Acyclic Stereoselection in the Michael Addition of Ketone Enolates to Metalloenoates

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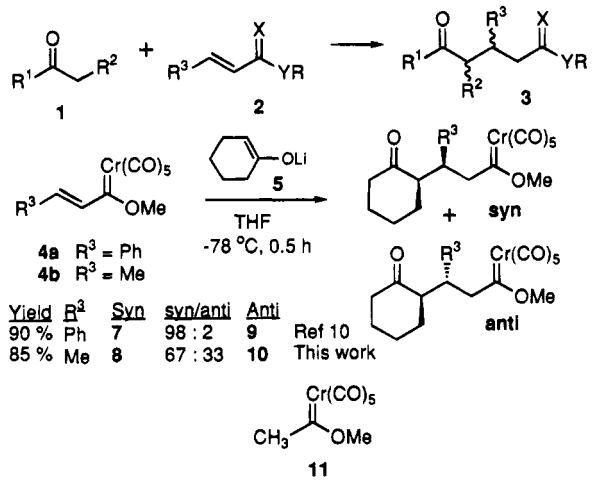
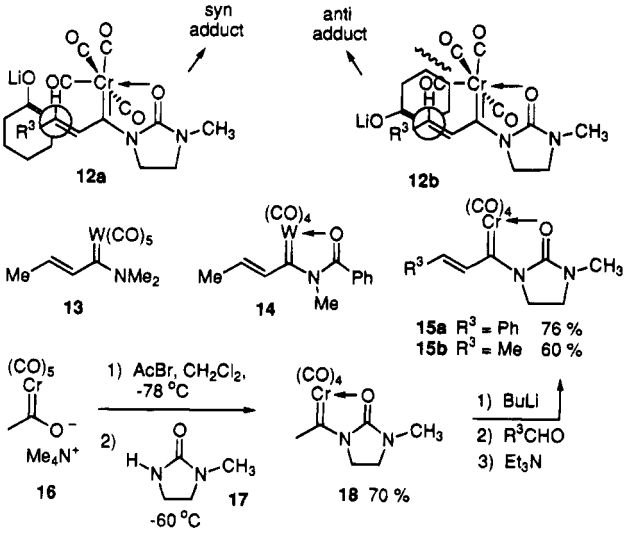
Summary: A new class of α,β-unsaturated Fischer carbene complexes in which the heteroatom stabilizing group of the carbene carbon is an imidazolidinone nitrogen have been evaluated as Michael acceptors and have been found to be nearly as reactive as their alkoxy-stabilized counterparts but provide for much greater facial selectivity in their reactions with ketone enolates.

As a synthetic tactic the Michael reaction has been highly developed and can be implemented with a variety of nucleophiles for additions to any number of acceptors.[1] For reasons of energetics, one variation that is not often encountered is the addition of ketone enolates to α,β-unsaturated esters (enoates). Solutions that have emerged rely on either the activation of the ketone enolate, usually in the form of a hydrazone,[2] or the activation (with and without Lewis acids) of the acceptor by functional modifications of the ester carbon that maintain the ester oxidation state (structure **2**, Scheme 1). Examples of the latter include thioamides,[3] activated thioesters,[4] dithionium ions,[5] activated oxazolines,[6] and activated acyloxazolidinones.[7] For all of these methods in which the diastereoselection has been examined the major product **3** has been found to be the anti-diastereomer. α,β-Unsaturated Fischer carbene complexes can functionally be considered as metalloenoates of the type **2**. It was first recognized 17 years ago by Casey and Brunsvold that these complexes are potent Michael acceptors,[8] a fact which was foreshadowed by a report from the same laboratory that the metalloacetate derivative **11** is an extraordinarily strong carbon acid ($pK_a = 8$).[9] Recently, it has been found that the additions of ketone enolates to certain α,β-unsaturated methoxylcarbene complexes of the type **4** (R^3 = aryl) occur with high syn-selectivity.[10] We report our initial results on the development of O-chelated imidazolidinone carbene complexes of the type **15** as Michael acceptors with enhanced syn-diastereoselection.[11]

Scheme 1



Scheme 2



Whereas it has been reported that the reaction of cyclohexanone enolate and complex **4a** bearing a β-phenyl group occurs with high syn-selectivity (49:1),[10] we have found that the corresponding reaction of the *trans*-crotyl complex **4b** occurs with ineffectual levels of stereoselection (2:1). In pursuing solutions to this limitation, we were led to the development of imidazolidinone carbene complexes of the type **15** (Scheme 2). The Michael additions to the alkoxy complex **4a** were proposed to occur via an s-trans conformation of the carbene complex.[10] In contrast to this are the Diels–Alder reactions of N-heteroatom-stablized carbene complexes (such as **14**) which have been proposed to occur via an s-cis conforma-

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(1) For reviews on the Michael reaction, see: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 87. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol 4. (d) *Conjugate Addition Reactions in Organic Synthesis*; Perlmutter, P., Ed.; Pergamon Press: New York, 1992.

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(3) Tamaru, Y.; Harada, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1979**, *101*, 1316.

(4) Kobayashi, S.; Tamura, M.; Mukaiyama, T. *Chem. Lett.* **1988**, 91.

(5) (a) Hashimoto, Y.; Mukaiyama, T. *Chem. Lett.* **1986**, 1623. (b) Hashimoto, Y.; Sugmi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1691. (c) Hashimoto, Y.; Sugmi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1695.

(6) Michelon, F.; Pouilhes, A.; Van Bac, N.; Langlois, N. *Tetrahedron Lett.* **1992**, *33*, 1743.

(7) Corey, E. J.; Houpis, I. N. *Tetrahedron Lett.* **1993**, *34*, 2421.

(8) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391.

(9) Casey, C. P.; Anderson, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 1230.

(10) Nakamura, E.; Tanaka, K.; Fujimura, T.; Aoki, S.; Williard, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 9015.

(11) For Michael additions of the enolate of carbene complexes, see: Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602 and references cited therein.

(12) The synthesis, characterization, and structures of imidazolidinone carbene complexes will be published separately: Wulff, W. D.; Powers, T. S.; Shi, Y. Unpublished results.

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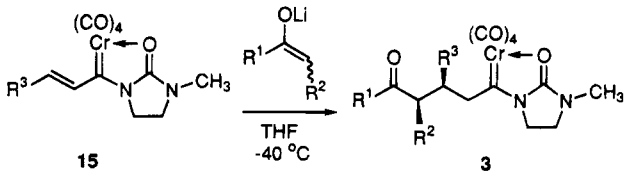
Table 1. Michael Addition of Ketone Enolates to Metalloenoate 15[a]



15 3

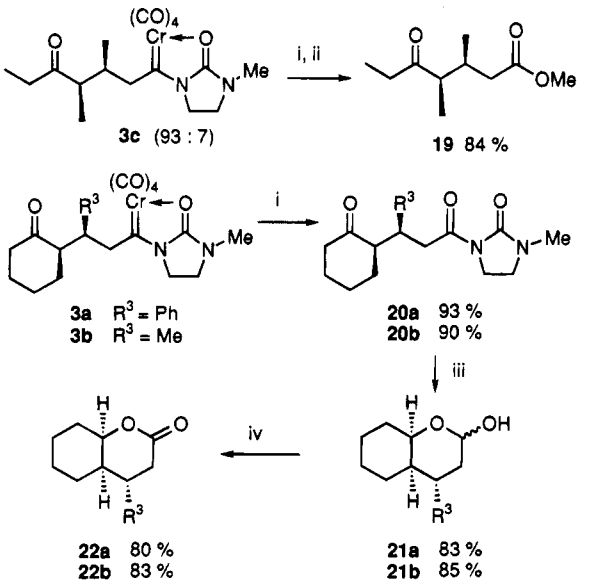
R^3	enolate	product	% Yield 3	syn / anti [b]
Ph		**3a**	81 % [c]	> 99.5 : 0.5 [d,e]
Me		**3b**	92 %	98.3 : 1.7 [d]
Me	 E:Z = 98:2 [f]	**3c**	84 %	93 : 7
Me	 Z:E ≥ 96:4 [g]	**3c**	93 %	55 : 45
Me		**3d**	93 %	55 : 45 [h]

[a] All reactions were carried out at −40 °C for 15 min using 1.2 equiv of enolate except entry 1 where 2.0 equiv of enolate was used and the temperature was −20 °C for 1 h. All reactions were quenched with acetic acid. All enolates were generated from the corresponding trimethylsilyl enol ethers with *n*-BuLi in THF at 0 °C for 30 min. [b] Unless otherwise specified, ratios determined by ^{1}H NMR. [c] Based on 15% recovery of **15**. [d] Ratios determined by capillary GC after oxidative removal of the metal with Ce^{IV}. [e] The same ratio was obtained when the enolate was generated with LDA. [f] Reference 17. [g] Reference 18. [h] Stereochemistry not determined.

tion of the carbene complex.[13] If these complexes were to react in Michael additions via an s-cis conformation, then high syn selection might be expected since transition state **12b** would be disfavored relative to **12a** due to the close contacts between the cyclohexane ring and the metal carbonyl ligands.

The dimethylamino carbene complex **13** is completely inert to reaction with the enolate of cyclohexanone. Complex **13** was recovered in 90% yield after exposure to the lithium enolate of cyclohexanone in THF at 25 °C for 6 h.[14] This is not surprising since alkylamino carbene complexes have been observed to be relatively unreactive in Diels–Alder reactions[13] and since alkylamino complexes analogous to **11** are much less acidic than **11**.[15] The amino complex **14** was found to be much more reactive as a dienophile presumably due to the activating effect of the *N*-acyl substituent.[13] However, *N*-acyl complexes such as **14** are not stable enough for routine use (the chromium analog of **14** is even less stable). The imidazolidinone complexes **15** were expected to be more stable since the carbene carbon N-substituent is more electron-rich. The successful preparation of these complexes was achieved as indicated in Scheme 2.[12] These complexes are as stable as the corresponding alkoxy complexes and give exo products in their Diels–Alder reaction suggesting that, like **14**, they may also react via s-cis conformations.[16]

Scheme 3[a]



[a] Key: (i) excess $Ce(NH_4)_2(NO_3)_6$, ether/acetone/H_2O, 25 °C, 1 min; (ii) NaOMe, HOMe, 0 °C, 3 h; (iii) $LiBEt_3H$, THF, −78 → 0 °C, 1 h; (iv) 2 equiv of PCC, NaOAc, 4 Å MS, CH_2Cl_2, 25 °C, 36 h.

We were pleased to find that as anticipated the Michael addition of ketone enolates to the α,β-unsaturated imidazolidinone carbene complexes occur with much higher syn-selectivity than α,β-unsaturated alkoxy carbene complexes. This is most clearly indicated in the reaction of complex **15b** with the enolate of cyclohexanone where the syn product **3b** is produced with a 58:1 selectivity (97% de) and the same reaction with complex **4b** produces the syn-product **8** with a 2:1 selectivity (33% de). The transition states **12a** and **12b** also can account for the reduced selectivity with 2-methylcyclohexanone enolate, but the difference in selectivities observed for the *E*- and *Z*-isomers of the enolates from 3-pentanone would not be readily predictable from this model. While the mechanism of these reactions it is not yet clear, the fact that high syn selectivity was predicted from models that have s-cis conformations of the imdiazolidinone carbene complexes is interesting, and this issue will be further pursued.

The chemical yields of the Michael additions to imidazolidinone carbene complexes are excellent as are the yields for the removal of the metal as indicated in Scheme 3. The keto ester **19** can be obtained in 84% yield from the Michael adduct **3c** by an oxidative removal of the metal with Ce^{IV} and then cleavage of the resultant *N*-acylimidazolidinone with sodium methoxide in methanol.[19] The stereochemistry of **19** was determined to be syn by comparison to an authentic sample of the anti-

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(14) *N,N*-Dimethylcrotamide has been reported to suffer Michael addition by the lithium enolate of cyclohexanone in the presence of HMPA (stereoselectivity not reported): Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823.

(15) Wulff, W. D.; Anderson, B. A.; Toole, A. J.; Xu, Y. C. *Inorg. Chim. Acta* **1994**, *220*, 215.

(16) Wulff, W. D.; Powers, T. S. Unpublished results.

(17) The silyl enol ether was generated from cyclohexanone with LBAA in the presence of 1.0 equiv of HMPA according to the published procedure: Sakuman, K.; Gilchrist, J. H.; Romesberg, F. E.; Cajthami, C. E.; Collum, D. B. *Tetrahedron Lett.* **1993**, *33*, 5312.

(18) (a) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Org. Synth.* **1983**, *61*, 122. (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.

(19) Drewes, A. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663.

isomer of **19** prepared by the method of Enders.[2a] The stereochemistry of the adducts **3a** and **3b** was assigned by conversion to the lactols **21** and the lactones **22**. The lactols **21** were generated by the equatorial reduction of the cyclohexanones **20** which resulted in an intramolecular lactonization with loss of the imidazolidinone.[10] The lactols were obtained as a mixture of isomers which were oxidized to the lactones **22** with PCC. The lactol **21a** with the indicated stereochemistry has been previously reported[10] and was used in the present study to secure the stereochemical assignments of **3a** and **3b** (see the supplementary material).

Carbene complexes provide the only known method for syn-selective Michael additions of ketone enolates to α,β-unsaturated esters (or their synthons), and the high level of stereoselection observed here with imidazolidinone complexes is a result of the propitious methodology for the Michael reaction provided by this new class of carbene complexes.

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Supplementary Material Available: Procedures and spectral data for all new compounds (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.