Reviews

Asymmetric Synthesis with Fischer Carbene Complexes: The Development of Imidazolidinone and Oxazolidinone Complexes

William D. Wulff

Searle Chemistry Laboratory, Department of Chemistry, University of Chicago, Chicago, Illinois 60637

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Fischer carbene complexes are certainly among the most versatile organometallic reagents for organic synthesis that have ever been developed.[1] The number and utility of different types of reactions of these complexes that have been reported since their discovery[2] are far too numerous to list, and the discovery process continues unabated. A select set of these reactions are presented in Schemes 1 and 2, chosen in an attempt to illustrate the diversity of available processes. The set of reactions shown for α,β-unsaturated complexes of the type **1** shown in Scheme 1 include Michael additions[3] of a variety of carbon and hetereoatom nucleophiles to both alkenyl and alkynyl (not shown) complexes to give complexes of the type **2**.[1] The reaction with 1,3-dienes to give Diels−Alder adducts of the type **3**[4] is illustrative of a wide range of cycloaddition reactions that can produce four-, five-, and six-membered carbocyclic and heterocyclic carbene complexes.[1] The formation of the dihydroazepine **4**[5] and the cyclopentapyrans **5**[6] are two of many examples that illustrate the unique chemistry of carbene complexes. A number of 1,1-addition reactions have been described over the years,[1] and a recent example is the reaction with tin hydrides to give the allyl stannane **6**.[7] Perhaps the longest studied reaction of Fischer carbene complexes is the cyclopropanation of alkenes,[8] and importance advances in this reaction are still being reported.[9] The reaction of α,β-unsaturated carbene complexes with alkynes can give either cyclohexadienones[10] or 4-methoxylphenols,[11] and these two reactions, along with the cyclopropanation reaction, are perhaps the most widely utilized reactions in organic synthesis.[1]

The reactions of saturated Fischer carbene complexes illustrated in Scheme 2 by complex **10** (R^4 = Me, Ph), like those of α,β-unsaturated complexes, can be classified as either those in which the chromium−carbon bond is retained in the product or those in which the chromium−carbon bond undergoes reaction. The "enolates" generated from alkyl complexes undergo a variety of C-alkylation reactions, including aldol additions,[12] conjugate additions,[13] and alkylations with activated carbon electrophiles.[14] In some cases products arise from apparent Cr alkylation and subsequent reductive elimination, as illustrated for the reaction with chlorostannanes.[15,16] By far the most important photochemical reaction[17] of Fischer carbene complexes is the β-lactam synthesis discovered by Hegedus and McGuire.[18] Another major class of reactions that has been developed by Rudler is the generation of pyrrolinones via the rearrangement of nitrogen ylides generated from the reactions of amino carbene complexes with alkynes.[19]

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(2) Fischer, E. O.; Maasbol, A. *Angew. Chem., Int. Ed., Engl.* **1964**, *3*, 580.

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(11) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.

(12) (a) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 503. (b) Wang, H.; Hsung, R. P.; Wulff, W. D. *Tetrahedron Lett.* **1998**, *39*, 1849.

(13) (a) Casey, C. P.; Brunsvold, W. R.; Scheck, D. M. *Inorg. Chem.* **1977**, *16*, 3059. (b) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602.

(14) (a) C. P. Casey In *Organometallic Reagents in Organic Synthesis*; J. Organomet. Chem. Libr. 1; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976. (b) Xu, Y. C.; Wulff, W. D. *J. Org. Chem.* **1987**, *52*, 3263. (c) Wulff, W. D.; Anderson, B. A.; Isaacs, L. D. *Tetrahedron Lett.* **1989**, *30*, 4061.

(15) (a) McDonald, F. E.; Schultz, C. C.; Chatterjee, A. K. *Organometallics* **1995**, *14*, 3628. (b) For a related reaction giving vinyl halides, see: Herndon, J. W.; Reid, M. D. *J. Am. Chem. Soc.* **1994**, *116*, 383.

(16) Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357.

(17) For a review, see ref 1c and: Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

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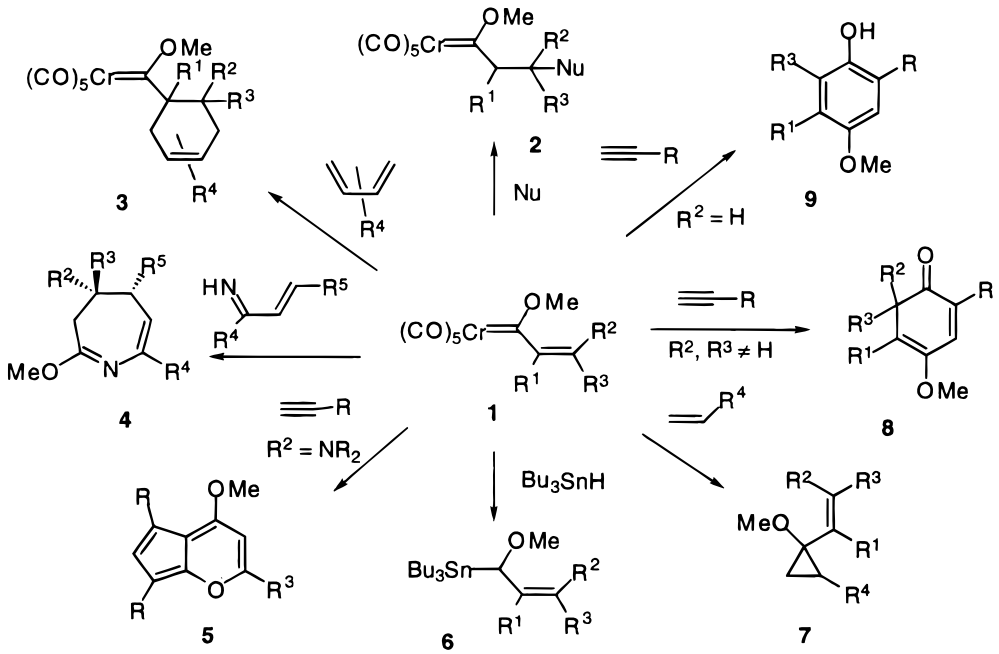
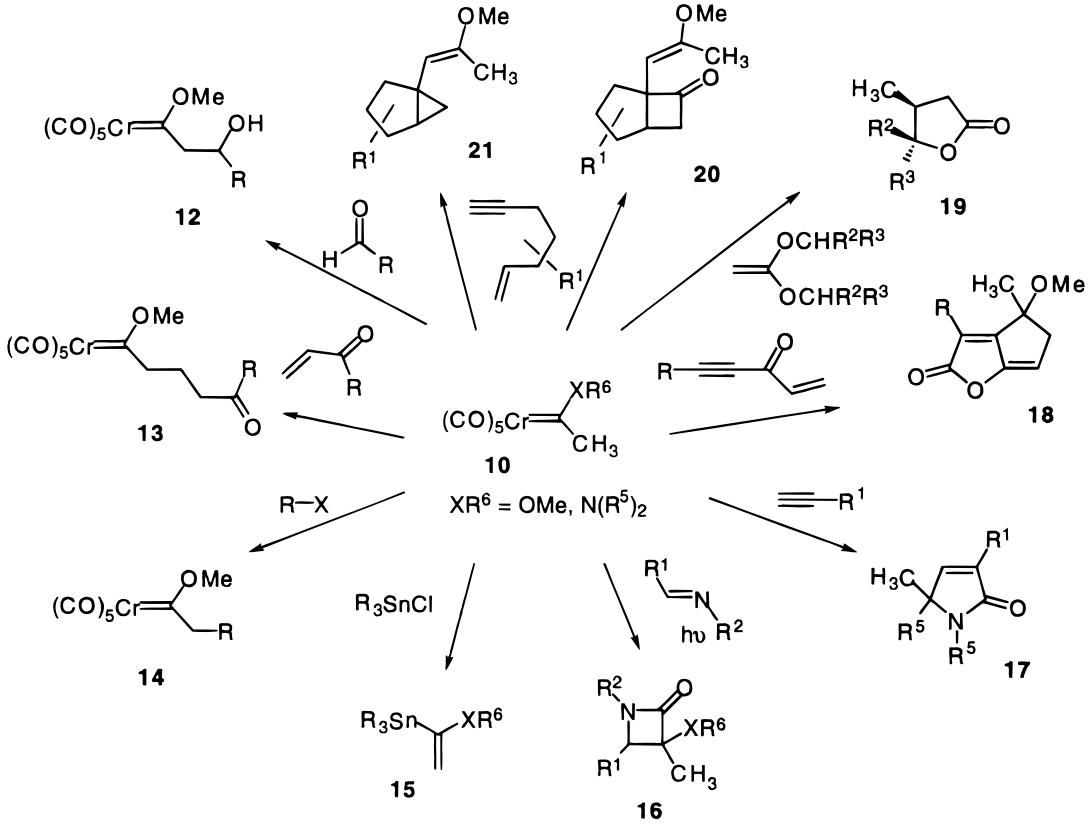
Scheme 1



Scheme 2

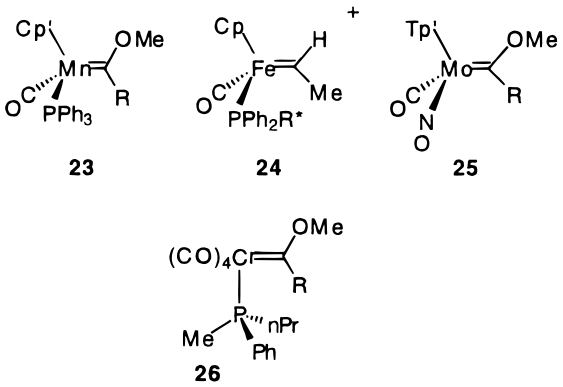


A number of different bicyclizations of cross-conjugated vinyl ketene complexes have been reported, with the formation of the lactone **18** from an alkynyl vinyl ketone as an example of one of the four different possible modes of closure.[20] The reaction of Fischer carbene complexes with ketene acetals proceeds through an addition rearrangement that generates a non-heteroatom-stabilized carbene complex intermediate with a final intramolecular insertion of the metal into a C−H bond.[21] The sequential reactions of carbene complexes with an alkyne and then an alkene is a tandem process that has been investigated extensively. The two most synthetically useful outcomes are illustrated in Scheme 2 for an intramolecular version, which has the alkyne and

(20) (a) Brandvold, T. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 1645. (b) Brandvold, T. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1991**, *113*, 5459.

(21) Wang, S. L. B.; Su, J.; Wulff, W. D.; Hoogsteen, K. *J. Am. Chem. Soc.* **1992**, *114*, 10665.

Chart 1



23 **24** **25** **26**

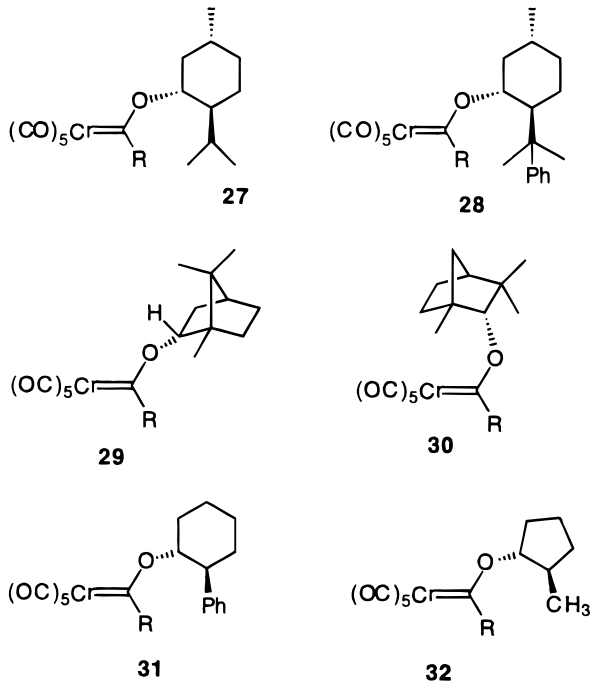
alkene tethered together to give either the bicycloheptanone **20**[22] or the bicyclohexane **21**.[23]

Chiral Carbene Complexes

The development of asymmetric versions of the various reactions of Fischer carbene complexes has been extensive only for the photoinduced reaction of imines to generate β-lactams.[17] There have been a few reports of chiral carbene complexes used in a small number of other reactions, but overall, asymmetric synthesis with chiral carbene complexes remains in the early stages of development. This will probably change quickly, since a number of chiral carbene complexes have been developed. These can be divided into four different classes. The first are those complexes that are chiral at the group VI metal, and the study of their chemistry has been limited to three reports. The "enolate" of manganese complex **23** can be generated but undergoes elimination to form an acetylide complex which can be alkylated with good diastereoselectivities[24] (Chart 1). The cationic iron carbene complex **24** has been used with good success in asymmetric cyclopropanation reactions (80−90% ee).[25] In a limited study, the enolate of complex **25** was found to undergo asymmetric alkylation with only modest diastereomeric excesses, attributed to unselective enolate formation.[26] The major reason that complexes that are chiral at metal have not received further attention is that their utilization will at some point require resolution of the metal center.

The second class of chiral carbene complexes is that in which the carbene complex contains a chiral center in the form of a coordinated chiral phosphine. There is a single report of this type of complex which describes the reaction of complex **26** in a cyclopropanation reaction.[27] The amount of induction was not measured, although the cyclopropane was found to be optically active. It can be anticipated that the rather facile isomerization of the chiral phosphine ligand between

Chart 2



27 **28** **29** **30** **31** **32**

cis and *trans* positions in complexes of this type might render high asymmetric inductions a rather difficult undertaking.[28]

The third class of complexes that has been investigated is that prepared from chiral alcohols with oxygen as the heteroatom stabilizing substituent. Along with complexes derived from chiral amines, these complexes have the attractive feature that chirality is readily available from the naturally occurring chiral pool. Complexes derived from menthol have been employed with only moderate success for cyclobutanone-forming reactions,[29] Diels−Alder reactions,[30] aromatic nucleophilic additions,[36b] and benzannulation reactions.[31,32] The performance of the phenmenthol analogue **28** (Chart 2) has been variable but has seen applications in Michael additions,[33,34] [3 + 2] cycloadditions,[35] [2 + 1] cycloadditions,[36a] aldol additions,[37] and benzannulations.[31,32] The complexes **29**−**32** have been employed in chiral benzannulations with little success in most cases.[31,32] One of the limitations of chiral carbene

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(26) Gunnoe, T. B.; White, P. S.; Templeton, J. L. *Organometallics* **1997**, *16*, 370.

(27) Cooke, M. D.; Fischer, E. O. *J. Organomet. Chem*. **1973**, *56*, 279.

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

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(32) Hsung, R. P.; Wulff, W. D.; Chamberlin, S.; Wang, S. L. B.; Liu, R.; Liu, Y.; Quinn, J. F., manuscript in preparation.

(33) (a) Barluenga, J.; Montserrat, J. M.; Florez, J.; Garcia-Granda, S.; Martin, E. *Chem. Eur. J*. **1995**, *1*, 236. (b) Barluenga, J. M.; Montserrat, Florez, J.; Garcia-Granda, S.; Martin, E. *Angew. Chem., Int. Ed. Engl*. **1994**, *23*, 1392.

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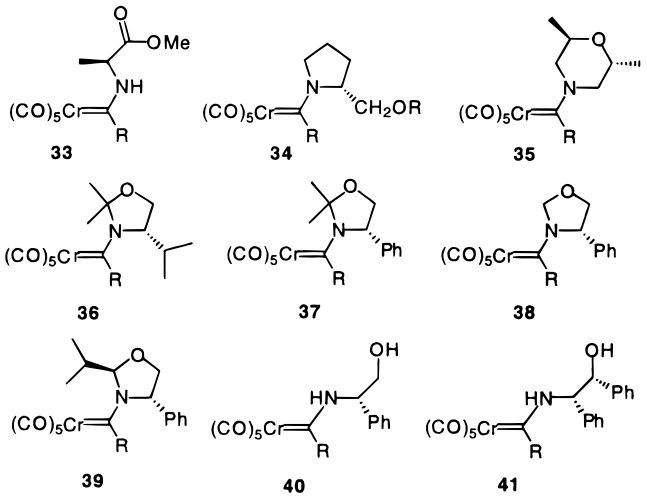
(35) Barluenga, J.; Fernandez-mari, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2267.

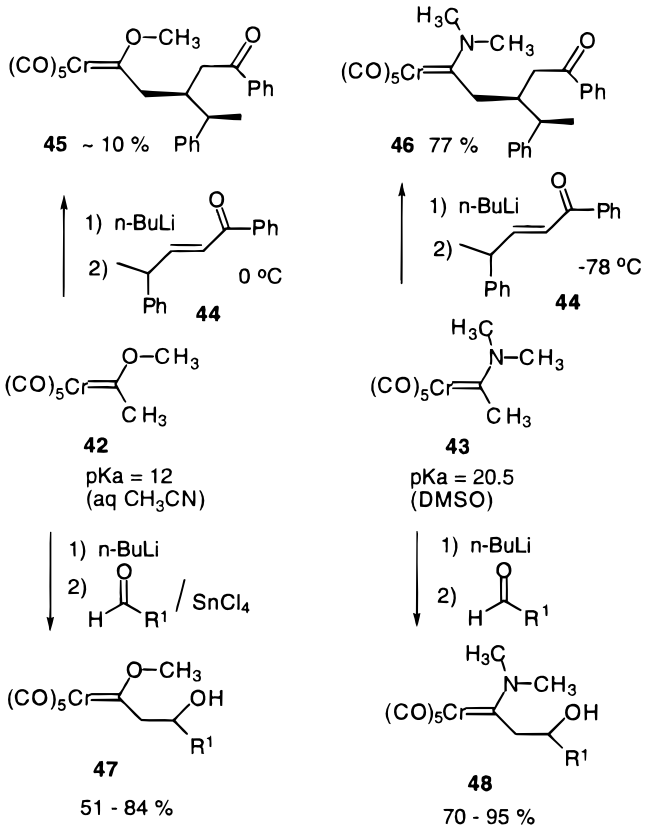
(36) (a) Barluenga, J.; Bernad, P. L., Jr.; Concellon, J. M.; Pinera-Nicolas, A.; Garcia-Granda, S. *J. Org. Chem*. **1997**, *62*, 6870. (b) Barluenga, J.; Trabanco, A. A.; Florez, J.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc*. **1996**, *118*, 13099.

(37) Shi, Y. Ph.D. Thesis, The University of Chicago, Chicago, IL, 1995; p 28.

Chart 3



Scheme 3



complexes derived from chiral alcohols is that the chiral centers are connected to the carbene carbon via two C−O single bonds; thus, there are likely to be many accessible conformations about those bonds.

The fourth class of chiral carbene complexes that has been studied is the one derived from chiral amines, and this class has received the lion's share of the attention to date. The use of a chiral amine to prepare a carbene complex has two distinct advantages over those generated from chiral alcohols. The first is that the barrier to rotation about the nitrogen single bond to the carbene carbon is quite high; therefore, rotation does not occur readily even at elevated temperatures. Thus, complexes of type **33** (Chart 3) would be expected to have one less degree of freedom than a complex bearing a similar chiral alcohol. The induction resulting from reactions of complex **33** have only been investigated for a pyrrolinone-forming reaction where low stereoselection was observed.[38] The second advantage of chiral amines over chiral alcohols is that if a cyclic amine is used, both degrees of freedom of the chiral auxiliary can be removed. An example is complex **34**, which is readily preparable from prolinol and has been used with good success in β-lactam-forming reactions[39] and Michael additions,[34,40] but not for aldol reactions[37] and benzannulation reactions.[32] A disadvantage of complex **34** is that it exists as two rotamers that cannot be thermally interconverted. However, in the reactions of the enolates of **34** (R = CH_3), interconversion occurs faster than Michael addition and a mixture can be employed.[40] This problem is avoided in complex **35**, and it was found to give inductions comparable to those of complex **34** in Michael additions.[41] However, complex **35**, like **34**, gave low inductions in benzannulation reactions.[32] Furthurmore, the chiral amine necessary for the preparation of complex **35** is not commercially available. The ability of oxazolidine complexes **36**−**39** to provide asymmetric induction in β-lactams via the photoinduced reaction of carbene complexes with imines has been examined.[42] The complex that has been most widely used in the synthesis of optically active β-lactams is the complex **37**, derived from phenylglycinol.[17] Complex **37** has also given good to excellent inductions in aldol reactions.[45] The two complexes **40**[43] and **41**,[44] which are derived from glycinol derivatives, have been used in the synthesis of vinyl carbamates and oxazinones.

Nitrogen- versus Oxygen-Stabilized Carbene Complexes

As summarized above, the most successful chiral carbene complexes that have been established to date are those derived from either chiral alcohols or chiral amines. To a large extent, the utilization of these two classes of compounds involves complimentary sets of reactions which is a consequence of their different reactivities. The reactions shown in Schemes 3−5 are selected to illustrate this point. The acidity of the dimethylamino complex **43** is clearly much less than that of the methoxy complex **42**, but it is difficult to know the precise extent, since the acidities were measured in different solvents (**43**, pK_a = 20.5 in DMSO;[46a]

(38) Dötz, K. H.; Weber, R. *Chem. Ber.*, **1991**, *124*, 1635.
(39) Hegedus, L. S.; Imwinkelreid, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.
(40) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602.
(41) Baldoli, C.; Del Bultero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Zanotti-Gerosa, A. *J. Organomet. Chem.* **1995**, *486*, 279.
(42) (a) Complex **36**: see ref 39. (b) Complexes **37**−**39**: Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelreid, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.
(43) (a) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 2814. (b) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923.
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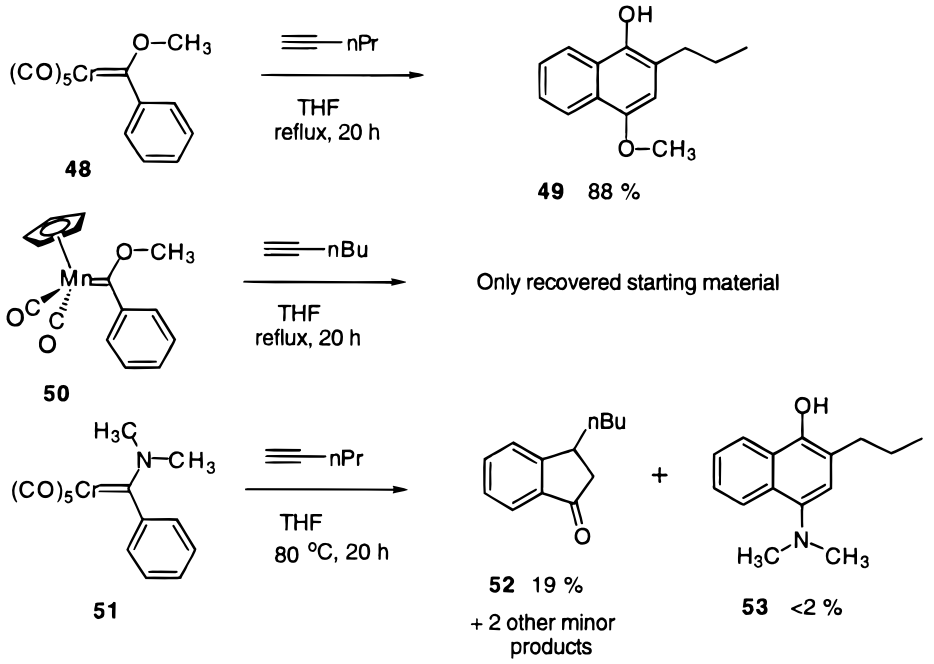
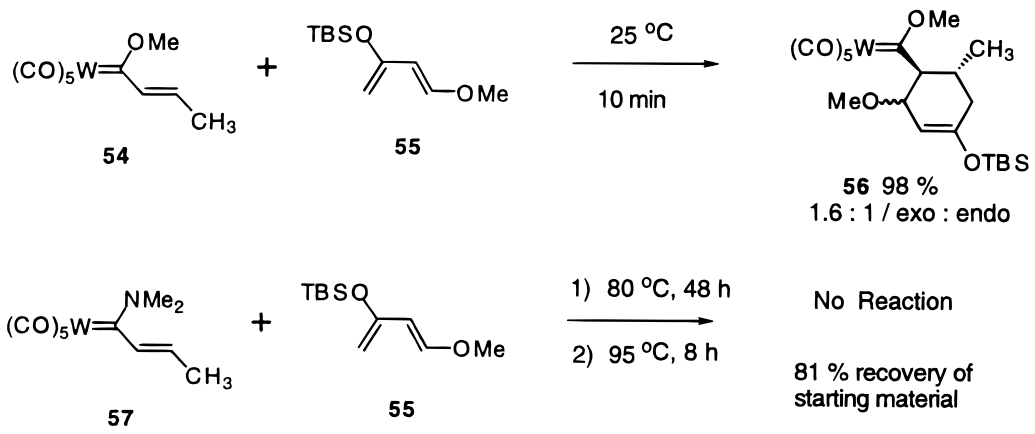
Scheme 4



Scheme 5



42, pK_a = 12 in acetonitrile[46b]). However, the difference in reactivity between the enolates of **42** and **43** is consistent with a large difference in acidities of these compounds. The Michael reaction of the enolate of **42** with enone **44** gives only a 10% yield of adduct **45**, whereas the same reaction of the amino complex **43** gives the adduct **46** in 77% yield, despite the fact that the reaction was run at much lower temperature. A similar difference is seen in the aldol reaction. High yields of aldol adduct **48** can be obtained simply by treating the enolate of **43** with a variety of aldehydes.[47] Under the same conditions, the enolate of **42** does not react with most aldehydes.[48] To obtain aldol adduct **47**, precomplexation of the aldehyde and Lewis acid is required.[12]

There is an even greater disparity between the benzannulations of amino and alkoxy complexes. As an example, the reaction of the phenyl methoxy complex **48** with 1-pentyne gives a high yield of the 4-methoxy phenol **49**,[49] whereas reaction of the corresponding dimethylamino complex **51** under the same conditions gives none of the 4-amino phenol **53** and instead gives a mixture of products, the major one being indanone **52** (Scheme 4).[50] The indanone products result from the failure to incorporate a carbon monoxide ligand from the metal. The indanones can be made in high yields if the reaction is run in DMF.[51] This result follows the general observation that electron-rich complexes tend to favor indene products over phenol products.[52] The importance of the five carbonyl ligands to the success of this reaction is evident in the fact that the cyclopentadienylmanganese complexes will not react with alkynes under the same conditions.[53] Certain complexes related to **50** will react under photochemical conditions. This

(47) Anderson, B. A.; Toole, A. J.; Wulff, W. D. *J. Am. Chem. Soc.* **1989**, *111*, 5485.
(48) Casey, C. P.; Boggs, R. A.; Anderson, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 8947.
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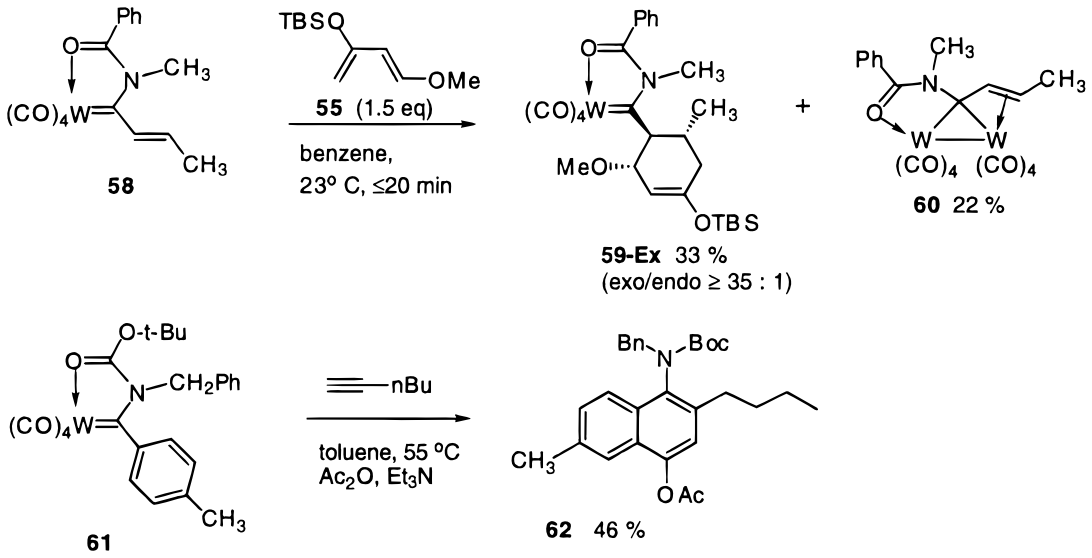
(53) Balzer, B. L.; Cazanoue, M.; Sabat, M.; Finn, M. G. *Organometallics* **1992**, *11*, 1759.

Scheme 6



result perhaps is indicative of the type of stark differences that may be encountered when chiral complexes of type **23** are further developed.[24]

The degree to which the reactivity of carbene complexes is attenuated by the incorporation of an amino group is perhaps most dramatically demonstrated in the Diels−Alder reactions shown in Scheme 5.[54] The *trans*-propenyl methoxy complex **54** displays high reactivity with Danishefsky's diene. The reaction is complete in 10 min at room temperature and gives the Diels−Alder adduct **56** in 98% yield. The dimethylamino analogue **57** fails to react under the same conditions. Furthermore, after a mixture of complex **57** and Danishefsky's diene **55** had been heated at 80 °C for 48 h and then at 95 °C for 8 h, the starting complex **57** was reisolated in 81% yield and no evidence for the presence of a cycloadduct was found. Clearly, the set of chiral amino carbene complexes that have been reported to date (Scheme 5) would not be useful for asymmetric Diels−Alder reactions.

The reactivity of alkenyl amino complexes in the Diels−Alder reaction can be enhanced if a carbonyl group is introduced on the nitrogen atom. The introduction of a benzoyl group can also be accompanied by the coordination of the benzoyl oxygen, which replaces one of the five carbon monoxide ligands on the metal center. The resulting complex **58** was found to rapidly react with Danishefsky's diene at room temperature to give the cycloadduct **59** in 33% yield.[54] This increase in reactivity compared to that of complex **57** is presumably due to the ability of the benzoyl group to remove some of the electron density from the nitrogen, thereby reducing the amount of electron density delocalized into the carbene linkage and making the carbene complex a better dienophile. One fascinating observation made for the Diels−Alder reaction of the chelated benzoyl complex **58** is that the Diels−Alder adduct **59** is formed exclusively as the exo diastereomer. The origins and the consequences of this observation will be discussed in detail below. A similar electronic effect has been reported for the benzannulation reaction of amino complexes. The major product of the reaction of the carbamate complex **61** with 1-hexyne is the 4-aminophenol derivative **62**.[55] Compare this with the reaction of complex **51** with 1-pentyne, which gives none of the 4-aminophenol **53** (Scheme 4). The change in solvent from THF to toluene has been shown to have little effect on these reactions[50] and assuredly does not explain the difference between the reactions of complexes **51** and **61**.

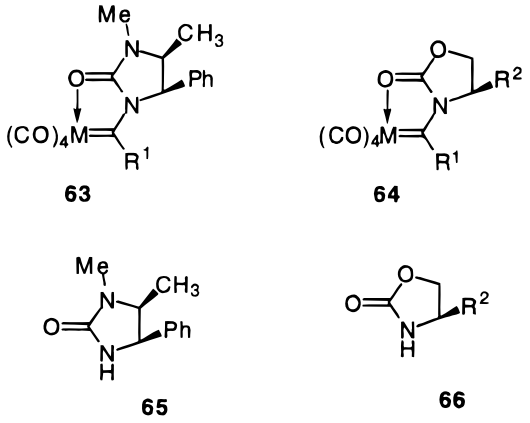
Preparation of Imidazolidinone and Oxazolidinone Carbene Complexes

The success in the activation of amino carbene complexes realized by incorporating a carbonyl group on the nitrogen in the benzoyl complex **58** and the carbamate complex **61** (Scheme 6) suggested that a class of carbene complexes could be found that would be as broadly useful as the methoxy complexes (Schemes 1 and 2) and would be readily available in chiral form. Our experience with complexes of type **58**, which are derivatives of simple amides, suggested that the utility of these complexes would be limited by their stability. For example, the Diels−Alder reaction of complex **58** with Danishefsky's diene gave the μ-carbene complex **60**, which is a decomposition product formed in competition with the Diels−Alder adduct **59**. With these considerations, we set out to prepare and evaluate the reactivity of imidazolidinone and oxazolidinone carbene complexes of the types **63** and **64** (Chart 4). These complexes were expected to have at least four advantages: (1) they would be sufficiently electron-rich to be more stable than the amide complex **58** but more electron-deficient than simple amino compounds and thus have an expanded range of reactivity, (2) the chiral center α to nitrogen would be immobilized in a five-membered ring, (3) the entire chiral auxiliary would be immobilized by the chelation of the carbonyl oxygen to the metal, and (4) the complexes could potentially be

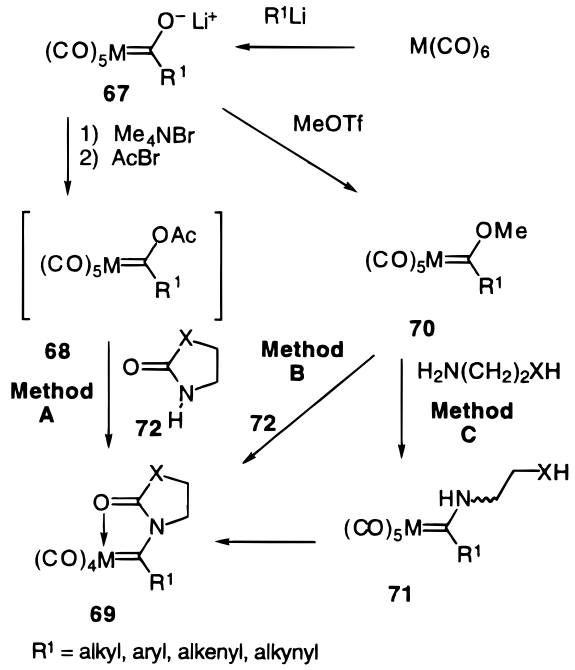
(54) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784.

(55) Dötz, K. H.; Grotjahn, D.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1384.

Chart 4



Scheme 7

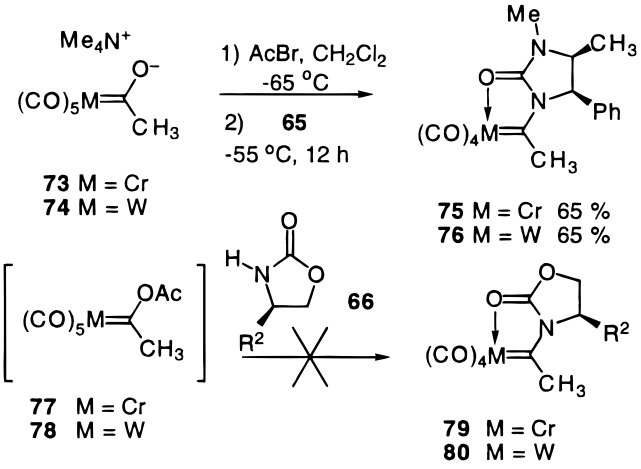


directly prepared from the widely used imidazolidinone and oxazolidinone chiral auxiliaries **65** and **66**.[56,57]

Imidizolidinone and oxazolidinone complexes have been prepared by the three methods summarized in Scheme 7 which are either two or three steps from chromium hexacarbonyl.[58] Method A is a two-step process involving the generation of lithium acylate **67** followed by *in situ* cation exchange of lithium for tetramethylammonium. The ammonium salt is usually isolated by crystallization and then reacted with acetyl bromide to generate the reactive acyloxy complex **68**, which is reacted *in situ* with the chiral auxiliary to generate the chelate imidazolidinone or oxazolidinone complex **69**. Method B is a minor variation of method A, involving the isolation of the methoxy complex **70**. This method, using the direct replacement of the methoxy group with a chiral imidizolidinone or oxazolidinone, is somewhat limited and is usually only successful with

(56) For leading references, see: Bongini, A.; Cardillo, G.; Mingardi, A.; Tomasini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1457.
(57) For leading references, see: Sudharshan, M.; Hultin, P. G. *Synlett* **1997**, 171.
(58) For procedures, see refs 32 and 67.

Scheme 8



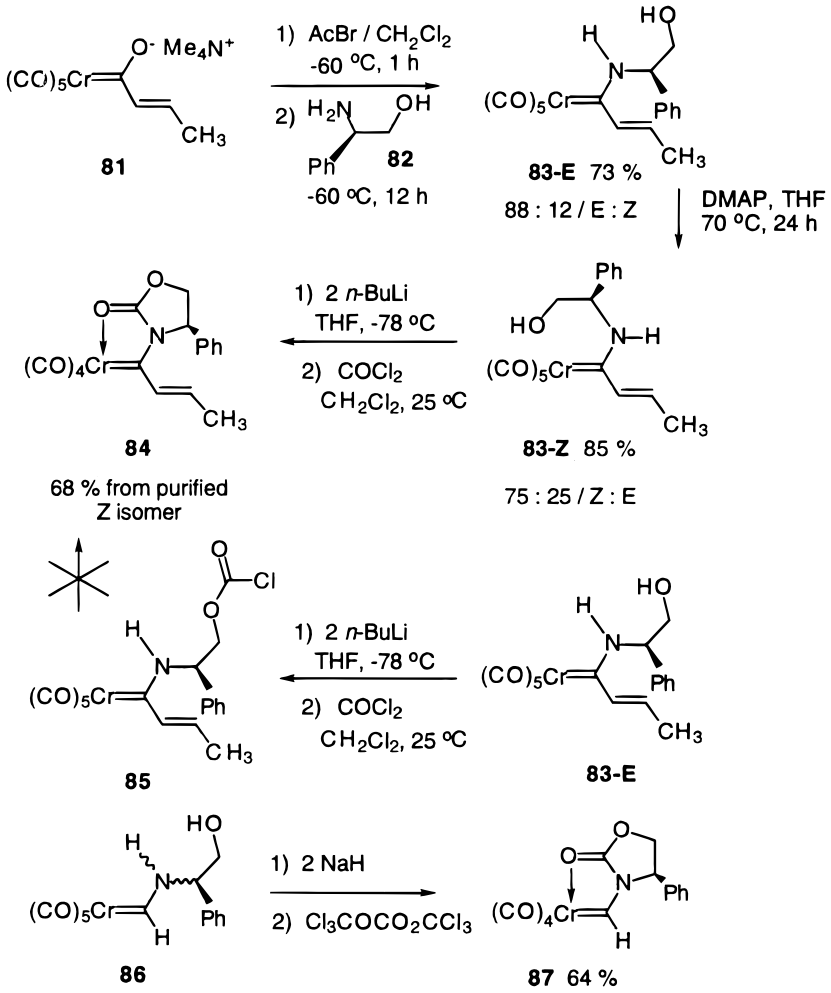
a deprotonated form of the auxiliary and with methoxy carbene complexes that are nonenolizable. Method C is a three-step method that involves the reaction of the methoxy complex **70** with a glycinol derivative. The final step in this approach involves the synthesis of the chiral auxiliary by closure of the imidazolidinone or oxazolidinone ring.

The methyl-substituted imidazolidinone carbene complexes **75** and **76** have been prepared by method A, as shown in Scheme 8.[58] The chromium tetramethylammonium acylate **73**[59] was treated with acetyl bromide at −65 °C for 1 h, and then the commercially available (4*R*,5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone (**65**)[60] was added; the reaction was allowed to proceed at −55 °C for 12 h to give the methyl imidazolidinone chelate complex **75** in 65% yield.[58] All attempts to prepare the corresponding oxazolidinone carbene complex **79** failed for complexes where R^2 was either phenyl or hydrogen.[61] The methyl oxazolidinone complex **79** is apparently quite unstable to base. Hegedus, Montgomery, and Wieber have reported that their attempts to prepare complex **79** (R^2 = Ph) via method C gave a solution that was thought to contain small amounts of this compound, but all attempts to isolate this product failed.[62] They observed the formation of an ene carbamate that appears to be formed by a base-induced decomposition of **79**. In contrast, the methyl imidazolidinone complex **75** can be handled with no special precautions and has approximately the same stability as the methyl methoxy complex **42**.

Oxazolidinone carbene complexes can be prepared with alkenyl substituents by method C, as is illustrated for the preparation of the *trans*-propenyl complex **84** in Scheme 9.[58] The aminolysis of the acetoxy complex generated from **81** with (*R*)-2-phenylglycinol gave the amino carbene complex **83** as a mixture of *E* and *Z* isomers due to hindered rotation about the nitrogen−carbene carbon bond. The *E* isomer is the major isomer

(59) Hegedus, L. S.; McGuire, M. A.; Schultz, L. M. *Org. Synth*. **1987**, *65*, 140.
(60) Both enantiomers of **65** are commercially available and can be prepared in one step from urea by the method of Close: (a) Close, W. J. *J. Org. Chem*. **1950**, *15*, 1131. (b) Cardillo, G.; D'Amico, A.; Orena, M.; Sandri, S. *J. Org. Chem*. **1988**, *53*, 2354.
(61) Powers, T. S. Ph.D. Thesis, The University of Chicago, Chicago, IL, 1993.
(62) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc*. **1990**, *112*, 6255.

Scheme 9



produced from the reaction and could be separated cleanly from the minor *Z* isomer by silica gel chromatography. The *E* isomer of **83** could not be closed to the oxazolidinone complex **84**. Reaction of the dianion of **83-E** with phosgene gave the chloroformate **85**, but all attempts to close **85** failed. The mixture of diastereomers of **83** obtained from the aminolysis of **81** could be isomerized with DMAP from an 89:12 *E*:*Z* mixture to a 25:75 *E*:*Z* mixture in 85% yield. The dianion of the *Z* isomer of **83** could be closed to the oxazolidinone complex **84** in 68% yield. Phosgene was required for this closure and was accomplished with a commercially available 15% solution in toluene. Several phosgene equivalents failed in this closure, including carbonyl diimidazole, dimethyl carbonate, diphenyl carbonate, methyl chloroformate, and triphosgene. Some of the reasons for this have been discussed.[61,62] The aminoglycinol carbene complex **86** was found to close to the oxazolidinone complex with triphosgene.[63]

Applications of Imidazolidinone and Oxazolidinone Carbene Complexes in Asymmetric Synthesis

The aldol reaction provides one of the fundamentally most important processes available to the synthetic organic chemist, and this fact is in concert with the level of activity associated with the development of asymmetric versions of this reaction over the last two decades.[64] One of the more difficult problems faced in asymmetric aldol reactions was achieving high induction with α-unsubstituted (acetate) enolates.[65,66] As a result, our initial studies of the asymmetric aldol reactions of imidazolidinone carbene complexes focused on the unsubstituted methyl complex **75**.[67] As summarized in Scheme 10 the aldol reactions of complex **75** gave high inductions for three major classes of aldehydes: aryl, aliphatic, and α-branched aliphatic.[67] The enolate of **75** was generated with *n*-butyllithium or LDA and reacted directly with an aldehyde to give, after a proton quench and oxidative removal of the metal, the aldol adduct **88** in 60−90% yield with greater than 95% stereoselectivity in each case. The product could be easily separated from the minor diastereomer by silica gel chromatography, and as a result, subsequent methanolysis gave the *β*-hydroxy ester **90** in complete optical

(63) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.

(64) For citations to the literature, see: Evans, D. A.; Ripin, D. H. B.; Johnson, J. S.; Shaughnessy, E. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2119.

(65) See footnotes 13−15 in ref 67.

(66) For recent solutions, see: (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (b) Keck, G. E.; Kirshnamurth, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4078.

(67) Powers, T. S.; Shi, Y.; Wilson, K. J.; Wulff, W. D.; Rheingold, A. L. *J. Org. Chem.* **1994**, *59*, 6882.

Scheme 10

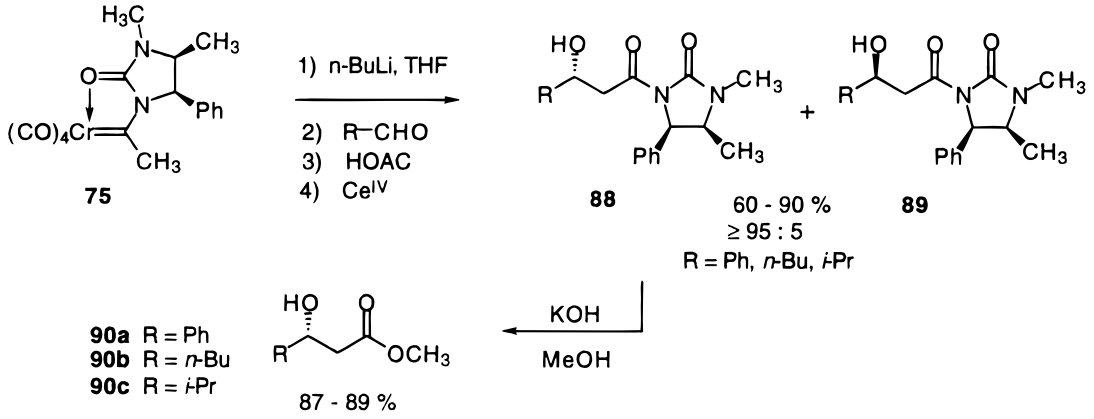


Table 1. Temperature and Lithium Effects on the Aldol Reaction of Complex 75[a]

entry no.	*T*, °C	R	LiCl (amt, equiv)	time (min)	ratio (**88**:**89**)[b]	% yield **88** + **89**[c]	% yield **91**	% yield **92**
1	23	*n*-Pr	no	1	86:14	76		10
2	0	*n*-Pr	no	1	90:10	82		5
3	−10	*n*-Pr	no	2	93:7	83		4
4	−20	*n*-Pr	no	5	92:8	83		3
5	−30	*n*-Pr	no	30	88:12	88		2
6	−50	*n*-Pr	no	60	84:16	83		2
7	−78	*n*-Pr	no	120	55:45	85	5	
8	−78	*n*-Pr[d]	no	660	73:27	85	7	
9	−78	*n*-Pr[e]	no	120	62:38	80	3	
10	−95	*n*-Pr	no	60	28:72	30	60	
11	−10	*i*-Pr	no	10	90:10	83		5
12	−30	*i*-Pr	no	30	95:5	88		3
13	−50	*i*-Pr	no	180	95:5	85		2
14	−78	*n*-Pr	no	600	19:9	87	1	
15	−95	*n*-Pr	no	300	69:31	30	50	
16	−10	*n*-Pr	yes (1)	1	93:7	72		8
17	−20	*n*-Pr	yes (1)	2	94:6	75		3
18	−30	*n*-Pr	yes (1)	5	94:6	80		4
19	−40	*n*-Pr	yes (1)	30	95:5	80		3
20	−50	*n*-Pr	yes (1)	60	92:8	85		3
21	−78	*n*-Pr	yes (1)	120	81:19	59	20	
22	−78	*n*-Pr	yes (3)	120	79:21	72	10	
23	−78	*n*-Pr	yes (10)	120	65:35	68		10

[a] Unless otherwise specified, all reactions were performed in THF at 0.07 M in **75**. The enolate was generated at −78 °C and warmed (cooled) to the indicated temperature for 5 min before the aldehyde was added. [b] Determined by ^{13}C NMR by integration of *C*HOH. [c] Combined isolated yield of **88** and **89**. [d] This reaction was performed with the enolate concentration at 0.007 M. [e] The enolate of **75** was warmed to −30 °C for 10 min and then recooled to −78 °C before addition of aldehyde.

purity. The enolate of **75** was sufficiently reactive to undergo unassisted addition to a number of aldehydes, but it was found that if the aldehyde was precomplexed with a Lewis acid (Bu_3B) that the stereoselectivity could be enhanced. Surprisingly, the selectivity was reversed with Bu_2BOTf and the adduct **89** became the major product.

An unexpected temperature dependence of the induction observed in the aldol reactions of complex **75** was observed and is illustrated by the data shown in Table 1.[67,68] The first 10 entries reveal that the optimal temperature for the aldol reaction with *n*-butyraldehyde is −10 °C, where adduct **88** is formed with 93:7 selectivity. The selectivity drops with decreasing temperature and crosses over at low temperature to give the adduct **89** as the major product with a 3:1 selectivity at −95 °C. The aldol reaction with *iso*-butyraldehyde is much less sensitive and does not cross over at low temperature. The aldol reaction with benzaldehyde is slow at low temperature and is completely selective at −30 °C, giving adduct **88** in greater than 98% selectivity.[67] The selectivity of addition to *n*-butyraldehyde is enhanced in the presence of 1 equiv of lithium chloride, giving a 95:5 ratio at −40 °C. The presence of lithium chloride

(68) Shi, Y. Ph.D. Thesis, The University of Chicago, Chicago, IL, 1995.

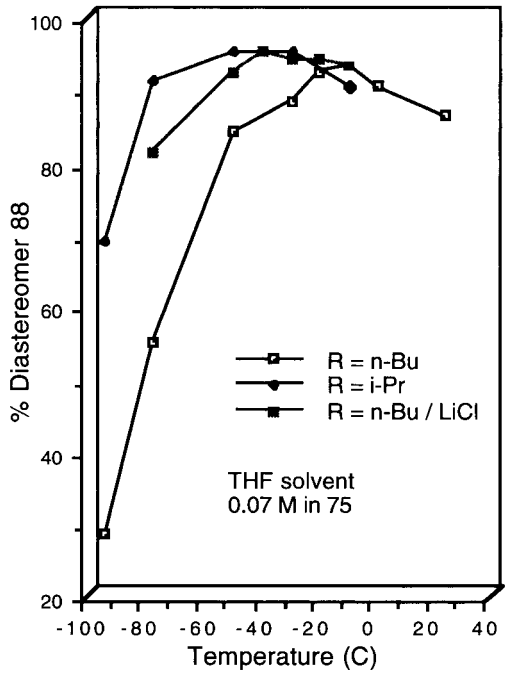


Figure 1.

also attenuates the temperature dependence of the reaction with *n*-butyraldehyde, and this can be more easily seen in the plot in Figure 1. The yields of the aldol reactions are usually quite high, with the formation of the elimination product **92** limited to small amounts. In some cases where the reaction is slow, the starting material is recovered in the form of the acetylimidazolidinone **91**, which results from the oxidation of complex **75**. A possible explanation of this temperature effect will be presented in Scheme 14.

A significant solvent effect was observed for the reaction of complex **75** with *n*-butyraldehyde. The aldol adduct **89** becomes the major product of the reaction when the solvent is changed from THF to methylene chloride, even if the reaction is carried out at −30 °C.[68] At −95 °C, the adduct **89** is formed with 81:19 selectivity in methylene chloride, although the reaction is slow with only 33% conversion after 2 h. While this study of solvent effects is limited, the data suggest that adduct **88** is favored with coordinating solvents and the adduct **89** is favored in less coordinating solvents. The source of these effects is not understood at this time; however, some possible explanations will be discussed below.

The selectivity of the addition of **75** to *n*-butyraldehyde is the same whether *n*-butyllithium, LDA, or lithium hexamethyldisilazide is used as the base to generate the enolate.[68] However, the data in Table 3 reveal a strong cation effect. The reaction is essentially unselective with sodium and potassium enolates, and the rates of reaction are noticeably slower as well. The effect of the addition of HMPA is also quite interesting. The selectivity of the reaction is not affected by the addition of increasing amounts of HMPA but the reactivity is greatly attenuated to the point where, with 5 equiv of HMPA, the reaction is completely shut down. These kinds of observations have not been made for the enolates of alkoxy complexes.[14a] These observations are also quite preliminary and need to be confirmed in furthur experiments designed to probe the nature of these reactions. Some suggestions to explain the observations we have made to this point will be presented below.

Table 2. Effect of Solvent on the Addition of 75 to *n*-Butyraldehyde

entry no.	solvent	*T*, °C	time (min)	ratio (**88**:**89**)[b]	% yield **88** + **89**[c]	% yield **91**
1	THF	−30	30	88:12	88	
2	CH_3CN	−30	60	69:31	50	30
3	toluene	−30	5	50:50	59	20
4	CH_2CL_2	−30	35	36:64	30	50
5	THF	−95	60	28:72	30	60
6	CH_2CL_2	−95	120	19:81	33	50

[a] All reactions were carried out with the following procedure except for entries 1 and 5. A 0.07 M solution of the enolate of **75** was generated with *n*-BuLi at −78 °C in THF. The mixture was placed under high vacuum and the solvent removed while the temperature was kept below −20 °C. After the mixture was dry, the indicated solvent was injected to make a 0.07 M enolate solution at the indicated temperature. *n*-Butyraldehyde was then added, and the reaction was quenched with acetic acid after the indicated time and the crude mixture stirred with aqueous ceric ammonium nitrate for 30 min to remove the metal.

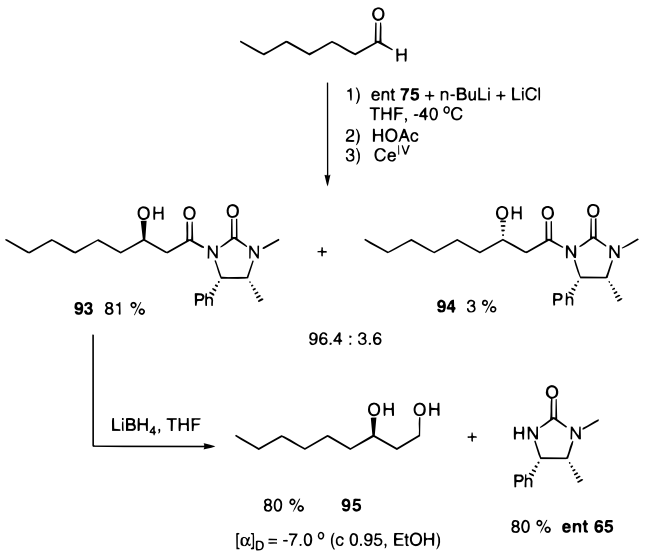
Table 3. Effect of Cations and HMPA on the Addition of 75 to *n*-Butyraldehyde at −30 °C[a]

entry no.	base	LiCl (amt, equiv)	time (min)	ratio **88**:**89**	% yield **88** + **89**[c]	% yield **91**
1	*n*-BuLi	no	30	88:12	88	
2	LDA	no	60	87:13	85	
3	$LiN(TMS)_2$	no	60	90:10	76	5
4	$NaN(TMS)_2$	no	360	55:45	61	10
5	$KN(TMS)_2$	no	420	53:47	58	20
6	*n*-BuLi	no	30	88:12	88	
7	*n*-BuLi	yes (1)	120	90:10	66	15
8	*n*-BuLi	yes (2)	240	89:11	49	25
9	*n*-BuLi	yes (3)	240	90:10	10	50
10	*n*-BuLi	yes (5)	2400			80

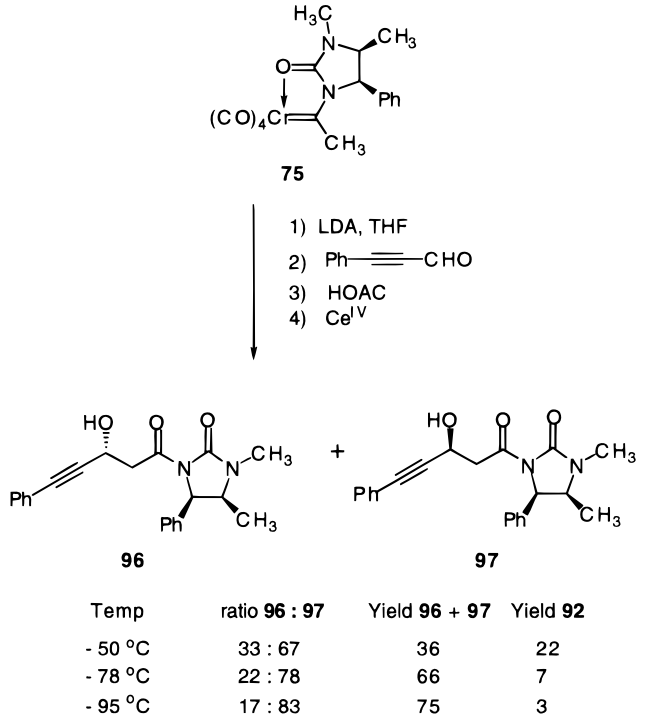
[a] Reactions carried out in THF at 0.07 M in **75**. The enolate was generated from the indicated base at −30 °C, and aldehyde was added after 5 min. The HMPA was added to the enolate before the aldehyde.

The assignment of the major diastereomer produced in the aldol reactions of complex **75** has been confirmed by several methods. The stereochemistry of the adduct with benzaldehyde has been confirmed by an X-ray structure and the absolute stereochemistry of the three adducts in Scheme 10 have been confirmed by comparison of the optical rotations of the β-hydroxy esters with those known for these compounds.[67] In addition, the direction of the induction of these aldol reactions was confirmed in the synthesis of (3*R*)-1,3-nonadiol, a constituent of the rectal gland secretion of the male cucumber fly.[68] The reaction of the enolate of the enantiomer of complex **75** with *n*-heptaldehyde in the presence of 1 equiv of lithium chloride gave the aldol adduct **93** in 81% isolated yield (Scheme 11). A small amount of the aldol adduct **94** was also isolated from the reaction, but the two adducts could be completely separated by silica gel chromotagraphy with a single pass. Treatment of the aldol adduct **93** with lithium borohydride gave the nonadiol **95** in 80% yield, with the same optical rotation reported for the 3*R*-isomer.[69] The chiral auxiliary was recovered in 80% yield from this reaction. In all other aldol reactions where the auxiliary was recovered, this represents a minimum value.

Scheme 11



Scheme 12



Temp	ratio **96 : 97**	Yield **96** + **97**	Yield **92**
- 50 °C	33 : 67	36	22
- 78 °C	22 : 78	66	7
- 95 °C	17 : 83	75	3

In connection with a synthetic program aimed at the total synthesis of polyene natural products containing allylic functionality, we initiated a program to investigate the aldol reaction of acetylenic aldehydes.[70] As illustrated in Scheme 12, the reaction is most useful at low temperatures, where the reaction produces adduct **97** with the stereochemistry reversed from that observed for simple aldehydes at higher temperatures. The reaction cannot be performed at higher temperatures, since substantial amounts of the elimination product **92** are observed. In contrast to the reactions with simple aldehydes, the reactions of acetylenic aldehydes at low temperature are synthetically useful, since they are much faster and are complete in 1 h at −95 °C. The stereoselectivities observed with most acetylenic aldehydes are greater than 90:10.[70]

If dicobalt hexacarbonyl adducts of the acetylenic aldehyde are employed, both enantiomers of the aldol adducts with acetylenic aldehydes are available from the same chiral carbene complex.[70] This is illustrated by the aldol reactions of the (4*E*,6*E*)-octa-4,6-dien-2-ynal **98** (Scheme 13). Direct aldol reaction of **98** with carbene complex **75** at −95 °C gives aldol adduct **100** in 74% yield with greater than 95:5 selectivity. The alkynal **98** can be converted to the cobalt complex **99** in high yield simply by stirring with cobalt carbonyl at room temperature for 15 min. Aldol reaction of the cobalt complex **99** alkynal with complex **75** occurred with reversed stereoselection, giving the adduct **101** in 91:9 selectivity. Thus, the cobalt-complexed alkynal **99** simply behaves as an aldehyde bearing a sterically bulky substituent. Presumably the stereoselectivity of this reaction could be improved by increasing the temperature (Figure 1); however, substantial amounts of elimination products are observed when the temperature is raised above −78 °C. Nonetheless, this methodology can provide either enantiomer of the aldol adduct with acetylenic aldehdyes in good yields and high stereoselectivities from the same chiral carbene complex.[70]

The temperature dependence of the induction in the aldol reactions of carbene complex **75** is quite interesting, and at this point this phenomenon is not clearly understood. One possible explanation is that the enolate of **75** can form aggregates. This explanation would require that the more aggregated enolate **102** would react with an aldehyde to preferentially form diastereomer **89** and that the less aggregated enolate **103** would react with the same aldehyde to preferentially give diastereomer **88**. This explanation would be consistent with the temperature effects described in Table 1 and with the observation that at a given temperature (−78 °C) a decrease in concentration results in a higher preference for the formation of **88** (entries 7 and 8). If this is the case, then formation of aggregates is reversible, as revealed by the data in entry 9, where warming the enolate to −30 °C and then recooling to −78 °C before addition of the aldehyde gives the stereoselectivity associated with −78 °C and not −30 °C. Many additional experiments will need to be done to further probe the possibility of the mechanism shown in Scheme 14, including a more comprehensive concentration study on the induction.

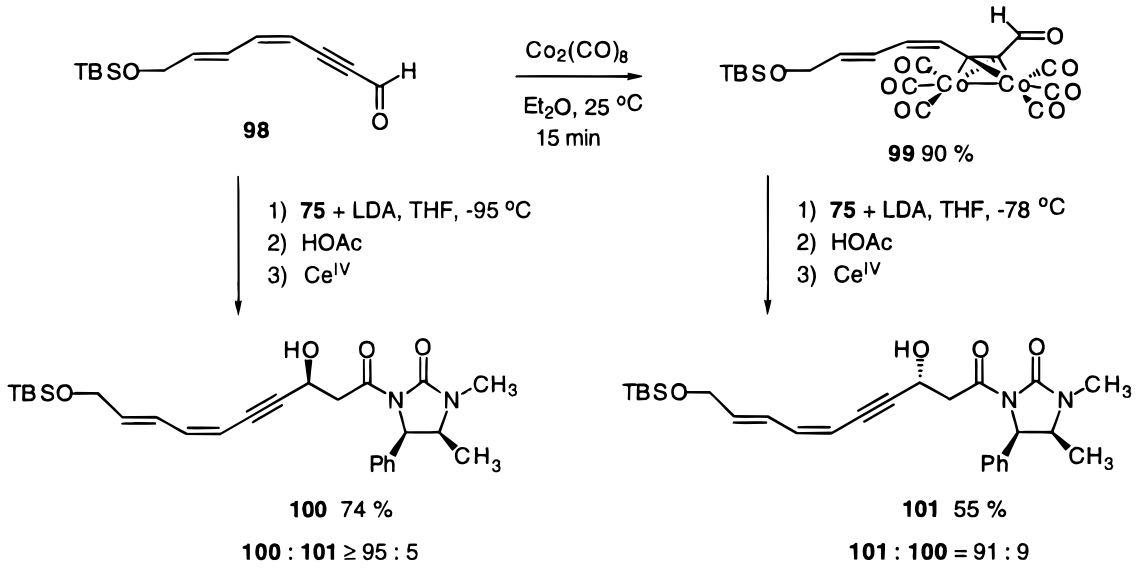
The only solid-state structural information on the enolate of a Fischer carbene complex was reported by Floriani for the potassium enolate of the methyl methoxy carbene complex **42**[71] (Scheme 15). A single crystal was obtained in the presence of 18-crown-6. This structure reveals that the potassium cation is coordinated to the oxygen of the carbon monoxide ligand that is trans to the carbene carbon. It is possible that, in the absence of a crown ether, potassium enolate could aggregate. We propose that the aggregation of the

(69) (a) Kitching. W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; Konig, W. A.; Francke, W. *J. Org. Chem*. **1989**, *54*, 3893. (b) Katch, O.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1935.

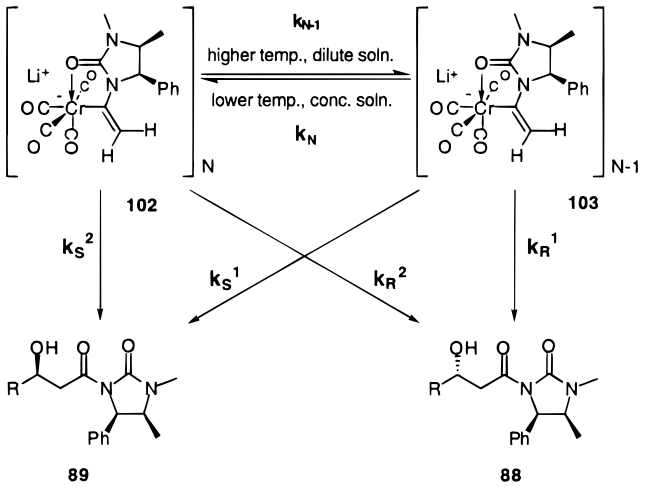
(70) Wilson, K. J.; Parisi, M. P.; Wulff, W. D.; Rheingold, A. L. *J. Org. Chem*., submitted for publication.

(71) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1994**, *13*, 214.

Scheme 13



Scheme 14



lithium enolate **106** (from **75**) occurs by coordination of the lithium in structure **106** to the carbon monoxide ligand that is *trans* to the imidazolidinone carbonyl in a second molecule of the enolate, which would give structure **105**. This is supported by ^{13}C NMR studies on the lithium enolate of the tungsten carbene complex analogous to **75**.[68] The tungsten enolate did not produce the line broadening noticed for the chromium complex and, furthermore, the tungsten complex displays a temperature dependence on the stereoselectivity that is essentially the same as that reported in Table 1. The ^{13}C NMR spectrum of the tungsten enolate was taken over several temperatures between −78 and 22 °C in d_8-THF at 0.07 M, and a substantial chemical shift was seen only for the two carbon monoxide ligands that were assigned as those *trans* to the carbene ligand and *trans* to the imidazolidinone carbonyl.

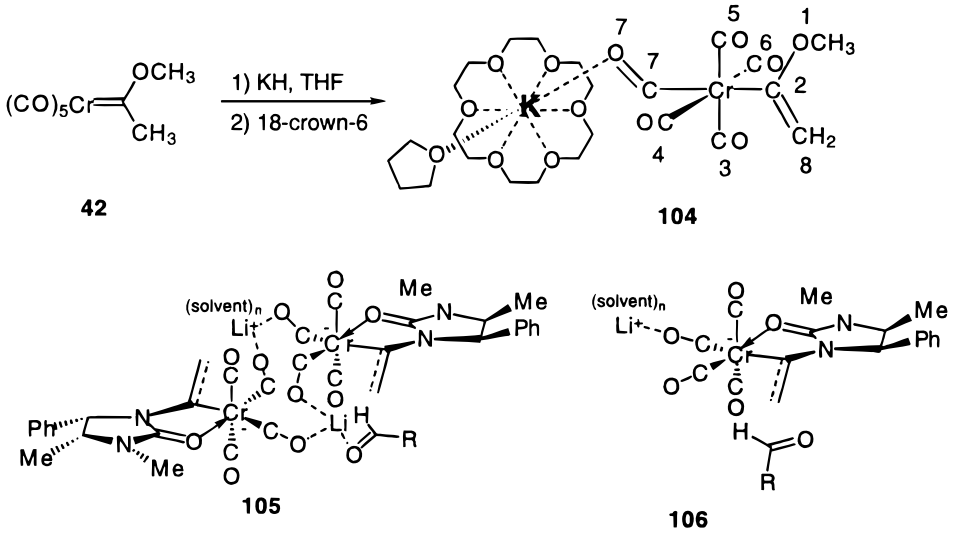
If species **105** and **106** are involved in the reaction, then an explanation of the stereoselection can be provided. Since the lithium in enolate structure **106** is far removed from the enolate carbon, an open transition state might be expected. If this is the case, then an examination of space-filling models suggests that an approach may be favored in which the hydrogen of the aldehyde is oriented toward the metal center and the alkyl substituent is *anti* to the carbene carbon. This alignment will minimize dipole−dipole interactions with the oxygen approximately *anti* to the chromium. The reversal in selectivity at low temperatures can be explained by a closed transition state for the aldol reaction of the aggregated dimer **105**. Coordination of the aldehyde carbonyl to the bridging lithium then would lead to the expectation that the preferred orientation of the aldehyde would project the hydrogen, not the alkyl group, toward the metal center.

The solvent effects on the reaction (Table 2) would be consistent with the observation that more coordinating solvents give higher selectivity for adduct **88**, since aggregation would be disrupted. It is not clear how the cation effects (Table 3) could be accounted for, since it is not clear how aggregation is dependent on the alkali-metal cation. For example, the lithium, sodium, and potassium enolates of pinacolone have been isolated as an unsolvated hexamer, a un-enolized ketone solvated tetramer, and a solvated (THF) hexamer, respectively.[72] The effect of added lithium (Table 1) could be the result of enhanced stereoselection in the open transition state **106** as a consequence of lithium cation coordinating to the aldehyde.[67] Finally, the drop in reactivity seen with HMPA is quite puzzling and will be investigated further. Normally, the "naked enolates" of ketones and esters are more reactive than enolates with more oxophilic cations. One might speculate that since the lithium in the coordinated species **106** is *trans* to the enolate carbon, it serves to keep the negative charge accessible to the enolate carbon relative to the dissociated ion pair caused by HMPA, in which the negative charge would be dispersed over all of the carbon monoxide ligands, leading to a less reactive species.

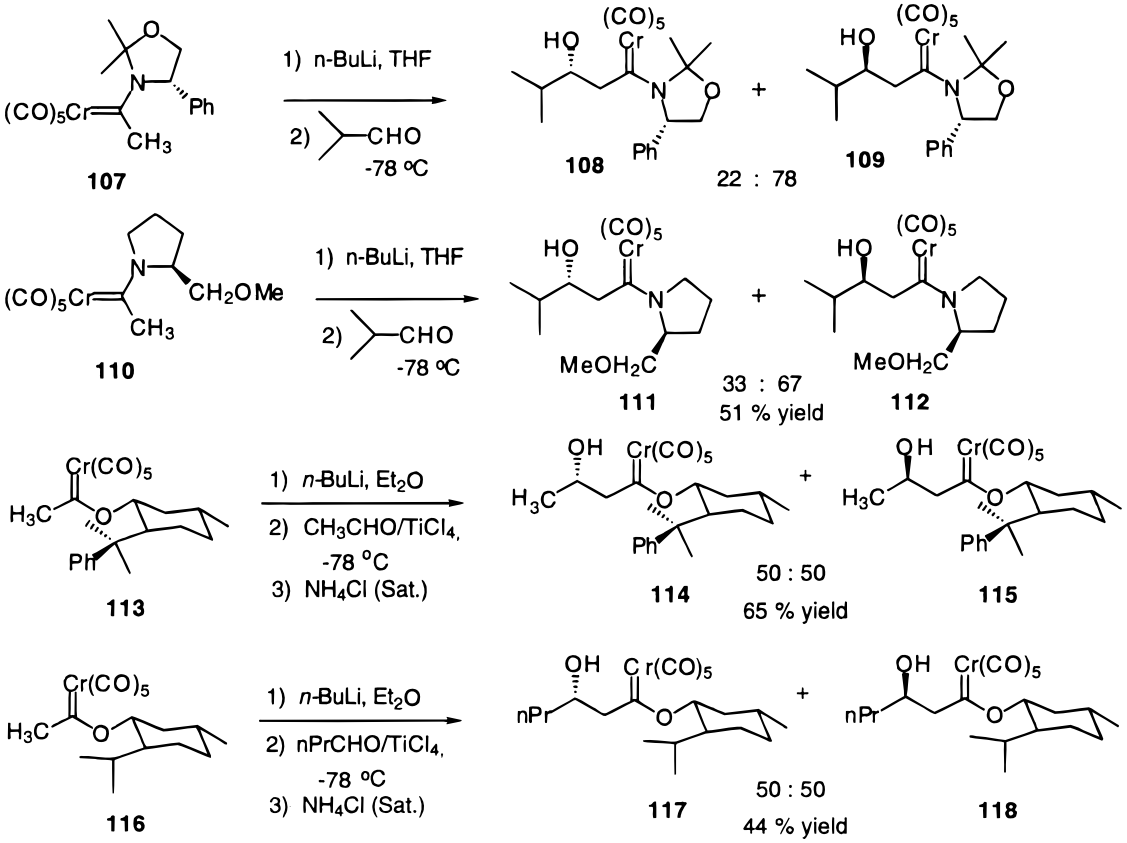
Most of the studies of the aldol reactions of chiral carbene complexes have been with the imidazolidinone complex **75**.[61,68,68,70] There have been investigations of asymmetric aldol reactions of four other chiral complexes, illustrated in Scheme 16. The aldol reactions of complex **107** have been investigated with a number of aldehydes.[45] Like the aldol reaction of complex **75**,

(72) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

Scheme 15



Scheme 16

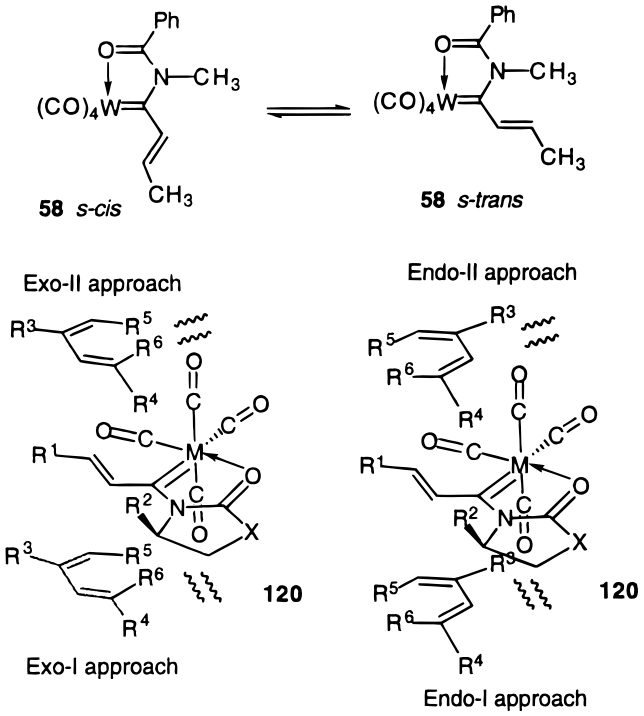


the aldol reaction of complex **107** with benzaldehyde gives high stereoselectivity. The aldol reaction of complex **107** with isobutyraldehyde at −78 °C is not as selective as complex **75** under the same conditions (Table 1) but, interestingly, gives a selectivity reversed from that with benzaldehyde. The aldol reactions of the chiral complexes **110**,[37] **115**,[37] and **116**[73] have only been investigated with the aldehydes shown in Scheme 16. The aldol reactions of the complex shown in Scheme 16 have only been performed at −78 °C, and given the observations made for the aldol reactions of complex **75**, it may be interesting to reexamine the aldol reactions of these complexes at different temperatures and concentrations.

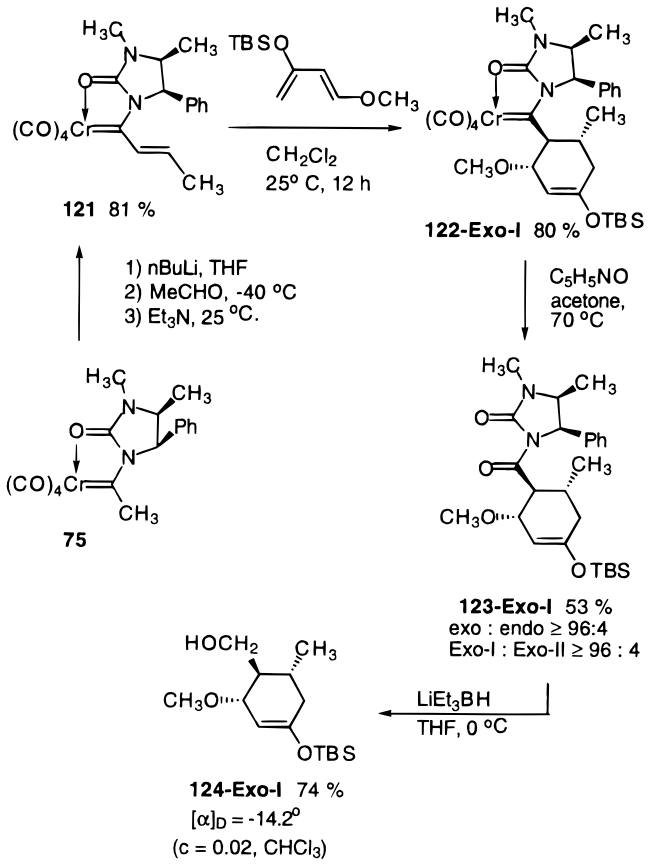
The observation that the *N*-acyl carbene complex **58** gave only the *exo* adduct **59** (Scheme 6) was quite surprising, since the reaction of the corresponding methoxyl complex **54** with the same diene was not a selective reaction (Scheme 5).[54] This was also quite an exciting discovery, since most Diels−Alder reactions are *endo* selective. While some dienes and dienophiles are *exo* selective, there is no general solution to *exo* selective control in the Diels−Alder reaction.[74] Thus, we decided

(73) Wilson, K. J.; Wulff, W. D., unpublished results.

Scheme 17



Scheme 18



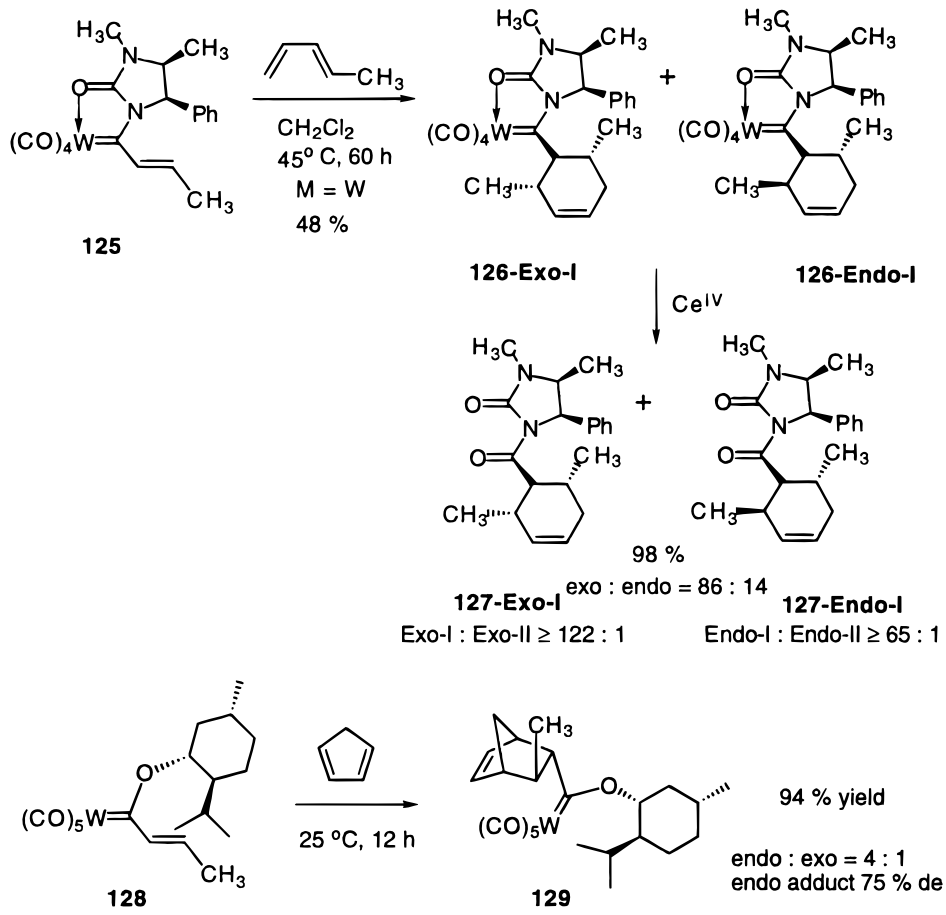
to pursue the lead provided by the reaction of complex **58** with Danishsefsky's diene and set out to determine the scope of these Diels−Alder reactions. Our model for the *exo* stereoselection is shown in Scheme 17. To explain the *exo* selectivity, we initially assumed that the Diels−Alder reaction of **58** occurred via the *s-cis* and not the *s-trans* conformation. This is because upon consideration of the *s-cis* conformation of **120** (Scheme 17), it can be seen that *endo* approach of a diene leads to close contacts with the apical CO ligand on the metal. The reaction of a chiral complex should reveal whether these complexes are in fact reacting via an *s-cis* conformation, as originally proposed.[54] Assuming that the approach of the diene to a chiral complex would occur from the face of the vinyl group opposite that containing the substituent R^2, then a determination of the absolute stereochemistry of the product should tell whether the addition occurs to the *si* face (*s-cis* conformation) or the *re* face (*s-trans* conformation) of the vinyl group. Also, the development of a chiral complex of type **120** could possibly provide for the first general enantioselective *exo*-selective Diels−Alder reaction.

The *trans*-propenyl imidazolidinone carbene complex **121** was best prepared from methyl complex **75** by an aldol condensation. Addition of the enolate of **75** to acetaldehyde at −40 °C followed by addition of triethylamine and warming to room temperature gave an 81% yield of the condensation product. As did the *N*-benzoyl complex **58** (Scheme 6), imidazolidinone complex **121** reacted with Danishefsky's diene at room temperature to give exclusively the *exo* adduct **122**.[75] In addition, this adduct was formed as only one of the two possible *exo* diastereomers. An X-ray diffraction study revealed that the relative stereochemistry of the product is that indicated in Scheme 18. The observation of this stereochemistry leads to the conclusion that the dienophile must react via the *s-cis* conformation, if it is assumed that the diene approaches the dienophile from the side opposite the phenyl and methyl groups on the chiral auxiliary. The level of stereoselection was determined on the imide **123** obtained by oxidative removal of the metal from **122**. Because of the sensitive enol ether function, this step could not be performed with the Lewis acid ceric ammonium nitrate. The stereochemical purity of imide **123** was found to be ≥96:4 *exo* to *endo* and ≥96:4 *exo*-I to *exo*-II on the basis of ^{1}H NMR analysis of all four possible diastereomers of **123** prepared by independent synthesis. The chiral auxiliary could be removed by reduction with lithium triethylborohydride to give alcohol **124** in 74% yield.

Danishefsky's diene is one of the more reactive dienes used in Diels−Alder reactions. To probe the other extreme in reactivity, we examined the reaction of chiral imidazolidinone complexes with *trans*-piperylene, since this is the simplest diene that can give *exo* and *endo* products.[75] This reaction was much slower and could not be performed with the chromium complex, since substantial decomposition of the carbene complexes occurred. However, the more robust tungsten complex **125** reacted at 45 °C in 60 h to give a 48% yield of the cycloadduct (Scheme 19). In this case the *exo*:*endo* selectivity was 86:14 and the *exo* diastereoselectivity was ≥122:1, as determined by capillary GC. The scope of this enantioselective exo Diels−Alder reaction does not extend to cyclopentadiene. Complex **121** reacts with cyclopentadiene to give only moderate *exo* selectivity (80:20), and the *exo* isomer is formed in only modest diastereoselectivity (62:38). The above observations are

(74) See footnote 2 in ref 75.
(75) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438.

Scheme 19



consistent with the model shown in Scheme 17. *trans*-Piperylene would not be expected to be as *exo* selective as Danishefsky's diene, since when $R^3 = H$ the *endo* approach should not be as strongly disfavored. trans-Piperylene would be expected to exhibit high facial selectivity since $R^4 \neq H$. For cyclopentadiene, both R^3 and R^4 are hydrogen. Further studies with other dienes are underway to continue to test this model and define the scope of this new method for asymmetric *exo* selective Diels–Alder reactions.

The only other asymmetric Diels–Alder reaction of a chiral carbene complex that has been investigated is the reaction of the *trans*-propenyl complex **128** prepared from (−)-menthol.[30] This complex gave cycloadducts with cyclopentadiene in 94% yield after 12 h at room temperature. The major isomer was the *endo* adduct (*endo*:*exo* = 80:20), which is consistent with the stereochemistry seen for the same reaction of the corresponding methoxy complex.[76] The cycloadduct **129** was formed as a 88:12 mixture of *endo* diastereomers, and the absolute configuration of the major diastereomer was shown to be that drawn in Scheme 19. This was determined by oxidative cleavage of the metal and comparison of the resulting ester with an authentic sample made by an asymmetric Diels–Alder reaction with a chiral oxazolidinone and a change in chiral auxiliary to (−)-menthol.[77] On the basis of this result, it might be anticipated that a more highly asymmetric *endo*-selective Diels–Alder reaction may be possible with phenylmenthol-derived carbene complexes of the type **28** (Chart 2).

It has been shown that Fischer carbene complexes can be used to synthesize 1,5-dicarbonyl compounds by serving as Michael acceptors for enolates of carbonyl compounds,[13] by serving as Michael donors to α,β-unsaturated carbonyl compounds,[3] or even by serving both functions in the same reaction[78] (Scheme 20). In principle, it should be possible with the proper choice of chiral carbene complex to develop an asymmetric synthesis of 1,5-dicarbonyl compounds with either of these approaches. In fact, both methods have been realized. Phenylmenthol complexes of type **28** have been reported as Michael acceptors,[33] and imidazolidinone complexes of type **63** have been reported as asymmetric Michael donors.[79] A survey of methods in the literature reveals that the only viable and widely applicable method of adding chiral enolates to α,β-unsaturated carbonyl compounds is the Enders protocol, involving the addition of a chiral ketone enolate in the form of a chiral hydrazone.[80] Examples involving the addition of a chiral ester enolate have not been as

(76) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642.

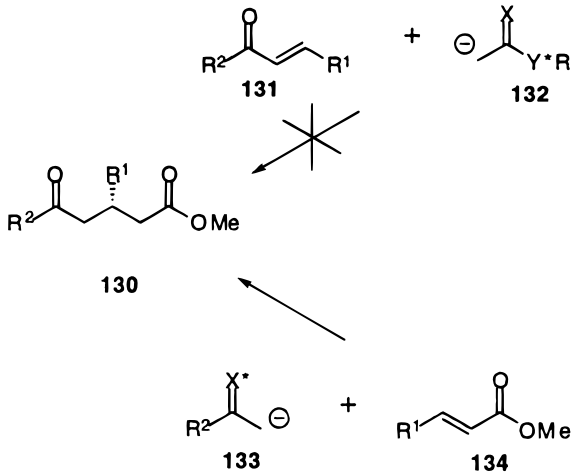
(77) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(78) (a) Casey, C. P.; Brunsvold, W. R. *J. Organomet. Chem.* **1975**, *102*, 175. (b) Macomber, D. W.; Hung, M. H.; Verma, A. G.; Rogers, R. D. *Organometallics* **1988**, *7*, 2072.

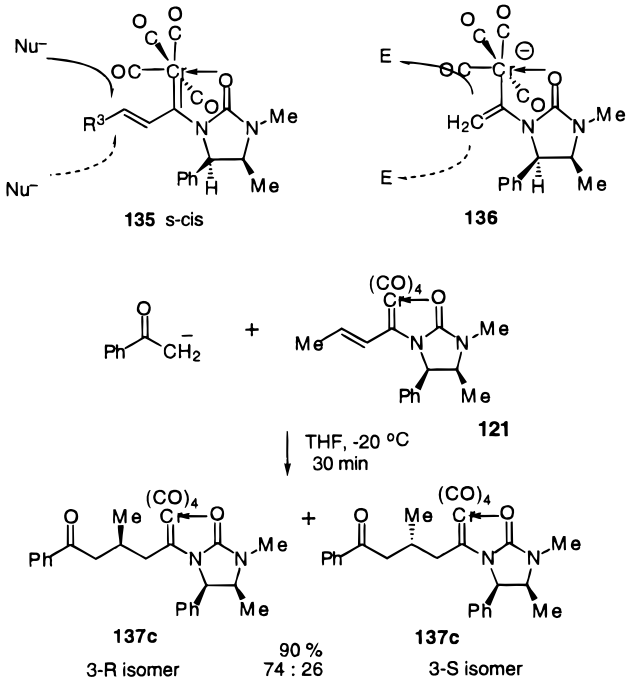
(79) Shi, Y.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *J. Chem. Soc., Chem. Commun.* **1996**, 2601.

(80) (a) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967. (b) Enders, D.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1223.

Scheme 20



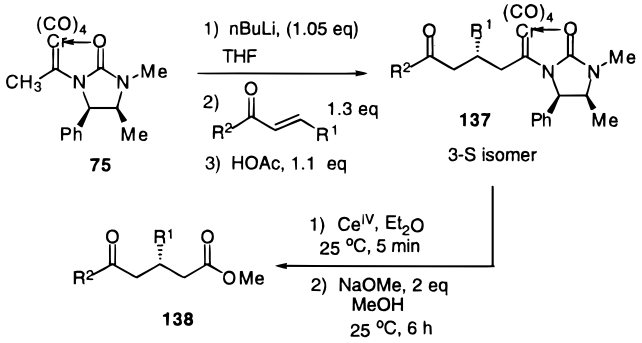
Scheme 21



successful and represent an opportunity for chiral carbene complexes.[81,82]

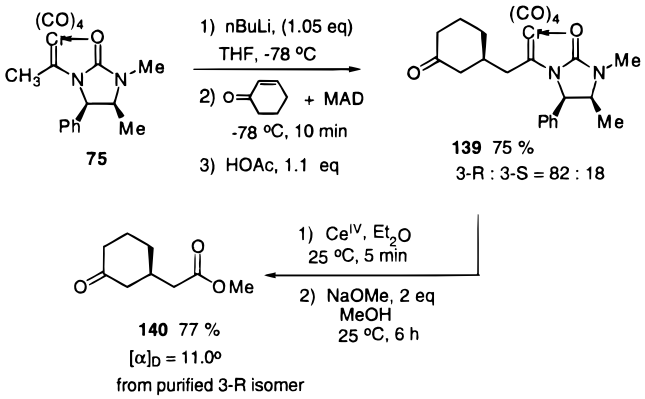
The finding that the Diels−Alder reactions of α,*β*-unsaturated imidazolidinone complexes react via an *s-cis* conformation had an influence on the strategy we developed to apply these complexes to asymmetric Michael additions. If the Michael additions to complexes of type **135** (Scheme 21) also occur via an *s-cis* conformation, then based on an analysis of space-filling models it did not appear that high facial selection on the alkenyl substituent of the carbene complex would be likely, since the *β*-carbon of the alkenyl group is too far away from the chiral centers on the imidazolidinone ring. This expectation was borne out in the addition of acetophenone enolate to complex **121**, which gave a 3:1 mixture of diastereomers.[79] The model shown in Scheme 21 did correctly predict that the major isomer would be

Scheme 22



series	R^1	R^2	Temp	Yield **137**	Yield **138**	Ratio 3-S : 3-R
a	Ph	Me	0	87		88 : 12
a	Ph	Me	-20	91	81	94 : 6
a	Ph	Me	-60	85		86 : 14
b	Me	Me	-20	59	72	88 : 12
c	Me	Ph	-20	87	83	97 : 3
d	Me	i-Pr	-20	90	83	96 : 4
e	Me	t-Bu	-20	91	87	97 : 3

Scheme 23



the 3-*R* isomer; however, the level of induction was not high enough to warrant further investigations of this approach.

The model outlined in Scheme 21 suggests that higher stereoselections should result from the use of chiral imidazolidinones as Michael donors than as Michael acceptors. Approach of an enone to the enolate carbon of the anion **136** should result in a closer pass by the phenyl group of the chiral auxiliary than the approach of a nucleophile to the *β*-carbon of the alkenyl group of the complex **135**. This expectation was also confirmed by experiment, as summarized in Scheme 22.[79] Specifically, complex **137c** can be obtained as a 97:3 mixture of diastereomers from complex **75**, in comparison to only a 74:26 mixture of diastereomers from α,*β*-saturated complex **121** (Scheme 21). The selectivities can be slightly enhanced in most cases by precoordination of the enone with a Lewis acid. For example, the selectivity for the formation of complex **137a** can be increased to 97:3 at −20 °C (82% yield) if methylaluminum bis(di-2,6-*tert*-butyl-4-methylphenoxide), or MAD,[83] is employed. The configurations at the 3-position of the Michael adducts were determined by conversion to the *δ*-keto esters **138** and comparison of the optical rotations with known values.

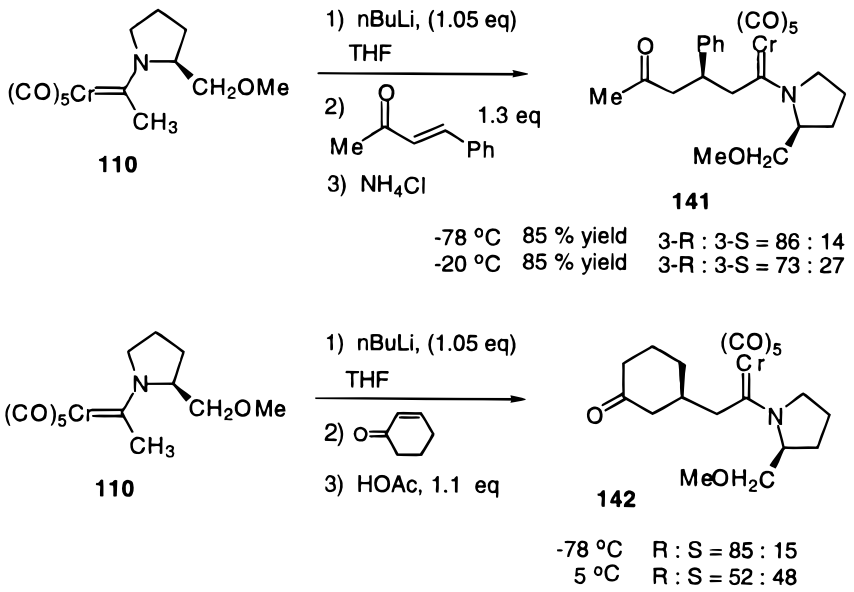
The asymmetric Michael addition of the enolate of complex **75** to cyclic enones did not give inductions as

(81) For citations to chiral catalysts, see footnote 4 in ref 79 and: Arai, T.; Sasai, H.; Aoe, K.-I.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104.

(82) For related systems, see footnote 5 in ref 79.

(83) Maruoka, K.; Itoh, T.; Sakurai, M.; Nomoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.

Scheme 24



high as those observed with acyclic enones.[68] For example, addition to cyclohexanone occurred with the formation of adduct **139** in 77−80% yield with a low stereoselection that was not highly temperature dependent (68:32 at −78 °C and 60:40 at −10 °C). As shown in Scheme 23 the stereoselectivity could be enhanced to 82:18 if the enone was precomplexed with MAD.[83] The two diastereomers of **139** could be easily separated by silica gel chromatography and thus, after purification, the metal in the 3-*R* isomer of **139** was removed by oxidation and the auxiliary removed by basic methanolysis to give the known keto ester **140** in high optical purity in 77% yield.

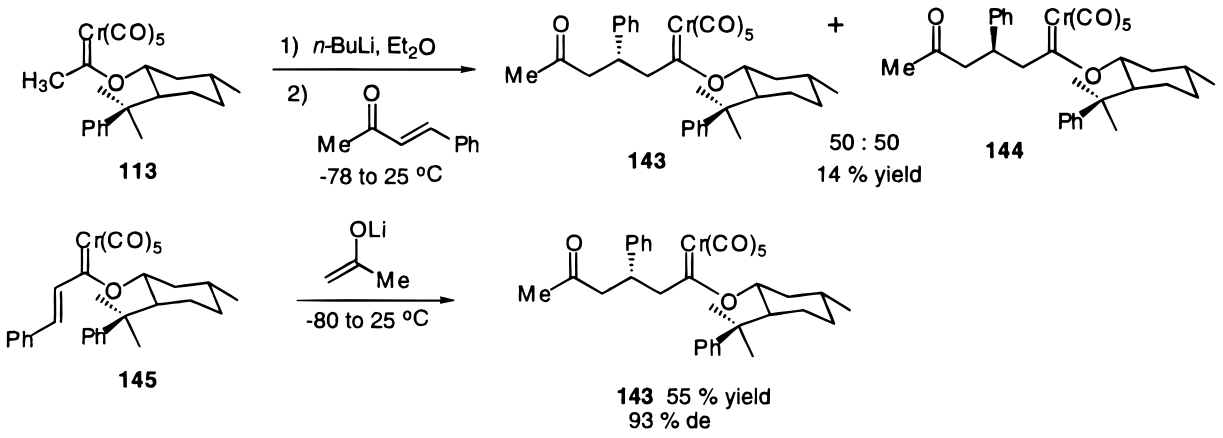
The asymmetric Michael addition of the chiral amino carbene complex **110** has been reported for several cyclic enones, including cyclohexenone, which is shown in Scheme 24.[40] The maximum selectivity for this Michael addition is approximately the same as that observed for the addition of complex **75** to cyclohexenone in the presence of MAD (Scheme 23). However, the advantage of imidazolidinone complex **75** is apparent in the comparison with the additions to 4-phenyl-3-buten-2-one. Complex **110** shows a normal temperature dependence with a maximum selectivity at −78 °C of 86:14,[34] whereas complex **75** shows an inverse dependence with a maximum selectivity at −20 °C of 96:4. An additional advantage of complex **75** is in the ease of separation of the Michael adducts **137**. The Michael adducts **141** and **142** prepared from prolinol complex **110** exist as a mixture of four diastereomers, two of which are atropisomers resulting from the high barrier to rotation about the nitrogen−carbene carbon bond. Of course, the atropisomers do not exist after oxidative removal of the metal, but it is often useful and easier to separate the diastereomers with the metal on, since the 3-*S* and 3-*R* diastereomers are usually more difficult to separate after the metal is removed. In summary, while it may be possible that other prolinol derivatives may give improved asymmetric induction, the results show that the imidazolidinone complex **75** is superior to the prolinol complex **110** as Michael donors to α,β-unsaturated enones.

The model developed for the Michael additions of imidazolidinone complexes (Scheme 21) led to the correct prediction that these complexes would be more effective as Michael donors rather than Michael acceptors. Interestingly, the Michael addition of phenylmenthol complexes exhibits the reverse profile. The reaction of complex **113** with 4-phenyl-3-buten-2-one gave a 1:1 mixture of diastereomers,[34] while the α,β-unsaturated complex **145** gave high asymmetric inductions with a number of nucleophiles, including a variety of alkyllithiums and ketone enolates[33] (Scheme 25). The temperature dependence of the enolate of complex **113** has not been investigated. Nonetheless, the Michael additions to unsaturated complex **145** are highly selective, and synthetic applications of these reactions are expected.

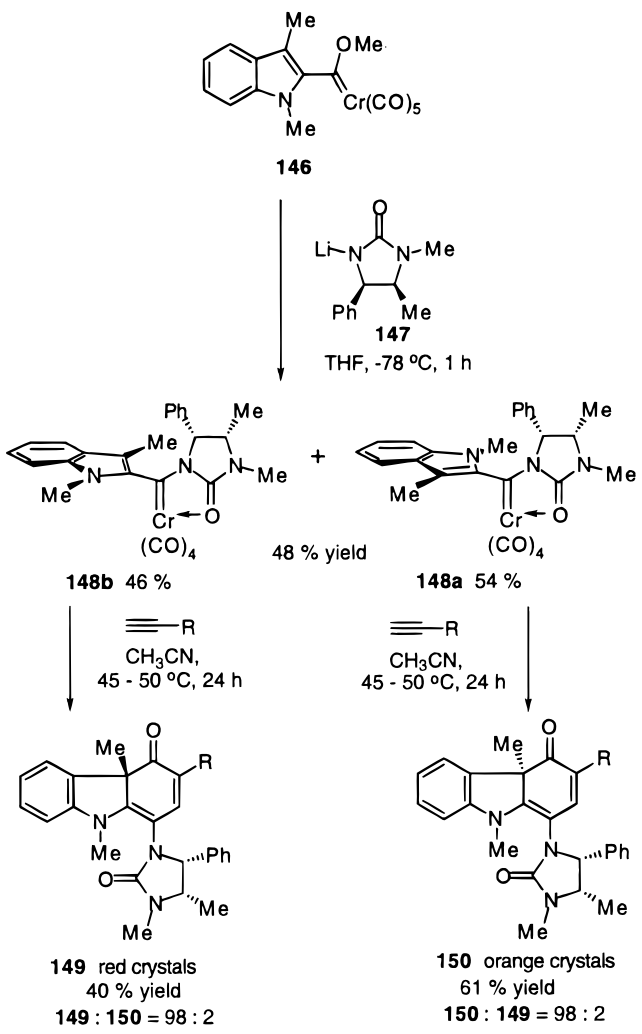
The first asymmetric cyclohexadienone annulation has recently been reported for an indole carbene complex that utilized an imidazolidinone chiral auxiliary.[84] The imidazolidinone was introduced by treating the methoxy indole complex **146** with the *n*-lithiated imidazolidinone **147** (Scheme 26). The approach produced a mixture of two atropisomeric carbene complexes which could be easily separated on silica gel. The reaction of these complexes with alkynes produces 4*H*-carbazol-4-ones with a new chiral center as a quaternary carbon adjacent to the carbonyl. It was found that the reactions of these complexes are stereoselective as well as stereospecific. The reaction of complex **148a** with 1-pentyne gave a 61% yield of carbazolone **150** as orange crystals with a 98:2 diastereoselectivity. Complex **148b** gave epimeric compound **149** as red crystals also with a 98:2 selectivity. The complexes **148a** and **148b** could not be interconverted either thermally or photochemically. Although these complexes can be easily separated, it would be advantageous if a method could be developed for the selective preparation of one of the atropisomers. Nonetheless, this initial finding shows that high asymmetric induction can be achieved in the synthesis of 4*H*-carbazol-4-ones from imidazolidinone

(84) Quinn, J. F.; Powers, T. S.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *Organometallics* **1997**, *16*, 4945.

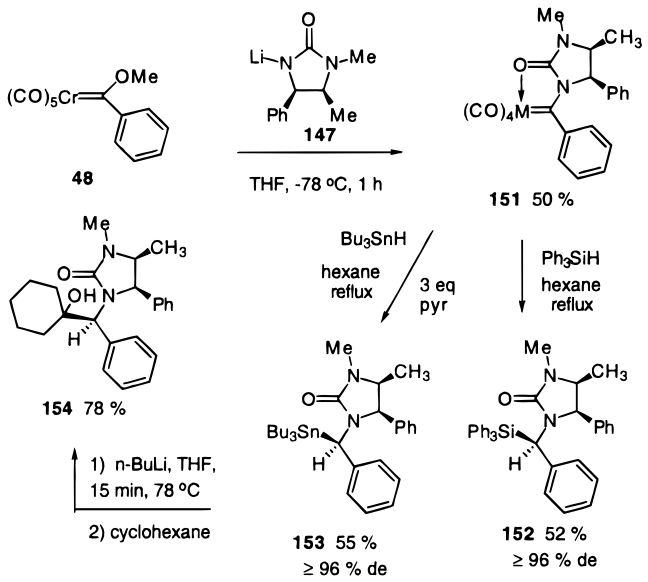
Scheme 25



Scheme 26



Scheme 27



carbene complexes and that either the 4-*R* or 4-*S* isomer can be obtained in high optical purity from the same chiral auxiliary. These results also suggest that high inductions might be possible for the cyclohexadienone annulations of other types of carbene complexes.

Chiral imidazolidinone carbene complexes can also be used to prepare chiral α-aminosilanes and α-aminostananes with high asymmetric inductions, as illustrated by the examples in Scheme 27.[85] The 1,1-addition of Si−H and Sn−H bonds to Fischer carbene complexes was first reported by Fischer and Connor,[86] but until now there have been no examples of this reaction with a chiral carbene complex. We have found that phenylimidazolidinone complex **151** will react with tributylstannane and triphenylsilane to give the formal M−H insertion products **153** and **152**, both with high asymmetric induction.[87] We have not yet extensively explored the synthetic applications of these materials; however, it is known that α-stannylimidazolidinones of type **153** will undergo exchange with alkyllithiums to give α-lithioamines which are configurationally stable and which can be alkylated with a variety of electrophiles.[87] Prompted by these studies, we have found that the stannane **153** rapidly exchanges with butyllithium. Subsequent reaction with cyclohexanone gave the *β*-amino alcohol derivative **154** in 78% yield as a single diastereomer. The configuration of **154** is assumed to be that shown, since Pearson and Lindbeck have shown that similar alkylations occur with retention.

(85) Parisi, M. P.; Solo, A.; Wulff, W. D.; Guzci, I. A.; Rheingold, A. L. *Organometallics* **1998**, submitted for publication.
(86) (a) Fischer, E. O.; Dötz, K. H. *J. Organomet. Chem.* **1972**, *36*, C4. (b) Connor, J. A.; Rose, P. D.; Turner, R. M. *J. Organomet. Chem.* **1973**, *55*, 111.
(87) Pearson, W. H.; Lindbeck, R. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622.

In conclusion, a number of successful applications of chiral carbene complexes in asymmetric synthesis have now been developed. Imidizaolidinone complexes were developed with a view that they would broadly apply to a number of different reactions. The imidazolidinone complexes have been found useful in asymmetric Michael additions, aldol reactions, Diels−Alder reactions, cyclohexadienone annulations, and insertions into Si−H and Sn−H bonds. The chemistry described here aside, it is clear that asymmetric synthesis with carbene complexes is in an early stage of development. A large number of reactions have yet to be investigated, and it is likely that no one class or type of chiral complex will be optimal for all applictions.

Acknowledgment. The National Institutes of Health has provided financial support for this work. We gratefully acknowledge that Professor Arnold L. Rheingold has determined all of the solid-state structures discussed in this review. We also acknowledge the contributions from all of the graduate students and postdoctoral fellows who helped to develop the chemistry of imidazolidinone carbene complexes, especially those of Timothy S. Powers, who initiated this work, and of Yan Shi, who has many unpublished results which appear in this review.

OM980020Y