21
(*Z*)-**2b**	–	82	>99:<1

reaction gave a mixture of the desired cyclopropyl products **4**, with an exclusive trans orientation of the substituents at the cyclopropyl ring, and the direct substitution product **3** in a 7:3 ratio. To avoid the direct substitution, we switched to a weaker leaving group X, which should react not with the glycine enolate directly but hopefully with the ester enolate formed in the Michael addition. And indeed, with phosphate **2b**, we could observe only the cyclopropyl products in 59% yield, but the α,*β*-diastereoselectivity was lower (anti:syn = 79:21) than before. In palladium-catalyzed allylic alkylations, the diastereoselectivities were raised significantly when (*Z*)-configured substrates were used instead of the (*E*)-isomers. A similar effect was also observed here. In the reaction of (*Z*)-**2b**, only one diastereomer was obtained (GC analysis), which was identical to the major isomer in the previous reactions.

After cleavage of the *t*-butyl ester moiety by treatment with trifluoroacetic acid, we could obtain crystals for X-ray structure analysis. The X-ray structure showed the trans substitution pattern at the three-membered ring and the anti configuration of the amino acid center relative to the neighboring carbon atom. With respect to the synthesis of optically active amino acids, we were interested in substrate **5** with an additional methyl group at the allylic position (Scheme 2).

Scheme 2. Syntheses of Cyclopropyl Amino Acids



The (*S*)-enantiomer of this chiral molecule could be obtained very easily by an enzymatic kinetic resolution[14] of the corresponding propargylic alcohol and subsequent Lindlar hydrogenation.[15] Michael addition of the chelated enolate to (*Z*)-**5** also gave the anti isomer exclusively, with the methyl group cis to the carboxy group (cis:trans = 96:4 in the crude product) in 86% yield and with complete retention of configuration.[16] In this case, four stereogenic centers were controlled and directed by only one in the allylic substrate. The relative stereochemical assignment was confirmed by the X-ray structure of **6a** (Figure 1).

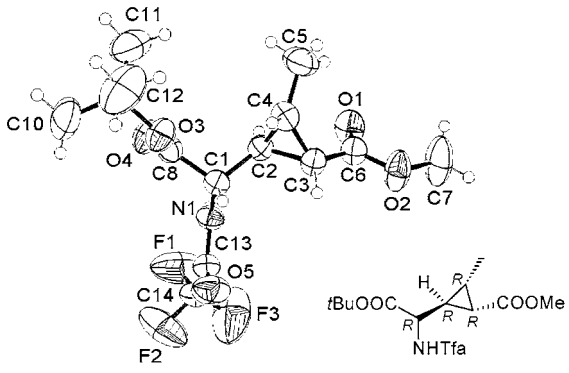


Figure 1. ORTEP plots of **6a**.

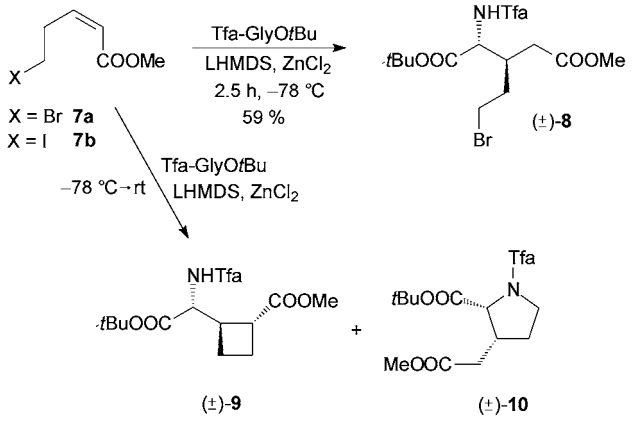
Interestingly, when the same experiment was carried out with (*E*)-**5**, we obtained four diastereomers in 74% overall

(12) Kazmaier, U. *Liebigs Ann./Recueil* **1997**, 285 and references therein.
(13) (a) Kazmaier, U.; Zumpe, F. L. *Angew. Chem.* **1999**, *111*, 1572. Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468. (b) Kazmaier, U.; Zumpe, F. L. *Angew. Chem.* **2000**, *112*, 805. Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802. (c) Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, 4067.
(14) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
(15) Analytical sample of the remaining alcohol in the enzymatic reaction was transferred to (+)-*β* Angelicalacton. Comparison with a sample that had been synthesized from (*S*)-lactic acid using Still's (*Z*)-selective olefination protocol (see: Still, W. C.; Gennari C. *Tetrahedron Lett.* **1996**, *37*, 8989) showed that both enantiomers were identical to each other.
(16) Cis/trans isomers can be separated by chromatography.

yield. Now, the main isomer in this reaction was not identical to the main product of the previous reaction. The diastereomers **6b** with the methyl group trans to the carboxy group were created preferably (trans:cis = 81:19). In this case, **6a** and **6b** showed almost the same ratio of anti:syn isomers (86:14 and 84:16, respectively). The assignment of the isomers was supported by NMR examinations. For **6b**, we could observe strong NOE contact between the methyl group and the amino acid C−H group, which could not be observed for **6a**.

To prove the generality of this domino reaction, we synthesized the corresponding (*Z*)-substrates **7** with leaving groups in homoallylic position. For these molecules, two different pathways concerning the second reaction are possible: either C-alkylation leading to a four-membered ring **9** or N-alkylation to give a five-membered ring **10** (Scheme 3).

Scheme 3. Reactions of Chelated Enolates with Homologated Michael Acceptors



For the brominated substrate **7a**, we could isolate the Michael product **8a** (only one diastereomer detectable) in 59% yield by quenching the reaction after 2.5 h at −78 °C. When the reaction mixture was allowed to warm to room-temperature overnight, we could obtain the cyclized products in excellent yield. Cyclobutane **9** was formed preferentially (52%) besides proline derivative **10** (39%). For both molecules, only one diastereomer could be detected by GC analysis. By using iodide as leaving group (**7b**), the yield of **9** could be increased to 78% and only 12% of **10** was obtained. X-ray structure analysis of **9** (Figure 2) again confirmed the relative configuration to be anti, trans.

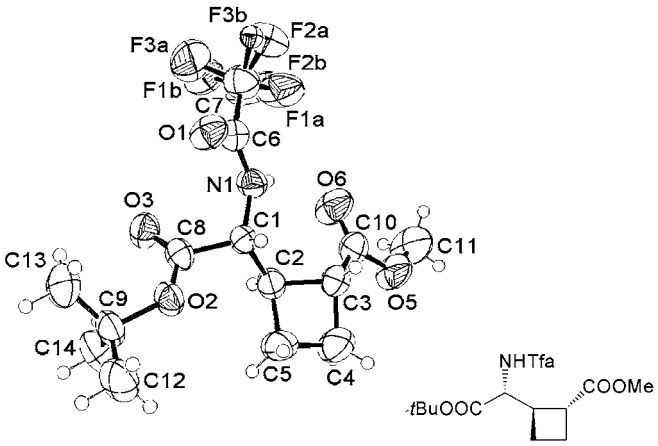


Figure 2. ORTEP plots of **9**.

In conclusion, we have shown that chelated amino acid ester enolates are versatile nucleophiles for stereoselective Michael additions. Subsequent cyclizations provide interesting constrained amino acids in high yield and excellent stereoselectivity. Up to four stereogenic centers can be created in one step.

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Supporting Information Available: Experimental procedures as well as analytical and spectroscopic data of all described compounds and XRAY data of **6** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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