Stereoselective Formation of (*E*)-β-Alkoxy Acrylates from Fischer Carbene Complexes and Chelated Amino Acid Ester Enolates

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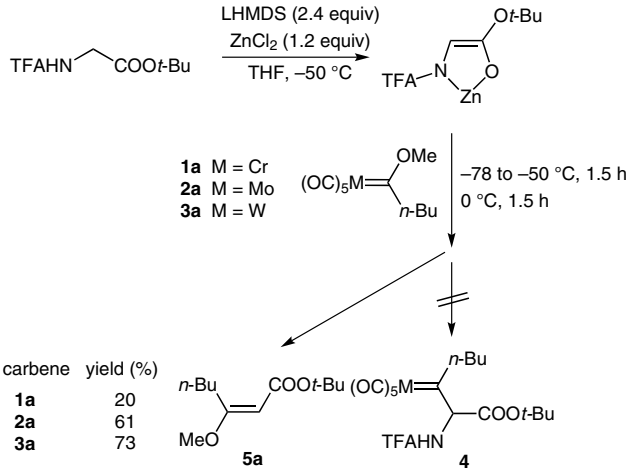
Abstract: Chelated amino acid ester enolates react with alkyl Fischer carbene complexes via nucleophilic attack on the electrophilic carbene center. Subsequent elimination of the metal fragment and trifluoroacetamide results in the formation of β-alkoxy-α,β-unsaturated esters in a highly *E*-stereoselective fashion.

Key words: acrylates, amino acids, carbene complexes, enolates, Fischer carbenes, α,β-unsaturated esters

Since their first description by Fischer and Maasböl in 1964,[1] Fischer carbene complexes developed to very powerful tools in organic synthesis.[2] In general, group 6 metals are incorporated into Fischer carbenes, while chromium is the most popular metal with the most applications. But also the chemistry of the analogous molybdenum and tungsten complexes is rich and complex. While alkenyl- and alkynyl carbene complexes are excellent substrates for cycloadditions, alkyl carbene complexes are isolobal analogues of Lewis acid complexed esters.[2] Nucleophilic attack on the carbene carbon results in an exchange of the alkoxy group and the formation of modified carbene complexes, and on deprotonation, the carbene complexes form enolates which can be reacted with a wide range of electrophiles.[2]

Since a couple of years, our group is involved in the development of synthetic protocols towards new amino acids based on reactions of chelated amino acid ester enolates.[3] These enolates show a higher thermal stability compared to unchelated enolates, and in addition chelate formation causes high selectivities in a wide range of reactions.[4] Especially good results are obtained with trifluoroacetylated (TFA) *tert*-butyl glycinate, which is an almost perfect nucleophile for transition-metal-catalyzed allylic alkylations,[5] Michael additions,[6] and Michael addition induced ring closures (MIRC).[7] Very recently, we also reported the 1,4-addition of chelated enolates towards alkynyl carbene complexes, resulting in the formations of substituted pyrroles.[8]

Therefore, we were interested to see if these enolates are also suitable nucleophiles for 1,2-additions towards alkyl carbene complexes **1**–**3** (Scheme 1), giving rise to amino acids with a carbene complex in the side chain **4**. We started our investigations with the butyl-substituted chromium carbene **1a**.[9] Interestingly, not the expected metalated amino acid **4** was obtained, but a mixture of various compounds, including the β-methoxylated α,β-unsaturated ester **5a**. Attempts to improve the purity and yield of this product by variation of the N-protecting group (Boc or Cbz) or the chelating metal salt [ClTi(O*i*-Pr)$_3$] failed, while an exchange of the carbene metal brought the desired success. With the molybdenum complex **2a** ester **5a** was obtained in 61% yield as a single stereoisomer. Only the formation of the *E*-configured product could be observed. With the tungsten complex **3a** the yield could be improved further.



Scheme 1 Reactions of chelated enolates with Fischer carbene complexes

Although these results were not expected, it should be mentioned that such a reaction behavior of Fischer carbene complexes is not unprecedented. Similar compounds **5** have been obtained previously in reactions of Fischer carbenes with stabilized ester enolates bearing electron-withdrawing groups, which can also act as leaving group. Sierra et al. investigated the reaction of chromium carbenes with ester-substituted sulfur ylides.[10] While under thermal conditions *E*/*Z* selectivities of around 1:1 were obtained, on irradiation the selectivity for the *E*-isomer could be increased to about 4:1 to 5:1. Concellon and Bernard obtained high yields (up to 95%) of 1:1 *E*/*Z* mixtures in reactions of α-bromo esters with aryl-substituted chromium carbenes, but this protocol seems to be limited to aryl- and heteroaryl-substituted carbenes.[11] Last, but not least, Barluenga et al. reported an interesting coupling of

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chromium carbene complex **1a** with diazoacetates in the presence of copper salts. They could show that under their conditions copper carbene complexes are formed in situ, but also these gave 1:1 *E*/*Z* mixtures.[12]

Therefore, the selective formation of the *E*-isomer forced us to investigate the scope and limitations of this reaction. Based on our experience made in the initial experiments, we focused on the corresponding tungsten complexes **3** and varied the substituent on the carbene carbon and also on the oxygen. While the TFA protecting group seems to be essential for the success of the reaction we varied the ester functionality of the amino acid (Table 1). Both modifications, the variation of the O-substituent and of the ester, had no significant influence neither on the yield nor the stereoselectivity. With all alkyl-substituted carbene complexes the *E*-configured product was formed exclusively in yields between 63% and 71%, independent of the chain length of the alkyl substituent. With phenyl-substituted carbenes **3d** and **3f** slightly higher yields could be obtained, but in this case always *E*/*Z* mixtures (1:1 to 2:1) were formed, comparable to the other ester enolates investigated before.[10–12]

To determine the configuration of the double bond generated, we subjected the β-methylated ester **7b** to saponification. The free carboxylic acid obtained gave crystals suitable for X-ray structure analysis (Figure 1), which clearly shows the formation of the *E*-isomer.

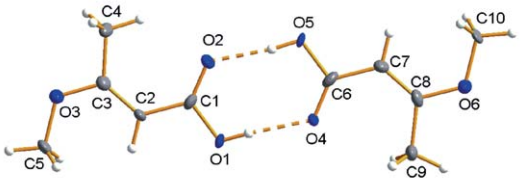
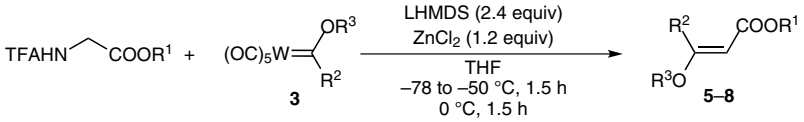


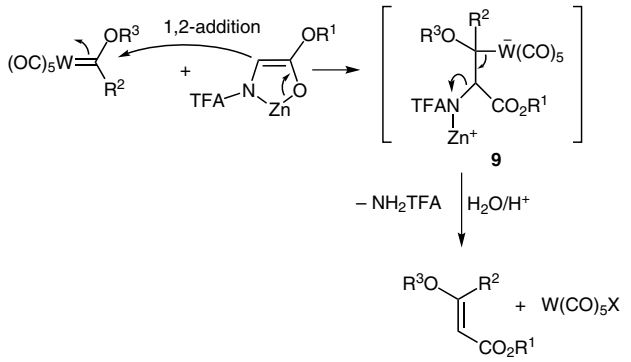
Figure 1 X-ray structure of (*E*)-3-methoxybut-2-enoic acid

To explain the outcome of this reaction, we assume that the formation of the β-alkoxylated α,β-unsaturated ester is initially triggered by an 1,2-addition of the chelated enolate onto the electrophilic carbon of the carbene complex. This results in the formation of a zwitterionic intermediate **9**[13] which undergoes a Wittig-like process, resulting in the elimination of the trifluoroacetamide (Scheme 2).[10]

Table 1 Syntheses of Unsaturated Ester **5–8**



Entry	**3**	R^1	R^2	R^3	Product **5–8**	Yield (%)	*E*/*Z*
1	**3a**	*t*-Bu	*n*-Bu	Me	**5a**	73	*E*
2	**3b**	*t*-Bu	Me	Me	**5b**	67	*E*
3	**3c**	*t*-Bu	Et	Me	**5c**	69	*E*
4	**3d**	*t*-Bu	Ph	Me	**5d**	67	2.3:1
5	**3e**	*t*-Bu	Me	Et	**5e**	65	*E*
6	**3f**	*t*-Bu	Ph	Et	**5f**	69	1.5:1
7	**3a**	Me	*n*-Bu	Me	**6a**	65	*E*
8	**3b**	Me	Me	Me	**6b**	64	*E*
9	**3c**	Me	Et	Me	**6c**	67	*E*
10	**3d**	Me	Ph	Me	**6d**	77	1.3.1
11	**3a**	Bn	*n*-Bu	Me	**7a**	63	*E*
12	**3b**	Bn	Me	Me	**7b**	71	*E*
13	**3c**	Bn	Et	Me	**7c**	71	*E*
14	**3d**	Bn	Ph	Me	**7d**	74	1.1:1
15	**3e**	Bn	Me	Et	**7e**	63	*E*
16	**3f**	Bn	Ph	Et	**7f**	64	2.1:1
17	**3b**	2-butenyl	Me	Me	**8b**	66	*E*
18	**3d**	2-butenyl	Ph	Me	**8d**	66	1.5:1



Scheme 2 Proposed reaction mechanism

This would also explain why this reaction works only well with the strong electron-withdrawing TFA group (relatively good leaving group), but not with other standard N-protecting groups such as carbamates. It should be mentioned that although we investigated a wide range of reactions of the TFA-protected glycine esters so far,[3–7] this is the very first time that we observed a cleavage of the amino acids C-N bond, with the trifluoroacetamides acting as a leaving group. When the reaction is quenched with D_2O, no deuterium incorporation into the product is found. This observation also supports the mechanism proposed.

In conclusion, we developed a straightforward protocol for the stereoselective synthesis of (*E*)-β-alkoxy-α,β-unsaturated esters based on the nucleophilic attack of chelated ester enolates on Fischer carbene complexes.[14] The reactions work well with alkyl- and aryl-substituted carbenes, but only with the alkyl derivatives the *E*-isomers were formed exclusively. Synthetic applications and mechanistic aspects are currently under investigation.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Preparation of (*E*)-*tert*-Butyl 3-Methoxyhept-2-enoate (5a)**
To a solution of trifluoroacetylated (TFA) *tert*-butyl glycinate (75 mg, 0.33 mmol) and $ZnCl_2$ (54 mg, 0.39 mmol) in THF was added LHMDS (1 M, 0.79 mL, 0.79 mmol) dropwise at –78 °C and the reaction mixture was stirred for 30 minutes at the same temperature. Then the Zn-chelated enolate formed was added dropwise to a solution of methoxybutyl carbene complex **3a** (140 mg, 0.33 mmol) in THF at –78 °C. The reaction mixture was stirred for 1.5 h while the temperature rose to –50 °C. Stirring was continued for another 1.5 h at 0 °C to complete the reaction, before it was quenched with distilled water. The organic phase was extracted with EtOAc, dried over anhydrous Na_2SO_4, and was evaporated in vacuo. The crude product was purified by column chromatography (PE) affording the title compound **5a** (51.4 mg, 0.24 mmol, 73%) as a colorless liquid. [TLC: R_f(**5a**) = 0.8 (PE)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, $^3J_{9,8}$ = 7.2 Hz, 3 H, 9-H), 1.29–1.38 (m, 2 H, 8-H), 1.46 (s, 9 H, 1-H), 1.48–1.54 (m, 2 H, 7-H), 2.69 (t, $^3J_{6,7}$ = 7.6 Hz, 2 H, 6-H), 3.58 (s, 3 H, 10-H), 4.89 (s, 1 H, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (q, C-9), 22.5 (t, C-8), 28.3 (q, C-1), 29.6 (t, C-7), 31.5 (t, C-6), 55.1 (q, C-10), 79.0 (s, C-2), 92.2 (d, C-4), 167.1 (s, C-3), 175.5 (s, C-5). GC–MS (EI): *m/z* (%) = 214 (2) [M], 158 (24) [M – 56], 141 (44) [M – 73], 116 (100) [M – 98].