Asymmetric Aldol Reactions of Chiral Imidazolidinone Fischer Carbene Complexes

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Summary: Highly selective aldol reactions with α-unsubstituted enolates are described for a new class of chiral carbene complexes derived from chiral imidazolidinones in which the position of the chiral center is specifically defined by the chelation of the chiral auxiliary to the metal center.

Any consideration to the design of chiral carbene complexes for applications to asymmetric synthesis would have to include the classes of complexes **1**–**4**. Those with chiral phosphine ligands could exist as either cis or trans complexes which are known to readily interconvert,[1] and complexes of the type **2** which are chiral at metal are limited by the need for resolution and by other concerns.[2] In complexes of the type **3** derived from chiral alcohols there will be uncertainty in the positioning of the chiral center relative to the metal center due to the two degrees of freedom associated with the single bonds of the oxygen atom.[3–5] One less degree of freedom is possible with complexes derived from chiral cyclic amines, and these complexes have been useful in photochemical reactions of carbene complexes[6] and in Michael addition reactions.[7] In the latter study it was found that the enolate **5a** bearing a prolinol methyl ether chiral auxiliary led to good induction in Michael additions to enones[7] but gave low selectivities in the addition to isobutyraldehyde.[8] There are at least two issues associated with the dynamics of the enolate **5a** that play a role in the selectivities of their reactions (Scheme 1). First, while the neutral complex **4a** exists as two noninterconvertable rotamers, the anions **5a**–***E*** and **5a**–***Z*** readily interconvert at low temperature.[7] Second, it is quite possible that enolate **5a**, like amide enolates,[9] are pyramidalized at nitrogen (complex **5a**′) leading to geometries in which the methoxymethyl group is nearer to the plane of the enolate and thus resulting in less facial selection at the enolate α-carbon. It was anticipated that the carbonyl group of the internally chelated imidazolidinone carbene complexes **9** and **10** would serve to both lock in the conformation of the chiral auxiliary by coordination to the metal[10] and to maintain planarity at nitrogen when the neutral complex is deprotonated to give the enolate. We herein report on the preparation of chelated imidazolidinone carbene complexes as a new class of chiral carbene complexes and the first asymmetric aldol reactions of Fischer carbene complexes.[11,12]

One of the more difficult problems associated with the development of the asymmetric aldol reaction over the last decade has been in achieving high asymmetric induction with α-unsubstituted (acetate) enolates.[13–15] For this reason we have chosen to first examine methyl-substituted carbene complexes. Our initial efforts involved attempts to prepare the oxazolidinone chelate complex **8**, but it was found that this compound was apparently too unstable to be isolated. This was subsequently confirmed by Montgomery, Wieber, and Hegedus who also found that the thermal decomposition product was a vinyl carbamate.[16] In contrast, the imidazolidinone complex **10** was directly preparable in 65% yield from the reaction of imidazolidinone **7**[17–20] and the chromium acylate **6**.[21,22] Complex **10** is remarkably stable to water,

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(2) Lugan, N.; Kelley, C.; Terry, M. R.; Geoffroy, G. L. *J. Am. Chem. Soc.* **1990**, *112*, 3220.

(3) Soderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

(4) Alcaide, B.; Casarrubios, L.; Dominguez, G.; Sierra, M. A. *J. Org. Chem.* **1993**, *58*, 3886.

(5) The anion of the mentholoxy complex[3] prepared from the salt **6** and *l*-menthol reacted with *n*-butanal in THF at −78 °C to give a 1.0:1.0 mixture of diastereomers: Gilbertson, S. R.; Wilson, K. J.; Wulff, W. D. Unpublished results.

(6) For leading references to asymmetric reactions of ketenes generated from chiral carbene complexes, see: Pulley, S. R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 9037.

(7) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602.

(8) The reaction of the anion **4a** with isobutyraldehyde in THF at −78 °C leads to 2.0:1.0 mixture of diastereomers: Shi, Y.; Anderson, B. A.; Wulff, W. D. Unpublished results.

(9) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(10) For previous examples of *N*-acyl chelates of amino carbene complexes, see: (a) Dötz, K. H.; Grotjahn, D.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1384. (b) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784.

(11) A preliminary account of this work was presented at the 202nd ACS National meeting, Aug 25–30, 1991, New York, NY, Inorg. Abstr. no. 112.

(12) For citations to the literature on aldol reactions of carbene complexes, see ref 5 and: Wulff, W. D.; Anderson, B. A.; Toole, A. J.; Xu, Y. C. *Inorg. Chim. Acta* **1994**, *220*, 215. For Michael additions to nonchiral imidazolidinone carbene complexes, see: Shi, Y.; Wulff, W. D. *J. Org. Chem.* **1994**, *59*, 5122.

(13) For a review, see: Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.

(14) For recent citations to the literature, see: Oppolzer, W.; Starkeman, C. *Tetrahedron Lett.* **1992**, *33*, 2439.

(15) For citations not found in ref 13 and 14, see: (a) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328. (b) Kobayashi, S.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (c) Soai, K.; Kawase, Y. *Tetrahedron Asymmetry* **1991**, *2*, 781. (d) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417. (e) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927. (f) Vasconcellos, M. L.; Desmaele, D.; Costa, P. R. R.; D'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 4921. (g) Cambie, R. C.; Coddington, J. M.; Milbank, J. B. J.; Paausler, M. G.; Rustenhoven, J. J.; Rutledge, P. S.; Shaw, G. L.; Sinkovich, P. I. *Aust. J. Chem.* **1993**, *46*, 583.

(16) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.

(17) Both enantiomers of **7** are commercially available (Aldrich) or directly preparable[18] in one step from urea and ephedrine by the Close method.[19]

(18) Cardillo, G.; D'Amico, A.; Orena, M.; Sandri, S. *J. Org. Chem.* **1988**, *53*, 2354.

(19) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

(20) For leading citations to the utility of **7** as a chiral auxilliary, see: Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663.

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Scheme 1

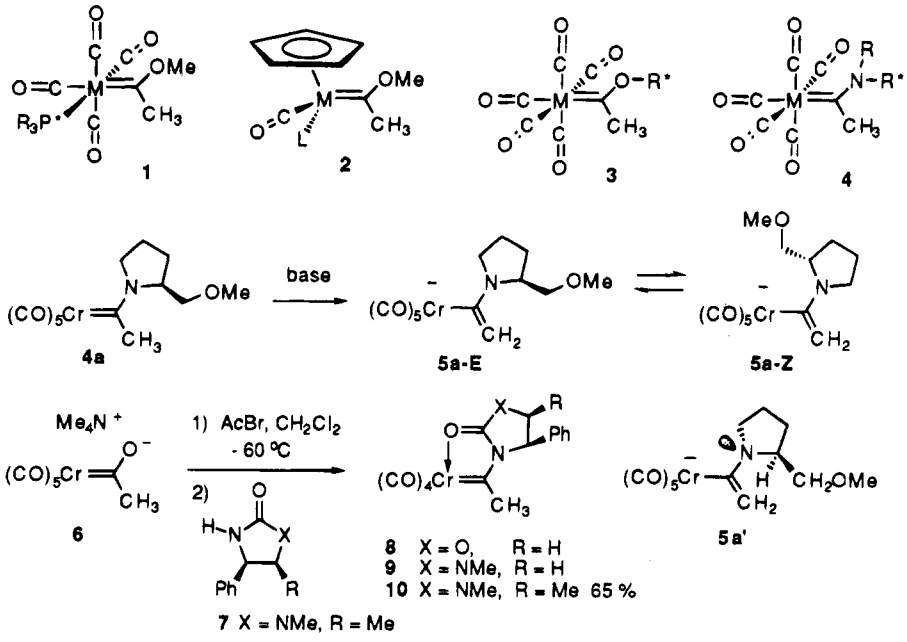
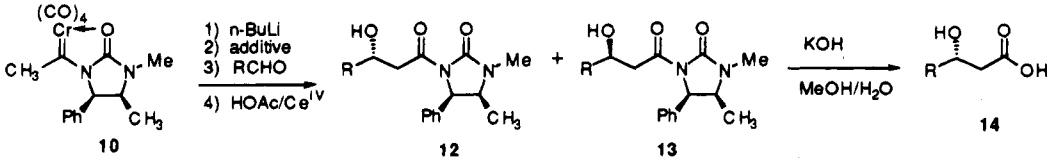


Table 1. Aldol Reactions of Imidazolidinone Complex 10[a]



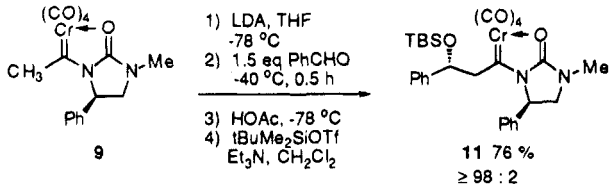
entry	aldehyde R	T, °C	time (min)	additive	ratio (12:13)[b]	yield (12 + 13),[c] %	elimination product 15,[d] %	product series	yield 14,[e] %
1	Ph	−35[f]	30	none	≥98:2	60	11	a	87 (+40.9)[g]
2	*i*-Pr	−78	600	none	91:9	87	2	b	
3	*i*-Pr	−30	30	none	95:5	88	3	b	
4	*i*-Pr	−10	10	none	91:9	83	6	b	
5	*n*-Pr	−78	120	none	55:45 (59:41)[h]	87 (85)[h]	3 (3)[h]	c	
6	*n*-Pr	−30	30	none	89:11 (87:13)[h]	87 (85)[h]	5 (3)[h]	c	
7	*n*-Pr	−20[i]	5	none	92:8	83	3	c	
8	*n*-Pr	−10[j]	2	none	93:7	83	4	c	
9	*n*-Pr	0[k]	1	none	91:9	83	4	c	
10	*n*-Pr	23[k]	1	none	86:14	76	10	c	
11	*n*-Pr	−78	660	none	73:27[l]	85	7	c	
12	*n*-Pr	−78	120	none	62:38[m]	80	3	c	
13	*i*-Pr	−60[f]	30	*n*-Bu_3B	98.6:1.4[n]	80	<1	b	89 (+39.1)[o]
14	*n*-Pr	−60[f]	30	*n*-Bu_3B	72:28[p] (77:23)[q]	80 (78)[q]	<1 (<1)[q]	c	88 (+28.2)[r]
15	*n*-Pr	−30	2	*n*-Bu_3B	(78:22)[q]	(78)[q]	(4)[q]	c	
16	*n*-Pr	−60[f]	30	*n*-Bu_3B[s]	(62:38)[q]	(78)[q]	(<2)[q]	c	
17	Ph	−78	30	*n*-Bu_2BOTf	10:90	37		a	
18	*i*-Pr	−60[f]	30	*n*-Bu_2BOTf	25:75 (22:78)[h]	55 (67)[h]	16 (<1)[h]	b	
19	*n*-Pr	−78	30	*n*-Bu_2BOTf	14:86	76	<1	c	

[a] Unless otherwise specified, all reactions were carried out with the following procedure. A 0.07 M solution of the anion of **10** was generated with *n*-BuLi at −78 °C in THF, and after 5 min 1.1−1.5 equiv of additive was added. After 5 min the solution was warmed to the indicated temperature for 5 min, and 1.1−1.4 equiv of aldehyde was added. The reaction was quenched at −78 °C by the addition of 5 equiv of HOAc, and the chromium was oxidatively removed by the addition of aqueous cerric ammonium nitrate. If an organoborane was employed, the crude reaction mixture was also oxidized with hydrogen peroxide in methanol at 25 °C for 90 min. [b] Determined with ^{13}C NMR by integration of *C*HOH. [c] Total isolated yield after purification on silica gel: **12** and **13** are readily separable ($\Delta R_f \approx 0.1$). [d] 3−5% of acetylimidazolidinone was recovered from entries 11, 15, and 16. [e] Isolated yield of **14** from purified **12**. The auxiliary **7** was recovered in 80−94% yield in each case. $[\alpha]_D$ values given in parentheses. [f] Aldehyde added at −78 °C. [g] **14a** was obtained as methyl ester by treatment of **12a** with MeOMgBr (ref 24). [h] Anion of **10** generated with LDA. [i] Enolate generated at −20 °C. [j] Enolate generated at −10 °C. [k] Enolate generated at 0 °C. [l] Reaction at 0.007 M in **10**. [m] Enolate was generated at −78 °C, warmed to −30 °C (10 min), and then cooled to −78 °C before addition of aldehyde. [n] Determined by capilliary GC after silylation of mixture. [o] $[\alpha]_D = +41.7$ lit. (ref 25). [p] The same ratio and yield was observed when 1 equiv of aldehyde and 2 equiv of *n*-Bu_3B were employed. [q] Aldehyde and *n*-Bu_3B premixed at −78 or −30 °C (15 min). [r] $[\alpha]_D = +28.3$ lit. (ref 25). [s] Reaction with the tungsten analog of **10**.

air, and silica gel and is approximately equal in stability as the methoxymethyl complex prepared by the methylation of **6**.[21]

As indicated in Table 1, excellent induction could be obtained with the three major classes of aldehydes: aryl (entry 1), α-branched aliphatic (entries 3 and 13), and

Scheme 2



α-unbranched aliphatic (entry 8). In the case of the adduct with benzaldehyde, the relative stereochemistry was determined for the silylated addition product **11**[23] by X-ray diffraction (Scheme 2). The crystal structure of **11** also reveals that the two five-membered rings of the chelated imidazolidinone lie essentially in one plane. In the general case the aldol reactions include an oxidative workup to give the acylimidazolidinones **12** and/or **13** from which the optically pure β-hydroxy acids **14** could be liberated in high yields and whose absolute configurations could be determined by comparisons with literature optical rotations. The reactions indicated in Table 1 appear to be kinetically controlled as judged by an attempted equilibration experiment of the carbene complexes **17c** and **18c** (corresponding to **12c** and **13c**) isolated from the reaction indicated in entry 5. In this case an oxidative workup was not employed. These complexes were isolated as a 60:40 mixture of **17c** and **18c** in 75% total yield and could be separated by silica gel chromatography. A THF solution of **18c** at −78 °C was treated with 1.0 equiv of *n*-BuLi and was then stirred at −30 °C for 30 min before the anion was quenched with acetic acid as describd in Table 1 which gave a 66% recovery of **18c** with no detectable amount of **17c** present in the crude mixture.

It was remarkable to find that that induction in the reaction of the enolate of **10** with *n*-butanal had an inverse temperature dependence with an optimal induction (93:7) at −10 °C and the lowest induction at −78 °C (55:45). This is not due to an irreversible autoreaction of the enolate since it was determined that if the enolate of **10** was generated at −78 °C, warmed to −30 °C, and then recooled to −78 °C, the low selectivity associated with this temperature was again observed (entry 12). Coupled with the fact that the selectivity is also dependent on the concentration (entries 5 and 11) it is likely that the lithium enolate of **10** can aggregate and that higher selectivities are observed under conditions in which deaggregation in favored.[26] The presence of diisopropylamine apparently does not affect this aggregation (entries 5 and 6). The selectivities for the reactions with isobutyraldehyde are much less sensitive to temperature (entries 2−4).

The stereoselectivities in these reactions could also be influenced by the presence of Lewis acids. The selectivity for the aldol adduct **12b** could be increased from 91:9 to 98.6:1.4 for isobutyraldehyde if the aldehyde was first precomplexed with tri-*n*-butylboron (entries 2 and 13). Surprisingly, the sense of induction is reversed when di-*n*-butylboron triflate is substituted for tri-*n*-butylboron. Also, it should be noted that the induction observed for the aldol reaction of the tungsten analog of **10** with *n*-butanal (entry 16) is lower than that for the same reaction of **10** (entry 14). This is in accordance with the general observation that tungsten carbon bonds are longer than chromium carbon bonds.[27] The results from the aldol reactions without an additive and also from those with tri-*n*-butylboron as additive can be explained by an open transition state model similar to that proposed for Mukaiyama-type aldol additions and a consideration of the six-gauche conformers that are possible from addition to both faces of the aldehydes.[28] The data for the reactions in the presence of di-*n*-butylboron triflate are suggestive of a change in mechanism to one in which a closed transition state is operative. Investigations are underway to further probe the nature of the mechanism of these aldol reactions.

The success achieved with the imidazolidinone carbene complex **10** as a chiral acetate enolate equivalent in the aldol reaction will undoubtedly prompt investigations of these complexes in other types of aldol reactions, and in the broader scope, the use of chiral imidazolidinone carbene complexes for the development of asymmetric versions of a variety of reactions of Fischer carbene complexes that posess synthetic potential.[27,29]

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Supplementary Material Available: Procedures and spectral data for all new compounds (12 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.

(21) The chromium acylate **6** is commercially available (Aldrich) or can be readily prepared by the method of Fischer: (a) Hegedus, L. S.; McGuire, M. A.; Schultz, L. M. *Org. Synth.* **1987**, *65*, 140. (b) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445.

(22) A 0.3 M solution of the acylate **6** in methylene chloride is treated with 1.0 equiv of acetyl bromide at −78 °C for 1 h and then with 1.0 equiv of **7**. After being stirred for 12 h at −60 °C the reaction mixture is rapidly warmed to room temperature, stripped of solvent, and loaded onto a silica gel column form which **10** is eluted with methylene chloride.

(23) The preparation of complex **9** will be published separately.

(24) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563.

(25) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495.

(26) (a) Veya, P.; Floriani, C.; Chiesi-Villa, V.; Rizzoli, C. *Organometallics* **1994**, *13*, 214. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(27) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984.

(28) See: Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 631.

(29) (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (b) Wulff, W. D. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press LTD: Greenwich, CT, 1989; Vol. 1, pp 209−393. (c) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 1065−1113.