Asymmetric Michael Reactions of Aminocarbene Complex Anions

Benjamin A. Anderson,[1] William D. Wulff,* and Annette Rahm

Contribution from the Searle Chemistry Laboratory, Department of Chemistry, University of Chicago, Chicago, Illinois 60637

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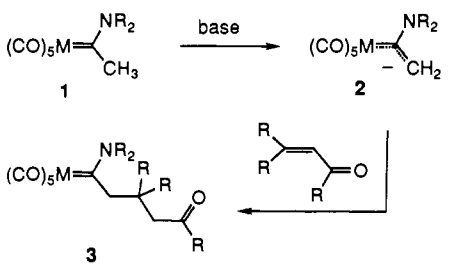
Abstract: The first Michael addition reactions of the anions of aminocarbene complexes to α,β-unsaturated carbonyl compounds are reported. Unlike their corresponding amide enolates, these anions give exclusive 1,4-addition to a number of enones. For chiral complex **27**, it was shown that the formation of the 1,4-addition product is not reversible and that the initial 1,4-addition is thus kinetically controlled. The anions of aminocarbene complexes are much more effective in this regard than the anions of alkoxycarbene complexes. It was demonstrated that aminocarbene complexes can serve as synthons for amides in Michael additions since the metal can be liberated from the Michael adducts to give amide products by oxidation with either DMSO or dimethyldioxirane. The steric bulk of the metal unit in the aminocarbene complex anions plays a role in the facial selectivity in the addition to 1,4-diphenyl-2-penten-1-one which produces a 21:1 mixture of diastereomers in the case of methyl pyrrolidino complex **12**. This is the highest facial selectivity that has ever been observed in the Michael additions of enolates to this enone. The Michael additions of the chiral amino complex **27** derived from prolinol methyl ether with several cyclic enones were investigated and represents the first examples of asymmetric reactions of any type of the "enolates" of either alkoxy- or amino-stabilized group 6 Fischer carbene complexes. Both enantiopodes of **27** were examined with cyclohexenone and found to give asymmetric induction in the range of 65–75% ee which is comparable with the best induction that has yet been reported for the addition of a chiral acetaldehyde equivalent to cyclohexenone.

Mutual regiocontrol and stereocontrol of nucleophilic additions to α,β-unsaturated enones is a synthetic challenge that remains without a general solution.[2] The problem is particularly complicated for the case of the Michael reactions of unsubstituted metal enolate derivatives because of the ineludible kinetic preference for 1,2-addition to the carbonyl group.[2b,3] Thermodynamic equilibration can drive reversible 1,2-addition products to the 1,4 product, but optimization of the regiochemistry comes at the expense of kinetic stereocontrol. In the course of our investigations of aminocarbene complex anions as carbonyl enolate equivalents, we anticipated that these reagents would be ideally suited to add to α,β-unsaturated enones with kinetically controlled 1,4 selectivity. The delocalized aminocarbene complex anion **2** is a "soft" nucleophile which should favor 1,4-addition, but the anion should be destabilized by the ancillary amino group to a degree that should provide a synthetically useful nucleophile. The amino substituent was also envisioned as a position in which chirality could be readily incorporated into the carbene complex. Enhanced relative stereocontrol has previously been demonstrated for the nucleophilic reactions of aminocarbene complex anions,[4] but the Michael reactions reported here are the first examples of asymmetric reactions of any type with either alkoxy- or amino-stabilized group 6 Fischer carbene complex anions (Scheme I).[5]

The conjugate addition of the enolates of carbene complexes to α,β-unsaturated carbonyl compounds were first explored by

Scheme I



Casey with the alkoxycarbene complexes **1a**, **7a**, and **7b**.[6] Relatively high temperatures were required to overcome thermodynamic barriers of the addition reactions. For example, the reaction of anion **2a** with methyl vinyl ketone would not proceed at −78 °C, but upon warming to 0 °C, the Michael adduct **4** could be obtained in 22% yield. In addition to methyl vinyl ketone, anion **2a** would also add to methyl acrylate (21%), but in this case, the dialkylation product was obtained in nearly the same yield. Casey also examined the reactions of the anions of **7a** and **7b** with a number of enones and enoates and found that all of the reactions are completely 1,4 selective; however, again the addition products were isolated in only moderate to low yields.[6] Recently, Macomber reported the preparation of bis-carbene complexes of chromium and tungsten of the type **6** via the addition of alkoxy- and aminocarbene complex anions to α,β-unsaturated alkoxy- and aminocarbene complexes, but no 1,4-additions of aminocarbene complex anions to organic substrates have been reported (Scheme II).[5]

Michael Additions of Anions of Nonchiral Aminocarbene Complexes. Several examples have recently been reported that demonstrate the enhanced reactivity of carbene complex anions which is realized upon substitution of the ancillary alkoxy group

(1) American Chemical Society Organic Division Rohm and Haas Fellow, 1989–90. William Rainey Harper Fellow, 1990–91.

(2) For recent reviews of stereoselective Michael reactions, 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.

(3) Duval, D.; Geribaldi, S. In *The Chemistry of Enones*, Part 1; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1989; Chapter 10.

(4) Wulff, W. D.; Anderson, B. A.; Toole, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 5485.

(5) For leading references to other asymmetric reactions of Fischer carbene complexes, see: (a) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1992**, *114*, 2991. (b) Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143. (c) Dötz, K. H.; Weber, R. *Chem. Ber.* **1991**, 1635. (d) Grotjahn, D. B.; Dötz, K. H. *Synlett* **1991**, 381. (e) Macomber, D. W.; Hung, M. H.; Madhuker, P.; Liang, M. *Organometallics* **1991**, *10*, 737.

(6) Casey, C. P.; Brunsvold, W. R.; Scheck, D. M. *Inorg. Chem.* **1977**, *16*, 3059.

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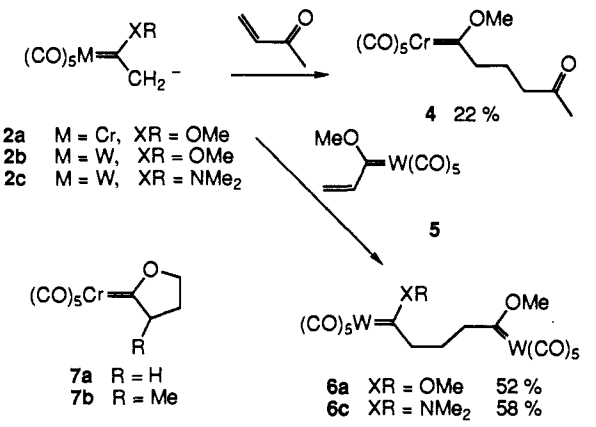
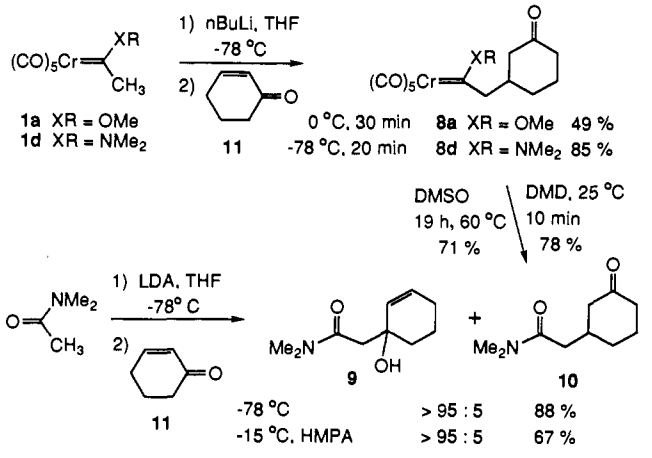
Scheme II

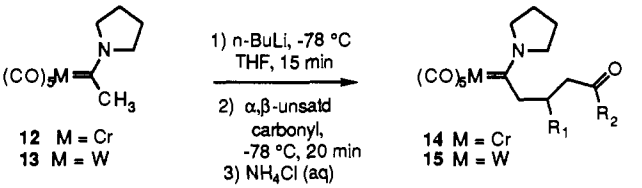


Scheme III



with an amino group.[4,5,7,8] Aminocarbene complexes (complex **1d** has pK_a = 20.4)[9] are much less acidic than alkoxycarbene complexes (pK_a = 8)[10] and are on the same order of acidity as ketones. These values, if considered reflections of the relative stabilities of the corresponding anions, lead to the prediction that Michael reactions of aminocarbene complex anions should also be more thermodynamically favorable than the alkoxycarbene complex reactions. This was born out in our initial studies of the addition of the anions of **1a** and **1d** to cyclohexenone. The anion generated from aminocarbene complex **1d** adds at −78 °C to yield, after 20 min, the 1,4 product **8d** in 85% yield (Scheme III). No reaction of the anion from the methoxy complex **1a** was observed by TLC under similar conditions, and it was not until the reaction mixture was warmed to 0 °C for 30 min that a reaction ensued which eventually led to the isolation of the 1,4 product **8a** in 49% yield (Scheme III). No trace of the 1,2-addition product could be detected for either complex. In addition to the higher reactivity of the amino complexes toward addition to enones, the amino complexes also have the advantage of greater stability than the alkoxy complexes. To demonstrate this, we allowed a sample of the pyrrolidino chromium complex **12** to stand on the laboratory bench in a clear screw-capped vial exposed to air, room temperature, and room light for more than 1 year. After this time, this complex was reacted without purification with butyllithium and cyclohexenone according to the conditions outlined in Table I to give an 81% yield of the adduct **14a**. The methoxyl complex **1a** can not be stored under these conditions

Table I. Michael Reactions of Aminocarbene Complexes



12 M = Cr
13 M = W

14 M = Cr
15 M = W

entry	α,β-unsatd carbonyl struct	no.	R_1 R_2	prodt	% yield[a] of 14/15	% recvy of 12
1		**11**	$-(CH_2)_3-$	**14a**	96	2
2		**11**		**15a**	77	
3		**16**[b]	$(CH_3)(CH_2)_3-$	**14b**		85 (64)[b]
4		**17**	$-C(CH_3)_2(CH_2)_2-$	**14c**	84	16
5		**18**	$-CH_2O-$	**14d**	50	49
6	Ph	**19**	Ph CH_3	**14e**	88	12
7	H	**20**	CH_3 H	**14f**	6[c]	

[a] Isolated yields of products purified by silica gel flash chromatography in air. [b] 85% after 30 min at 25 °C, and 64% after 17 h at 70 °C. [c] 1,2-Addition product **21** was the major product isolated in 78% yield.

for any period of time greater than 1 day and is usually completely decomposed after several days. The methoxy complex can be stored with no significant decomposition after several months in a vial that has been capped with a rubber septum, flushed with nitrogen, and stored in a refrigerator at 0 °C.

The regioselectivity of the addition of the aminocarbene complex anion is quite remarkable when compared to the analogous kinetically controlled reactions of unsubstituted lithium amide enolates with 2-cyclohexenone. For example, the reaction of the lithium enolate of *N,N*-dimethylacetamide with 2-cyclohexenone at −78 °C for 0.8 h has been reported to give the 1,2-addition product in >95:5 selectivity.[11] The reaction could not be thermodynamically driven to favor 1,4-addition even when the reaction was run at −15 °C for 16 h in the presence of HMPA. The 1,2 product **9** was still formed with >95:5 selectivity over the 1,4-addition product **10**.[11] Thus, in terms of regioselectivity, aminocarbene complexes have value as synthons for amides in Michael additions and this was demonstrated by liberating the metal from adduct **8b** by heating in DMSO[12a,b] and by treatment with dimethyldioxirane (DMD)[13] to give the Michael adduct **10** in 71% and 78% yield, respectively.

The Michael reactions of aminocarbene complex anions lead to 1,4-addition products in uniformly high yield (Table I). Dialkylation products were not observed for any of the reactions shown in Table I. Addition reactions of the aminocarbene complex anion to enones occurred in all cases studied except with a β,β-disubstituted compound, 3-methyl-2-cyclohexenone (**16**), which, even upon refluxing in THF for 17 h, failed to yield any product

(7) Wulff, W. D.; Anderson, B. A.; Isaacs, L. D. *Tetrahedron Lett.* **1989**, *30*, 4061.
(8) (a) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (b) Macomber, D. W.; Madhukar, P.; Rogers, R. D. *Organometallics* **1989**, *8*, 1275.
(9) Wulff, W. D.; Anderson, B. A. Unpublished result.
(10) Casey, C. P.; Anderson, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 1230.
(11) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.
(12) (a) Casey, C. P.; Burkhardt, T. J.; Bunnell, C. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 2127. (b) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 6726. (c) Schubert, V.; Fischer, E. O. *Chem. Ber.* **1973**, *106*, 3882. (d) Fischer, E. O.; Plabst, D. *Chem. Ber.* **1974**, *107*, 3326.
(13) Lluch, A.-M.; Jordi, L.; Sanchez-Baeza, F.; Richart, S.; Camps, F.; Messeguer, A.; Moreto, J. M. *Tetrahedron Lett.* **1992**, *33*, 3021.

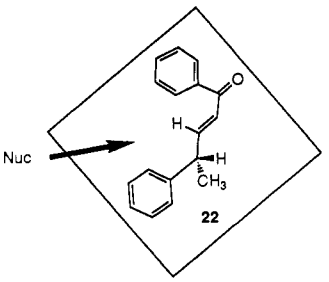


Figure 1.

(entry 3, Table I). It is interesting to note that the enolate of **12** was stable to 17 h of reflux in THF to the point where 64% of complex **12** could be recovered after workup. Michael additions with (*E*)-4-phenyl-3-butenone (**19**, entry 6) and 4,4-dimethyl-2-cyclohexen-1-one (**17**, entry 4) indicated that bulkier substitution at the β-carbon does not force 1,2-addition even though the carbonyl is less congested. This is in contrast to similar addition reactions of enolate anions. Increasing the steric congestion about the β-position of α,β-unsaturated carbonyl compounds typically results in an increase of 1,2-addition at the expense of 1,4-addition.[3,11,14] The reaction with 2(5*H*)-furanone (**18**) gave a comparatively lower yield of the addition product **14e** and was accompanied with a significant recovery of starting material (entry 5). Only in the case of crotonaldehyde (**20**) was a 1,2 product observed, and in that case, aldol adduct **21** was the major product isolated. This is not unexpected since preferential 1,4-additions to enals are known to occur only under special circumstances.[15] An addition reaction was attempted with methyl crotonate but led only to a complicated reaction mixture. The conjugate addition products are very robust compounds and can be handled in air and purified by flash silica gel chromatography.

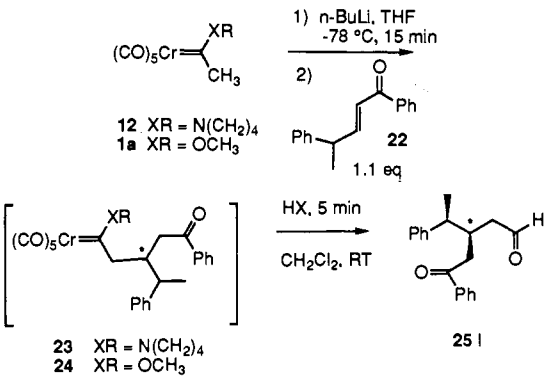
Diastereofacial Selectivity in Additions to Chiral Enones. It has previously been shown that lithium salts of aminocarbene complex anions demonstrate a dramatically greater degree of facial selectivity in aldol reactions with chiral aldehydes than the corresponding lithium amide enolates.[4] We sought to determine whether this intrinsic facial selectivity would be expressed in Michael additions to γ-chiral enones. The most diastereoselective method known for the 1,4-additions to γ-chiral enones involves the Lewis acid-mediated additions of enolsilanes.[16] Generally good diastereomer ratios were reported using this method, with ratios ranging from 5:1 up to >30:1. In all cases, the major isomer resulted from attack of the enolsilane on the *re* face of the *S*-enantiomer or the *si* face of the *R*-enantiomer of the racemic enones. The lowest diastereoselectivities (~5:1) were reported for the $TiCl_4$-mediated addition of the trimethylsilyl enol ether of 3,3-dimethylbutanone to 1,4-diphenyl-2-penten-1-one (**22**). This was the enone chosen for our studies (Figure 1).

The reaction of 1.1 equiv of racemic chiral enone **22** with the anion of carbene complex **12** gave, after purification by silica gel chromatography, 1,4 adduct **23** in 72% yield. No 1,2-addition was evident in the crude reaction mixture. In order to assign the stereochemistry of the major addition product, the chromium pentacarbonyl was protolytically cleaved to the corresponding aldehyde **25**.[12b-d,17] Since the chiral centers were at nonepimerizable carbons, it was assumed that the stereochemistry of aldehyde **25** reflected the same degree and sense of diastereomeric excess as **23**.

When the reaction sequence was carried out without purification of adduct **23**, analysis of the crude reaction mixture revealed a

(14) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.
(15) Kryshtal, G. V.; Kulganeck, V. V.; Kucherov, V. F.; Yanovskaya, L. A. *Synthesis* **1979**, 107.
(16) Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279.
(17) (a) Weiss, K.; Fischer, E. O. *Chem. Ber.* **1973**, *106*, 1277. (b) Schubert, U.; Fischer, E. O. *Chem. Ber.* **1973**, *106*, 3882.

Table II. Diastereofacial Selectivity of Carbene Complex Michael Additions to **22**



entry	carbene complex	temp (°C)	time (min)	% yield[a] **23**	HX	% yield[b] of **25**	ratio[c] *l*:*u*
1	**12**	−78	20	77	TFA	76	21:1
2	**12**	23	20		TFA	54	8:1
3	**1a**	0	20		HBr	10	20:1

[a] Isolated yield of **23** from separate run, not carried on to **25**. [b] Isolated yield based on starting carbene complex. [c] Ratio determined by ^{1}H NMR.

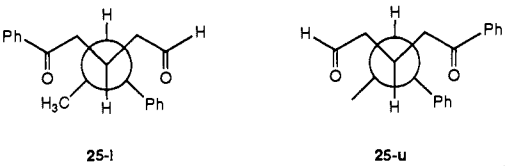


Figure 2.

21:1 (*l*:*u*)[18] ratio of diastereomeric aldehydes **25** (Table II).[19] The mixture was purified by chromatography and **25** (*l* + *u*) was isolated without diastereomeric enrichment in 76% yield based on **12**. When the reaction was carried out at 25 °C, the ratio decreased to 8:1 (*l*:*u*) and the isolated yield of **25** fell to 54%. Alkoxycarbene complex **1a** demonstrated a high degree of facial selectivity with **22** (20:1) even at 0 °C; however, the efficiency of the addition reaction was very low, and the aldehyde was subsequently isolated in only 10% yield.

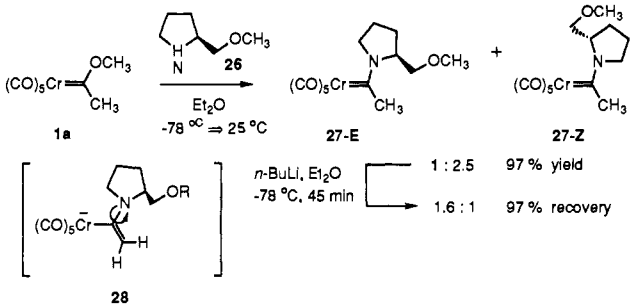
The preferred face of the carbene complex addition was the same as that which has been reported for 1,4-additions to this enone with other nucleophiles.[16] The stereochemical assignments were made by comparing the relative ^{1}H NMR chemical shifts of the diastereomeric aldehyde proton resonances. Acyclic compounds having vicinal stereocenters, each bearing one hydrogen, minimize gauche interactions by existing in conformers with anti disposition of the hydrogens. The appropriate Newman projections which illustrate the preferred conformations for the two diastereomers of **25** are shown in Figure 2.[20]

Heathcock pointed out that in such compounds the substituent gauche to the phenyl ring usually experiences an upfield shift due to the net shielding effect of the aromatic ring. This explains the relative chemical shifts of the aldehyde proton of the major diastereomer (**25**-l) which resonates at 9.57 ppm and the corresponding proton of the minor diastereomer (**25**-u) which resonates further downfield at 9.68 ppm. This phenomenon has been demonstrated to be a reliable method for assigning relative stereochemistry in a variety of similarly substituted acyclic compounds and has been supported in some instances by crystallographic analysis.[20]

Michael Addition of Optically Active Aminocarbene Complexes to Simple Enones. Asymmetric reactions of Fischer carbene

(18) The descriptors *l* and *u* are used as defined in the following: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
(19) Diastereomeric Michael addition product **25**-l represents the structure as drawn and its enantiomer.
(20) See examples cited in ref 16.

Scheme IV

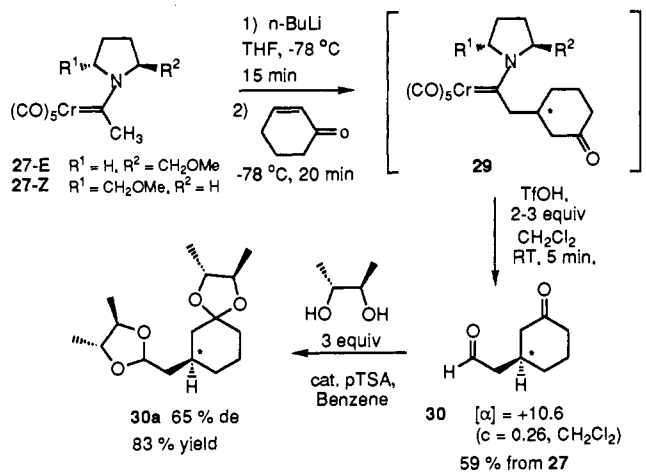


complex anions having chiral heteroatom substituents have not been reported. The Michael reaction of chiral aminocarbene complexes provides an important first study of this element of stereocontrol, since there are few existing methods for the asymmetric additions of α-unsubstituted enolates or enolate equivalents to simple cyclic enones.[2,21,22] Addition reactions can be very selective in some cases, but most methods tend to lack generality and are often highly substrate specific. The preparation of the chiral reagents, as well as the ensuing addition reactions, can also be somewhat cumbersome. A generally applicable, readily available, and high stereoselective reagent has not been identified.

Our initial investigations have focused on carbene complexes prepared from prolinol-derived chiral auxiliaries.[22] Complexes **27** derived from (*S*)-prolinol *O*-methyl ether (**26**) can be prepared in essentially quantitative yield by simply stirring the methoxy complex **1a** with 1 equiv of the amine. Complex **27** generated in this manner exists as a 1:2.5 mixture of *E*- and *Z*-rotamers (assignment made by a HETCOR experiment on the mixture, see Experimental Section).[41,42] In general, it has been found that the *E*- and *Z*-rotamers of aminocarbene complexes are not thermally interconvertible even upon heating to relatively high temperatures.[24] This is attributed to a significant amount of double-bond character for the N–C_{carb} bond due to the donation of the nitrogen lone pair electrons into the empty p_z orbital of the carbene carbon leading to a high barrier to rotation about the N–C_{carb} bond ($\geq$25 kcal/mol).[24] An exhaustive examination of different chromatographic conditions failed to reveal conditions under which the two isomers of **27** could be separated, but it was found that the mixture could be isomerized to a 1.6:1 mixture of *E*- and *Z*-rotamers by deprotonation/reprotonation with *n*-BuLi/H_2O. This isomerization probably involves the intermediate anion **28** which competes for the p_z orbital of the carbene carbon and allows free rotation about the N–C_{carb} bond. Complete isomerization to one rotomer could not be effected, and since chromatographic separations could not be developed, it was necessary, therefore, to carry out all reactions on rotomeric mixtures (Scheme IV).

As indicated in a typical asymmetric Michael addition of complex **27** with cyclohexenone (Scheme V), it was convenient to analyze the asymmetric induction by protolytic cleavage of the metal pentacarbonyl in **29** to give **30**,[12b-d] which is the formal

Scheme V



adduct of acetaldehyde. Analysis of the initial adduct **29** is complicated by the fact that it is a mixture of four diastereomers, two due to the newly formed asymmetric carbon and two due to rotamers about the carbene carbon–pyrrolidine bond. The determination of the absolute configuration of the keto aldehyde **30** was aided by the fact that the bis-dioxolanes derived from optically pure (–)-(2*R*,3*R*)-2,3-butanediol yield diastereomeric compounds, of which the stereochemistry has previously been assigned.[21h] The diastereomeric compounds have distinguishable ^{13}C NMR spectra allowing the optical purity (%) to be measured by integration. The overall yield of **30** is 59% from carbene complex **27**, and it appears that the most inefficient step is the protolytic cleavage since adduct **29** can be isolated in high yields (~90%) from the Michael addition step. Thus, if synthetic applications were to warrant it, efforts could be directed to either the development of alternate protolytic protocols or alternative cleavage methods such as oxidation to the amides with DMSO or DMD as illustrated in Scheme III. All attempts to recover chiral auxiliary **26** after protolytic cleavage to aldehyde **30** failed. Control experiments with chiral pyrrolidine **29** and triflic acid were followed by GC, showing that the chiral auxiliary decomposes to unidentified products. However, it is likely that the chiral auxiliary would survive oxidative liberation of the metal with DMSO.

The results of our studies on the asymmetric Michael additions of prolinol-derived carbene complexes with enones are summarized in Table III. The protolytic cleavage was more efficient with triflic acid than with trifluoroacetic acid (entries 1, 2), so all yields are reported for the triflic acid cleavage products. In every case, the absolute configuration of the cleavage product was the same as that of the chiral auxiliary. The selectivity of the reaction was independent of the rotamer ratio of the starting material (entry 2 vs 3), so reactions were run using the rotameric mixture as was isolated upon preparation of the carbene complex (2.5:1 mixture of *Z*- and *E*-isomers in all cases). A significant loss of selectivity was observed when the addition reaction was run at 5 °C (entry 6), but selectivity was not improved by running the addition reaction at –100 °C (entry 5). When the reaction was initiated at –78 °C and then warmed to 0 °C, no significant loss of selectivity was observed, indicating that the Michael addition is irreversible (entry 7) and that the 1,4-addition adducts are in fact the kinetic products. In an effort to identify any significance of Li chelation, a large excess of Li^+ was introduced into the reaction mixture (entry 4) but no notable changes in selectivity, or yield, were observed. Attempts to carry out the addition reaction in toluene failed to yield product, and only recovered starting material was isolated. The formation of unreactive carbene complex anion aggregates in the noncoordinating solvent might be responsible for the failure to isolate addition products. Changing the bulk of the oxygen substituent from a methyl group

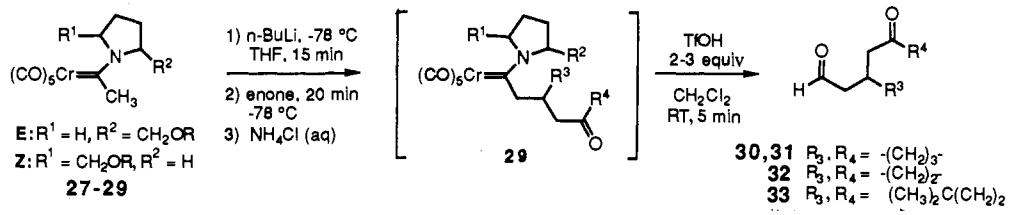
(21) (a) Mukaiyama, T.; Hirako, Y.; Takeda, T. *Chem. Lett.* **1978**, 461. (b) Takeda, T.; Hoshiko, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 797. (c) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 6347. (d) Yamamoto, K.; Iijima, M.; Ogimura, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 2813. (e) Yamamoto, K.; Iijima, M.; Ogimura, Y. *Tetrahedron Lett.* **1982**, *23*, 3711. (f) Hua, D. H.; Venkataramen, S.; Coulter, M. J.; Sinai-Zingde, G. *J. Org. Chem.* **1987**, *52*, 719. (g) Hua, D. H.; Sinai-Zingde, G.; Venkataramen, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (h) Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026.

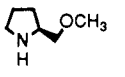
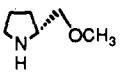
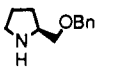
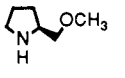
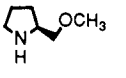
(22) For a recent example of a selective asymmetric Michael addition of an α-substituted enolate, see: Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.

(23) Seebach, D.; Kalinowski, H. O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H. A.; Schmid, M. *Helv. Chim. Acta* **1977**, *60*, 301.

(24) Moser, E.; Fischer, E. O. *J. Organomet. Chem.* **1968**, *13*, 387.

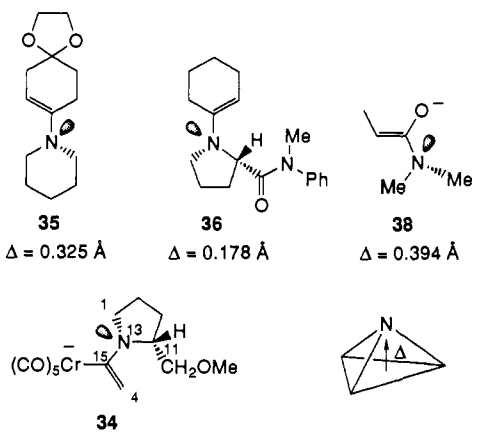
Table III. Asymmetric Michael Reactions of Prolinol-Derived Carbene Complexes



entry	carbene complex[a]	chiral auxillary	enone	reactn condtns (°C)	prodt	% yield[b]	% ee[c]
1	**27**			−78, TFA	**30**	41	64 (*S*)
2				−78		59[d]	65 (*S*)
3				−78[e]		40	63 (*S*)
4				−78, 10 equiv of LiCl		60	66 (*S*)
5				−100		55	61 (*S*)
6				5		27	4 (*S*)
7				−78, 20 min; 0, 20 min		32	52 (*S*)
8				−78, toluene			
9	**28**[f]			−78	**31**	57	76 (*R*)
10	**29**			−78	**30**	<79[g]	60 (*S*)
11	**27**			−78	**32**	46	64 (*S*)
12	**27**			−78	**33**	51	95 (*S*)

[a] Starting carbene complex was a 2.5:1 mixture of *Z*- and *E*-rotomers. [b] Isolated yield based on carebene complexes for the products purified by chromatography. [c] Determined by ^{13}C NMR of bis-dioxolane derivatives of the corresponding aldehydes. [d] The yield varied from 33% to 59% with 50% as the maximum. [e] Starting carbene complex was a 1:1.3 mixture of *Z*- and *E*-rotomers. [f] 3.4:1 mixture of *Z*- and *E*-isomers. [g] Slight impurity present.

Chart I



to a benzyl group had little effect (entry 10). The degree of asymmetric induction for the addition to 2-cyclopentenone **30** was no different than that for the reaction with 2-cyclohexenone (**11**).

In order to enhance the diastereoselectivity of the addition reaction, a substrate was chosen that was expected to provide a much greater degree of steric bias (entry 12). As was anticipated, bulky substitution adjacent to the reactive center of enone **17** had a dramatic effect on the degree of stereoselectivity, and the optical purity of cleavage product **33** increased to 95% ee. Cleavage product **33**, which had not been previously reported, was assigned as the *S* enantiomer based on correlation to the optical rotations of analogous compounds.[21h] The *S* enantiomer of all similar derivatives of cyclic enone addition products have positive (+) optical rotations, the cleavage product from the 4,4-dimethyl-2-cyclohexenone addition adduct also had a positive optical rotation ([α] = +7.4°). The assignment is also consistent with Lemiere's empirical rule for deducing absolute configuration of six-membered ring ketones.[25]

Origin of Diastereoselectivity. Several factors must be considered in order to explain the asymmetric induction that has been observed. In the absence of crystallographic, spectroscopic, or more extensive reaction data, a model is proposed here that has been loosely developed through analogy to structural features which have been crystallographically determined for enamines[26] and amide lithium enolates.[27] The disposition of the chiral center of the carbene complex anion is expected to be a function of (a) the degree of nitrogen atom pyramidalization, (b) configurational stability of the pyramidalized N, and (c) the torsional twist around the C_{carb}–N bond. Two crystal structures of lithium amide enolates have been reported,[28,29] and each indicates pronounced pyramidalization of nitrogen on the order of 68%.[30] This value is higher than those for most enamines;[26,31] however, it is still within the range of pyramidalities that have been observed. Several crystal structures of enamines have been reported, and a difference in the pyramidalities has been noted for piperidine and pyrrolidine enamines. Where the pyramidality is indicated by Δ as illustrated in Chart I, all piperidine enamines showed pyramidalities of Δ = 0.3–0.4 Å and all pyrrolidine enamines showed pyramidalities in the range of Δ = 0.1–0.2 Å.[31] While no crystal structures are known for amide enolates derived from pyrrolidines, the pyra-

(25) Lemiere, G. L.; Dommisse, R. A.; Lepoivre, J. A.; Alderweireldt, F. C.; Hiemstra, H.; Wynberg, H.; Jones, J. B.; Toone, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 1363.
(26) Cook, A. G. In *Enamines, Synthesis, Structure, and Reactions*; 2nd ed.; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 1.
(27) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
(28) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764.
(29) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.
(30) Percent pyramidalization as defined in ref 26: (360 − Σ three N-bond angles/360–328.5).
(31) Brown, K. L.; Damm, L.; Dunitz, J. D.; Eschenmoser, A.; Hobi, R.; Kratky, C.; *Helv. Chim. Acta* **1978**, *68*, 3108.

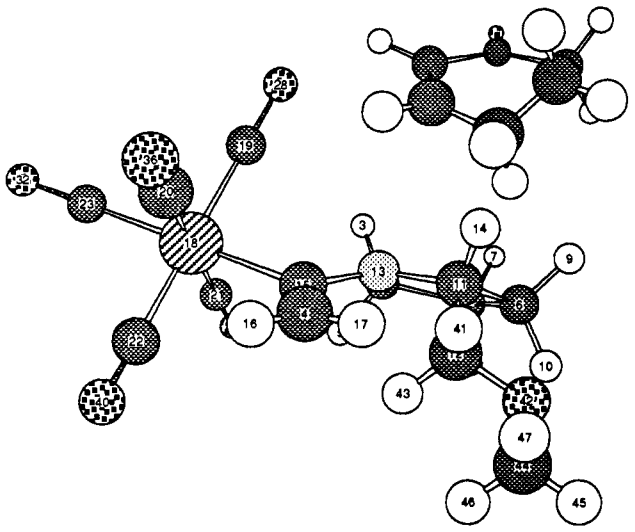


Figure 3. Chem-3D model of anion **34** (from **28**) with pyramidalization at N ($\Delta = 0.18$ Å) and eclipsing of the N13–C11 and the C15–C4 bonds. Approach of the re face of cyclohexenone is illustrated.

midality for such an enolate is expected to be similar to those of the pyrrolidine enamines since the pyramidalities of the enolates of dimethyl amides are similar to those of piperidine enamines.[28,29] Therefore, the pyramidality of carbene complex anion **34** (derived from **28**) is assumed to be same as that found for 2-substituted pyrrolidine enamine **36**.[31]

Little is known about the configurational stability of the pyramidalized nitrogen of amide enolates.[32,33] The free energy of activation for the inversion of the nitrogen atom in *N*-methylpyrrolidine has been found to be ~8 kcal/mol.[34] No corresponding data exist for nitrogen inversion in amides or amide enolates, which makes speculation concerning the present case difficult. Sufficient configurational stability of the nitrogen in carbene complex anion **34** on the time scale of the reaction at −78 °C will be assumed.

Twist about the N–$C_{carbonyl}$ of the amide enolates and the N–C_{sp2} carbon of enamines is observed in crystal structures for both species. The degree and direction of twist varies widely, but the preferred orientation of the twisted amine group appears to be most greatly influenced by steric interactions. For enamines, it is almost uniformly found that a C–N bond of the enamine substituent is eclipsed with the double bond of the enamine.[31] This has also been observed for amide enolate **38** in the solid state.[29] For 2-substituted pyrrolidines, both syn (as illustrated by **36**) and anti eclipsed conformations have been found in the solid state but in all cases the substituent at the 2-position is trans to the developing lone pair on the nitrogen.[31] Given the above observations, a model of chiral carbene complex anion **34** should include a pyramidalized nitrogen which is twisted out of the metal–carbene carbon plane such that bonds C15–C4 and N13–C11 are eclipsed and the methoxymethyl group is trans to the nitrogen lone pair. The alternate conformation with eclipsed C15–C4 and N13–C1 bonds is not considered due the anticipated steric interactions between the methoxymethyl group and the chromium pentacarbonyl unit. A mononuclear compound is supposed, but no experimental evidence exists to discount the possibility that oligomeric forms of the carbene complex anion provide the reactive species.

The model proposed here is illustrated by the Chem-3D drawing shown in Figure 3. A common intermediate structure of carbene complex anion **34** is presumed. This is supported by the observations that two rotameric forms of **27** could be interconverted by treatment with base and, furthermore, that the selectivity of the reaction was independent of the initial isomeric composition of **27** (entries 2 and 3, Table III). Pyramidalization of the nitrogen is drawn so as to move the methoxymethyl substituent of the pyrrolidine ring anti to the developing lone pair of the pyramidalized nitrogen. This is in accordance with the trend that has been observed in the crystal structures of proline-derived enamines.[31] The amine group is twisted in a fashion that provides minimal steric interaction between the methoxymethyl group and the metal pentacarbonyl. The indicated orientation results in a steric bias for nucleophilic addition, since the methoxymethyl group shields one side of the anionic carbon forcing the enone approach from the opposite face. A stereoelectronic bias might also play a role in the observed selectivity. Pyramidalization of the nitrogen results in a diastereomeric anion. If the lone pair develops in the indicated orientation, the facial selectivity of the nucleophilic addition might be assisted in a reaction that is isoelectronic with an S_E2' reaction. Eschenmoser has made this suggestion in the context of nucleophilic enamine reactions.[31]

The relative orientation of the enone with respect to the approaching chiral carbene complex anion ultimately dictates the stereochemical outcome. Avoiding interactions with the methoxymethyl group and the chromium pentacarbonyl unit is most easily minimized by approach from the top right quadrant of **34** as viewed in Figure 3. A syn approach is indicated (closed transition state) with the β-carbon of cyclohexenone over C-4 of enolate **34** and the carbonyl group of cyclohexenone over the nitrogen atom of the enolate. The corresponding anti approach would involve the formation of a carbon–carbon bond to the other face of cyclohexenone and lead to a product with a configuration opposite to that observed. At this point, we have no conclusive experimental evidence for a closed transition state nor are there any solid-state structures of the enolates of carbene complexes that would indicate where the counter cations are located. Nonetheless, the model involving a closed transition state provides the best explanation for the dramatic increase in selectivity observed for 4,4-dimethylcyclohexen-2-one (Table III, entry 12) where an open transition state would result in severe close contacts between the *gem*-dimethyl group and the pyrrolidine ring. The closed transition-state model arising from the relative approach indicated in Figure 3 accounts for the stereochemistry observed for the addition of all of the chiral aminocarbene complexes to all of the cyclic enones that have been examined so far.

The selectivity of the reactions reported here approach the best selectivities that have been reported for the asymmetric acetaldehyde enolate equivalent additions to cyclic enones.[21h] The carbene route, however, is potentially more flexible since the enantiomers of the starting complexes can both be directly prepared cleanly from either enantiomer of prolinol methyl ether and provide similar levels of selectivity with predictable absolute configurations. The results described in this work of the first examples of an asymmetric reaction of the "enolate" of a Fischer carbene complex suggest that these reactions do have potential in asymmetric synthesis and that further development of these and related reactions is warranted.

Experimental Section

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. DMSO used in oxidation reactions was used as received from commercial suppliers. All reactions involving organometallic species were carried out under an argon atmosphere. Flash chromatography was carried out on Merck silica gel, grade 60, 230–400 mesh, 60 Å. Solvent systems for chromatographic elution were ternary mixtures of dichloromethane, ether, and hexanes indicated by their volumetric ratios sequentially unless otherwise noted. Proton NMR data

(32) For a related study, see: Bennet, A. J.; Wang, Q-P.; Slebocka-Tilk, H.; Somayaji, V.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 6383.

(33) For a compilation of leading references concerning amide enolates, see: Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

(34) Lambert, J. B.; Oliver, W. L., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 7774.

were obtained either on a University of Chicago-built DS-1000 500 MHz instrument or a General Electric QE-300-MHz instrument. Carbon-13 spectra were obtained on the QE-300 instrument at 75 MHz or on a Varian XL-400 instrument at 100 MHz. HETCOR experiments were obtained either on a General Electric Ω-300 or Ω-500 MHz instrument. Infrared spectra were taken on a Nicolet 20SX FTIR. Low-resolution mass spectra were recorded on a Finnigan 1015 mass spectrometer. High-resolution mass spectra were recorded on a CG 70-250 instrument or obtained from the Midwest Center for Mass Spectrometry in Lincoln, NE. Elemental analyses were done by Galbraith Laboratories in Knoxville, TN.

Standard Procedure for the Michael Reactions of Nonchiral Aminocarbene Complexes. The appropriate aminocarbene complex (all reactions were run on a 1–5-mmol scale) was placed in a dry round bottom flask containing a Teflon-coated stir bar and fit with a rubber septum. The flask was maintained under an argon atmosphere while THF was injected. The resulting solution (0.17 M) was cooled to −78 °C and an *n*-butyllithium solution (1.6 M, 1.0 equiv) in hexane was injected. The resulting solution was stirred for 20 min, after which an α,β-unsaturated carbonyl compound (1.1–1.2 equiv) was injected. The mixture was stirred for ∼20 min before the reaction was quenched at −78 °C by the rapid addition of a saturated aqueous NH_4Cl solution. The mixture was diluted with ether, and the organic layer was washed with water and then brine. The organic solution was dried over anhydrous magnesium sulfate, filtered through a short plug of Celite, and concentrated. The product was separated from the concentrated residue by flash chromatography on silica gel in the presence of air.

Michael Reaction of Methoxycarbene Complex 1a with Cyclohexenone. Carbene complex **1a**[36] (0.371 g, 1.48 mmol) in 8 mL of THF was treated with a solution of *n*-butyllithium (0.96 mL, 1.6 M, 1.48 mmol) in hexanes under the conditions described in the standard procedure described above for aminocarbene complexes. 2-Cyclohexenone (0.24 mL, 0.24 g, 2.55 mmol) was injected and the solution stirred 30 min; however, no reaction was detected by TLC. The reaction was warmed to 0 °C for 30 min before the reaction was quenched. Silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:5) led to the isolation of Michael adduct **8a** (0.876 g, 1.69 mmol) in 49% yield. Spectral data for **8a**: R_f = 0.42; ^{1}H NMR ($CDCl_3$) δ 1.37–1.44 (m, 1H), 1.58–1.66 (m, 2H), 1.74–1.77 (m, 1H), 2.02–2.07 (m, 2H), 2.21–2.37 (m, 3H), 3.3 (dd, 1H, *J* = 15.2, 7.1 Hz), 3.42 (dd, 1H, *J* = 15.2, 6.5 Hz), 4.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 24.99, 31.10, 36.93, 40.98, 47.54, 67.88, 69.25, 210.08, 216.05, 222.80, 362.28; IR (thin film) 2063 m, 1985 shoulder, 1918 vs, 1713 m, 1452 w, 1265 w.

Michael Reaction of the (Dimethylamino)carbene Complex 1d[37] with Cyclohexenone. Separation of the products from this reaction by silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:1) led to a 12% recovery of **1d** and the isolation of Michael adduct **8d** as a pale yellow-green solid in 85% yield. Spectral data for **8d**: mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 1.53–1.67 (m, 2H), 1.86–1.89 (m, 1H), 2.09–2.12 (m, 1H), 2.21–2.42 (m, 5H), 3.14 (dd, 1H, *J* = 13.3, 6.4 Hz), 3.26 (dd, 1H, *J* = 13.3, 6.7 Hz), 3.35 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 25.29, 31.54, 38.09, 41.10, 43.97, 47.76, 53.91, 57.96, 209.76, 217.81, 222.89, 279.52; IR (thin film) 2957–2857 w, 2051 m, 1964 shoulder, 1897 s, 1712 m, 1535 m, 1460 w, 1401 w, 1225 w, 1140 w, 1019 w; mass spectrum, *m/e* (rel intensity) 359 (1), 303 (1), 275 (3), 247 (4), 219 (24), 204 (4), 189 (3), 176 (6), 167 (26), 148 (12), 139 (42), 124 (46), 110 (33), 96 (19), 85 (100), 80 (11), 70 (41). Anal. Calcd for $C_{15}H_{17}CrNO_6$: C, 50.14; H, 4.77; N, 3.90. Found: C, 49.55; H, 4.58; N, 3.68.

Oxidation of (Dimethylamino)carbene Complex Michael Adduct 8d with DMSO and DMD. Michael adduct **8d** (115 mg, 0.32 mmol) was dissolved in 0.8 mL of DMSO, heated to 60 °C, and stirred in air for 19 h.[12a,b] The DMSO was distilled off (0.2 mm, 50 °C), and the dark green residue was dissolved in CH_2Cl_2, filtered through Celite, and concentrated. Silica gel chromatography (1:4 acetone:CH_2Cl_2) led to the recovery of **8d** (18 mg, 0.048 mmol) in 16% yield and to the isolation of the amide **10** (42 mg, 0.227 mmol) as a colorless liquid in 71% yield. Spectral data for **10**: ^{1}H NMR ($CDCl_3$) δ 1.42 (qd, 1H, *J* = 11.2, 1.3 Hz), 1.65–1.76 (m, 2H), 2.01–2.05 (m, 2H), 2.11 (dd, 1H, *J* = 13.1, 11.1 Hz), 2.22–2.46 (m, 4H), 2.47 (br d, 1H, *J* = 13.7 Hz), 2.94 (s, 3H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 24.67, 30.94, 35.17, 35.36, 37.15, 39.17, 41.03, 47.56, 170.72, 210.60; IR (thin film) 3400 w, 2932 s, 2867 s, 1711 s, 1645 s, 1498 m, 1449 m, 1414 m, 1398 m, 1312 w, 1268 m, 1226 m, 1142 m, 1094 w, 1058 w; mass spectrum, *m/e* (rel intensity) 183 (34), 165 (2), 155 (10), 140 (26), 127 (6), 112 (25), 100 (4), 97 (8), 93 (1), 87 (100), 81 (4), 72 (72), 69 (8).

Michael adduct **8d** (89.8 mg, 0.25 mmol) was dissolved in 0.5 mL of acetone, and a solution of dimethyldioxirane[13,38] (33 mL, ca. 0.055 M, ca. 1.5 mmol) was added at room temperature over 10 min. After the addition was complete, no starting material was visible by TLC and a mild vacuum (30–40 mm) was applied to remove excess DMD. The mixture was filtered through Celite and silica gel, and the eluate was concentrated to give amide **10** (35.8 mg, 0.195 mmol) in 78% yield.

Preparation of (Methylpyrrolidinomethylene)pentacarbonyltungsten (0) 13. To a solution of (methylmethoxycarbene)tungsten pentacarbonyl complex[39] (2.427 g, 6.354 mmol) in ∼15 mL of diethyl ether was added pyrrolidine (0.85 mL, 0.72 g, 10.2 mmol) in one portion. The resulting solution was stirred for 5 min and then diluted with ether. The yellow solution was washed sequentially with diluted HCl (0.1 N), water, $NaHCO_3$, and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered through a plug of silica gel, and concentrated to yield analytically pure **13** (2.374 g, 5.64 mmol) as a very pale yellow solid in 89% yield. Spectral data for **13**: mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (pent, 2H, *J* = 6.8 Hz, CH_2), 2.18 (pent, 2H, *J* = 6.9 Hz), 2.75 (s, 3H, CH_3), 3.56 (t, 2H, *J* = 7.0 Hz, NCH_2), 4.02 (t, 2H, *J* = 6.8 Hz, NCH_2); ^{13}C NMR ($CDCl_3$) δ 24.82, 25.58, 42.40, 51.32, 63.08, 199.17, (J_{CW} = 127 Hz), 203.63, 248.84; IR (thin film) 2061 s, 1976 shoulder, 1904 vs, 1511 m; mass spectrum, *m/e* (rel intensity) 421 M^+ (12, ^{184}W), 393 (9, ^{184}W), 365 (6, ^{184}W), 363 (14, ^{184}W), 337 (5, ^{184}W), 335 (15, ^{184}W), 309 (20, ^{184}W), 307 (44, ^{184}W), 281 (5, ^{184}W), 279 (32, ^{184}W), 249 (12), 96 (78), 69 (100). Anal. Calcd for $C_{11}H_{11}O_5WN$: C, 31.38; H, 2.63; N, 3.33. Found: C, 31.33; H, 2.55; N, 3.03.

Michael Reaction of the Tungsten Pyrrolidinyl Carbene Complex 13 with Cyclohexenone To Give 15a. This reaction was relatively clean, and product **15a** was purified by silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:4, then 3:3:1) and obtained as a yellow solid in 77% yield. Spectral data for **15a**: mp 109–110 °C; ^{1}H NMR ($CDCl_3$) δ 1.50–1.56 (m, 1H), 1.73–1.76 (m, 1H), 1.89–1.92 (m, 1H), 2.03–2.20 (m, 6H), 2.24–2.30 (m, 1H), 2.41–2.46 (m, 2H), 2.68–2.72 (m, 1H), 3.03–3.12 (m, 2H), 3.65–3.70 (m, 2H), 4.05 (t, 2H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 37.79, 37.92, 38.48, 42.78, 48.54, 50.10, 55.04, 58.90, 64.05, 67.69, 168.67 (J_{CW} = 96), 171.13, 176.80, 209.73; IR (thin film) 2054 m, 1936 shoulder, 1897 vs, 1879 s, 1713 m, 1510 m. Anal. Calcd for $C_{17}H_{19}O_6WN$: C, 39.48; H, 3.70; N, 2.71. Found: C, 39.68; H, 3.90; N, 2.64.

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12[35] with Cyclohexenone To Give 14a. After separation by silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:4, then 3:3:1), this reaction led to a 2% recovery of **12** and the isolation of Michael adduct **14a** as a very pale yellow solid in 96% yield. Spectral data for **14a**: mp 114–116 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.50–2.44 (m, 12H), 2.60–2.70 (m, 1H, CH), 2.97–3.09 (m, 2H, CH_2), 3.66–3.71 (m, 2H, NCH_2), 4.14–4.17 (m, 2H, NCH_2); ^{13}C NMR ($CDCl_3$) δ 24.74, 24.82, 25.29, 31.05, 38.14, 40.88, 47.56, 54.00, 58.57, 62.00, 209.72, 218.18, 222.96, 271.37; IR (thin film) 2988 w, 2951 w, 2872 w, 2039 s, 1942 shoulder, 1875 vs, 1705 m, 1499 m, 1444 m; mass spectrum, *m/e* (rel intensity) 385 M^+ (2), 357 (1), 329 (2), 301 (3), 273 (10), 245 (72), 193 (44), 165 (46), 150 (54), 136 (62), 123 (38), 111 (98), 96 (32), 84 (100), 70 (55). Anal. Calcd for $C_{17}H_{19}O_6CrN$: C, 52.99; H, 4.97; N, 3.63. Found: C, 53.27; H, 4.98; N, 3.63.

As a demonstration of the stability of aminocarbene complexes, a sample of **12** was allowed to stand on the laboratory bench in a clear screw-capped vial exposed to air, room temperature, and room light for more than 1 year. After this time, the above reaction with 2-cyclohexenone was repeated and adduct **14a** was obtained in 81% yield.

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12 with 4,4-Dimethyl-2-cyclohexen-1-one To Give 14c. The products of this reaction were eluted through a silica gel column (1:1, hexane/ethyl acetate) and identified as **12** (16% recovery) and Michael adduct **14c** obtained as a pale yellow solid in 84% yield. Spectral data for **14c**: mp 109–112

(35) Connor, J. A.; Lloyd, J. P. *J. Chem. Soc., Dalton Trans.* **1972**, 1470. Fischer, E. O.; Schmid, K. R.; Kalbfus, W.; Kreiter, C. G. *Chem. Ber.* **1973**, *106*, 3893. Rudler, H.; Parlier, A.; Yefsah, R.; Denise, B.; Daran, J. C.; Vaissermann, J.; Knobler, C. *J. Organomet. Chem.* **1988**, *358*, 245.

(36) (a) Aumann, R.; Fischer, E. O. *Chem. Ber.* **1968**, *101*, 954. (b) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth.* **1987**, *65*, 140.

(37) Fischer, E. O.; Schmid, K. R.; Kalbfus, W.; Kreiter, C. G. *Chem. Ber.* **1973**, *106*, 3893.

(38) Eaton, P. E.; Wicks, G. E. *J. Org. Chem.* **1988**, *53*, 5353.

(39) These complexes have been reported[40a] and were prepared[40b] according to a modified procedure reported for chromium.[36]

°C; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.19 (s, 3H), 1.67–1.78 (m, 2H), 2.03–2.13 (m, 6H), 2.33–2.38 (m, 2H), 2.59–2.64 (m, 1H), 2.94–3.06 (m, 2H), 3.61–3.64 (m, 2H), 4.08–4.19 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.23, 24.67, 25.56, 28.03, 33.19, 37.89, 39.52, 41.99, 45.00, 52.75, 54.01, 62.09, 210.31, 218.05, 222.65, 272.72; IR (thin film) 2962 w, 2049 m, 1964 shoulder, 1899 vs, 1715 m, 1496 w, 1449. Anal. Calcd for $C_{19}H_{23}O_6CrN$: C, 55.20; H, 5.61; N, 3.39. Found: C, 55.16; H, 5.62; N, 3.44.

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12[35] with 2(5*H*)-Furanone To Give 14d. Flash chromatography on silica gel (1:1, hexane/ethyl acetate) led to the recovery of **12** in 49% yield and the isolation of Michael adduct **14d** as a pale yellow solid in 50% yield. Spectral data for **14d**: mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 2.03–2.20 (m, 5H), 2.75 (dd, 1H, J = 17.4, 8.0 Hz), 3.09–3.10 (m, 2H), 3.38–3.41 (m, 1H), 3.63–3.69 (m, 2H), 3.91 (dd, 1H, J = 9.4, 4.1 Hz), 4.09–4.17 (m, 2H), 4.43 (dd, 1H, J = 15.8, 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.87, 25.41, 34.38, 34.69, 53.96, 54.18, 62.22, 72.09, 175.95, 218.07, 222.40, 270.49; IR (thin film) 2975 m, 2948 w, 2909 w, 2875 vw, 2051 s, 1963 shoulder, 1905 vs, 1780 s, 1503 m, 1448 m, 1186 m, 1028 m; mass spectrum, m/e (rel intensity) 373 M^+ (1), 345 (1), 304 (10), 300 (12), 272 (66), 261 (7), 244 (12), 233 (49), 220 (70), 181 (100), 139 (27), 123 (35), 108 (63), 80 (70). Anal. Calcd for $C_{15}H_{15}O_7CrN$: C, 48.26; H, 4.05; N, 3.75. Found: C, 48.35; H, 4.06; N, 3.79.

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12[35] with 4-Phenyl-3-buten-2-one To Give 14e. This reaction was quite clean as silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:4) gave a 12% recovery of **12** and an 88% yield of Michael adduct **14e** as a yellow oil. Spectral data for **14e**: R_f = 0.23; ^{1}H NMR ($CDCl_3$) δ 1.61–1.80 (m, 1H), 1.72–1.83 (m, 2H), 1.94–1.97 (m, 1H), 2.06 (s, 3H), 2.52–2.55 (m, 1H), 2.92 (dd, 1H, J = 16.2, 5.3 Hz), 3.00–3.09 (m, 2H), 3.41–3.45 (m, 2H), 3.89–4.04 (m, 3H), 7.15–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.61, 25.07, 29.81, 39.15, 48.80, 53.51, 59.56, 61.89, 127.09, 127.41, 128.67, 142.15, 206.26, 218.40, 222.77, 269.44; IR (thin film) 2050 m, 1962 shoulder, 1900 vs, 1717 m, 1505 m, 1436 m, 1453 m, 1417 m. Anal. Calcd for $C_{21}H_{21}O_6CrN$: C, 57.93; H, 4.86; N, 3.22. Found: C, 57.53; H, 5.09; N, 3.35.

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12 with Crotonaldehyde To Give 21 and 14f. This reaction gave two products which were separated by silica gel chromatography (1:1, hexane/ethyl acetate) and identified as 1,2-addition product **21** in 78% yield and Michael adduct **14f** as a pale yellow oil in 6% yield. Spectral data for **21**: R_f = 0.71; ^{1}H NMR ($CDCl_3$) δ 1.40 (br s, 1H, OH), 1.71 (d, 3H, J = 6.5 Hz, CH_3), 2.03–2.11 (m, 4H, $(CH_2)_2$), 3.10 (dd, 1H, J = 12.3, 10.4 Hz, CH), 3.16 (dd, 1H, J = 12.3, 3.5 Hz, CH), 3.67 (m, 1H, NCH), 4.04–4.12 (m, 3H, NCH, NCH_2), 4.86 (m, 1H, CHO), 5.56 (ddd, 1H, J = 15.4, 7.1, 1.4 Hz, CH), 5.75 (dq, 1H, J = 15.3, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.49, 24.98, 25.31, 54.45, 59.07, 61.83, 71.52, 127.13, 133.24, 218.64, 223.19, 267.10; IR (thin film) 3593 br m, 3419 br m, 2954 m, 2954 m, 2915 m, 2876 m, 2049 s, 1959 shoulder, 1894 vs. Anal. Calcd for $C_{15}H_{17}O_6CrN$: C, 50.14; H, 4.77; N, 3.90. Found: C, 49.84; H, 5.17; N, 4.11. Spectral data for **14f**: R_f = 0.56; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 6 Hz), 1.98–2.18 (m, 5H), 2.41 (dd, 1H, J = 15, 7 Hz), 2.48 (dd, 1H, J = 15, 7 Hz), 2.91–3.01 (m, 2H), 3.62–3.80 (m, 1H), 4.07–4.18 (m, 3H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.03, 24.97, 25.56, 27.53, 50.74, 54.21, 58.78, 62.00, 201.47, 218.43, 222.91, 273.37; IR (thin film) 2962 w, 2925 w, 2879 w, 2723 w, 2050 m, 1962 shoulder, 1909 vs, 1725 m, 1500 m, 1448 m.

Preparation of 1,4-Diphenyl-2-penten-1-one (22).[16] To 60 mL of argon-purged dichloromethane in a 100-mL round bottom flask were added (benzoylmethylene)triphenylphosphorane (3.95 g, 10.4 mmol) and 2-phenylpropionaldehyde (1.40 mL, 1.4 g, 10.4 mmol). The flask was fitted with a straight condensor, and the mixture was refluxed under an argon atmosphere for 24 h. The solution was concentrated by rotary evaporation, and the residue was redissolved in a (1:1) hexane/ether solution. The precipitate was removed by filtration, and the filtrate was concentrated. The remaining oil contained a mixture of product **22** and starting aldehyde which was removed by vacuum distillation (45 °C, 0.5 mm). The residual oil was taken up in ether and stirred with Norit. The solution was filtered and concentrated to give **22** (1.55 g, 6.57 mmol) in 63% yield. Only the *E*-isomer could be detected. Spectral data for **22**: ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3H, J = 7.05 Hz, CH_3), 3.73 (quintet, 1H, J = 7 Hz, CHPh), 6.84 (dd, 1H, J = 1.4, 15.5 Hz, CH), 7.17–7.58 (m, 9H, ArH, CH), 7.88–7.91 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ 20.05, 42.08, 123.88, 126.32, 126.92 (2 signals), 128.08, 128.30, 132.23, 137.46, 142.97, 152.42, 190.10; IR (thin film) 2967 w, 1669 vs, 1650 w, 1619 vs, 1598 w, 1447 m, 1290 m, 1008 m, 689 vs; mass spectrum, m/e (rel intensity) 236 M^+ (19), 221 (5), 131 (37), 115 (15), 105 (100), 115 (12), 77 (35).

Michael Reaction of Chromium Pyrrolidinyl Carbene Complex 12 with the Chiral Enone 22 To Give 23. Michael adduct **23-l** from this reaction was purified by silica gel chromatography (3:1, hexane/ethyl acetate) and obtained as a yellow oil in 77% yield. The degree and sense of diastereofacial selectivity was determined by conversion to the corresponding aldehyde **25-l** by the method detailed in the following entry. Spectral data for **23-l**: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 7.1 Hz), 1.87–1.96 (m, 1H), 2.08–2.14 (m, 3H), 2.72 (dd, 1H, J = 13.5, 4.9 Hz), 2.83 (quintet, 1H, J = 7 Hz), 3.01 (dd, 1H, J = 17, 4 Hz), 3.12–3.24 (m, 2H), 3.36 (dd, 1H, J = 13.0, 11.8 Hz), 3.48–3.51 (m, 1H), 3.67–3.71 (m, 1H), 3.95–4.01 (m, 2H), 7.15–7.55 (m, 8H), 7.86–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.43, 24.51, 25.40, 36.86, 39.58, 44.69, 53.80, 56.25, 61.62, 126.46, 127.57, 127.78, 128.31, 128.49, 133.08, 136.47, 144.29, 198.83, 217.89, 222.81, 273.66; IR (thin film) 2049 m, 1964 shoulder, 1904 vs, 1677 m, 1487 m, 1435 m. Anal. Calcd for $C_{28}H_{27}O_6CrN$: C, 63.99; H, 5.18; N, 2.67. Found: C, 63.70; H, 5.56; N, 2.61.

Preparation of Aldehyde 25-l by Protolytic Cleavage of the Carbene Complex 23-l and Determination of the Stereoselectivity of the Additions to Enone 22. Carbene complex **23-l** (0.492 g, 0.937 mmol) was dissolved in 3 mL of dichloromethane and stirred at room temperature while trifluoroacetic acid (0.60 mL, 0.89 g, 7.8 mmol) was injected.[12b-d] The solution immediately turned orange and then green. After 5 min, the opaque green solution was diluted with ether and washed with a saturated (aqueous) solution of $NaHCO_3$, water, and brine. The organic solution was dried over anhydrous magnesium sulfate, filtered through Celite, and concentrated. Silica gel chromatography (1:1;4) led to the isolation of aldehyde **25-l** (0.188 g, 0.67 mmol) in 72% yield as a clear, colorless oil. The following spectral data were collected on an 8:1 mixture of **25-l** and **25-u**: R_f = 0.4; ^{1}H NMR ($CDCl_3$) **25-l** δ 1.25 (d, 3H, J = 6.9 Hz, CH_3), 2.39 (ddd, 1H, J = 8.2, 6.6, 1.6 Hz, CH_aCHO), 2.49 (m, 1H, CH_aCHO), 2.89–2.99 (m, 3H, PhCH, CH_aCOPh), 3.10–3.14 (m, 1H, CH_aCOPh), 7.18–8.82 (m, 10H, ArH), 9.57 (t, 1H, J = 1.6 Hz, CHO); **25-u** δ 9.68 (t, 1H, J = 1.6 Hz, CHO); ^{13}C NMR ($CDCl_3$) **25-l** δ 17.66, 35.56, 39.73, 42.09, 46.35, 126.49, 127.70, 127.89, 128.42, 128.47, 133.02, 136.71, 144.37, 199.30, 201.70; **25-u** (resolvable resonances) δ 17.65, 35.52, 40.82, 45.51, 126.44, 127.62, 127.88, 133.04, 136.72, 202.05; IR (thin film) 3060 w, 3027 w, 2967 m, 2892 w, 2825 m, 2725 m, 1722 s, 1683 s, 1597 m, 1449 m.

Diastereoselectivity of Addition of 12 at −78 °C. A portion (76.0%) of the unpurified crude product obtained from the Michael reaction of **12** (0.532 g, 1.842 mmol) with **22** (0.482 g, 2.041 mmol) at −78 °C was treated with triflic acid (0.24 mL, 0.41 g, 2.7 mmol). The reaction was quenched with a pH 4 buffer, and the mixture was stirred for 5 min prior to dilution with ether and subjection to the typical aqueous workup. The ^{1}H NMR spectrum of the crude reaction mixture indicated a 21:1 mixture of diastereomers by integration of the respective aldehyde protons. Silica gel chromatography (1:1:5, R_f = 0.4) led to the isolation of aldehyde **25-l** (0.2851 g, 1.02 mmol) without diastereomeric enrichment in 76% yield based on the starting carbene complex **12**.

Diastereoselectivity of Addition of 12 at 23 °C. The Michael reaction of **12** (0.220 g, 0.763 mmol) with **22** (0.180 g, 0.764 mmol) was carried out at 23 °C and worked up in the typical fashion. The crude reaction mixture was dissolved in dichloromethane and treated with trifluoroacetic acid (0.30 mL, 0.44 g, 3.90 mmol). After the typical aqueous workup, the ^{1}H NMR spectrum of the crude reaction mixture indicated an 8:1 mixture of the diastereomers by integration of the respective aldehyde protons. Silica gel chromatography (1:1:5) led to the isolation of aldehyde **25** (0.116 g, 0.41 mmol) without diastereomeric enrichment in 54% yield based on the starting carbene complex **12**.

Michael Addition of Methoxyl Carbene Complex 1a to Chiral Enone 22. Carbene complex **1a** (0.255 g, 1.02 mmol) in 6 mL of THF was deprotonated with a solution of *n*-butyllithium (0.66 mL, 1.55 M, 1.02 mmol) in hexanes at −78 °C under an argon atmosphere. 1,4-Diphenyl-2-penten-1-one (**22**) (0.259 g, 1.1 mmol) in 0.6 mL of THF was injected at −78 °C and the solution stirred for 30 min at 0 °C before the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution. The mixture was diluted with ether and the organic layer was washed with water and then brine. The organic solution was dried over anhydrous magnesium sulfate, filtered through a short plug of Celite, and concentrated. The crude reaction residue was dissolved in 3 mL of dichloromethane and treated with excess 49% HBr solution. The mixture was diluted with ether, washed with $NaHCO_3$ (saturated aqueous solution), water and brine. The ^{1}H NMR spectrum of the crude reaction mixture

indicated a 23:1 mixture of diastereomers. Silica gel chromatography (1:1:5, R_f = 0.4) led to the isolation of the diastereomeric aldehyde **25** (30 mg, 0.107 mmol, 20:1 mixture of l and u isomers) in 10% yield based on the starting carbene complex **1a**.

Preparation of [(*S*)- and (*R*)-Methyl(methoxymethyl)pyrrolidinocarbene]-pentacarbonylchromium(0) Complexes 27 and 28. To a solution of **1a**[36] (2.866 g, 11.46 mmol) in 20 mL of ether was added (*S*)-(+)-2-(methoxymethyl)pyrrolidine[23] (1.35 g, 11.75 mmol) at −78 °C under an argon atmosphere. After 30 min, the mixture was warmed to 23 °C for 15 min. The mixture was concentrated and purified by silica gel chromatography with a ternary mixture of ether/methylene chloride/hexanes (1:1:4) to give the desired aminocarbene complex **27** (3.715 g, 11.16 mmol) as a 2.5:1 mixture of *Z*- and *E*-rotomers in 97% yield. The *R* enantiomer was prepared in an identical manner to give **28** in 91% yield. While slightly enriched samples could be obtained by silica gel chromatography, pure samples of the *Z*- and *E*-isomers of **27** could not be obtained and were characterized and used in subsequent reactions as a mixture. The following spectral data assignments for **27-E** and **27-Z** were made on the basis of data collected on varying mixtures of the two isomers: R_f = 0.5; ^{1}H NMR ($CDCl_3$) *Z* δ 2.00–2.35 (m, 4H, $(CH_2)_2$), 2.68 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.52–3.66 (m, 4H, $-CH_2O-$, NCH_2-), 4.73–4.79 (m, 1H, NCH–); *E* δ 2.06–2.20 (m, 4H, $(CH_2)_2$), 2.83 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 3.30–3.40 (m, 2H, $-CH_2O-$), 4.12–4.22 (m, 2H, NCH_2-), 4.46–4.52 (m, 1H, NCH–); ^{13}C NMR ($CDCl_3$) *Z* δ 22.51 (t), 26.12 (t), 41.53 (q), 51.80 (t), 59.18 (q), 70.04 (d), 73.22 (t), 218.06 (s), 223.43 (s), 269.02 (s); *E* δ 22.24 (t), 27.99 (t), 40.52 (q), 59.18 (q), 60.40 (t), 62.01 (d), 72.30 (t), 218.18 (s), 223.55 (s), 270.75 (s); IR (thin film) 2050 m, 1958 shoulder, 1893 vs, 1496 m, 1657 m. Anal. Calcd for $C_{13}H_{15}O_6CrN$: C, 46.85; H, 4.54; N, 4.20. Found: C, 46.93; H, 4.71; N, 4.14. The assignment of stereochemistry was made on the basis that the methine proton for the *Z*-isomer would be expected to be further downfield than the methine proton for the *E*-isomer.[41,42] An unambigous assignment of the methine proton for each complex was made by a HETCOR experiment since the carbon bearing the methine proton in each complex is uniquely a doublet in a proton-coupled ^{13}C NMR spectrum and is thus readily assignable. This experiment revealed that the carbon doublet at δ = 70.04 correlated with the major proton absorption at δ = 4.73–4.79 and the carbon doublet at δ = 62.01 correlated with the minor proton absorption at δ = 4.46–4.52.

Base-Induced Isomerization of the *Z*- and *E*-Rotomers of 27. To a solution of **27** (0.0228 g, 0.068 mmol) as a 2.2:1 (*Z*:*E*) mixture of rotomers in 14 mL of ether was added a solution of *n*-butyllithium (0.040 mL, 1.6 M, 0.064 mmol) in hexanes at −78 °C. The solution was stirred for 45 min before water was added to the resulting orange-red solution. The mixture was diluted with ether and washed with water and brine, and the organics were dried over anhydrous magnesium sulfate. The solution was filtered and concentrated to give pure **27** (22.1 mg, 0.066 mmol) as a 1:1.6 (*Z*:*E*) mixture of rotomers in 97% recovery.

Preparation of [(*S*)-Methyl(benzyloxymethyl)pyrrolidinocarbene]-pentacarbonylchromium(0) 29. To a solution of **1a**[36] (0.217 g, 0.869 mmol) in 3 mL of ether was added (*S*)-(+)-2-(benzyloxymethyl)-pyrrolidine[23] (0.186 g, 0.97 mmol) in two portions at −78 °C. The solution was stirred for 35 min and then diluted with ether and washed successively with dilute aqueous H_2SO_4 (0.2 M) and a saturated solution of aqueous $NaHCO_3$, water, and brine. The organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The ^{1}H NMR spectrum of this mixture indicated the presence of the desired product **29** as a 3.2:1 mixture of rotamers. The product was purified by silica gel chromatography (1:1:4) to give pure **29** (0.250 g, 0.61 mmol) in 70% yield as a 3.4:1 mixture of rotamers which were not separable but were characterized and utilized as a mixture. The major rotamer was tentatively assigned as the *Z*-isomer on the basis of the correlation of the chemical shifts of the protons in the methyl groups of both isomers with those of the known isomers of complex **27**. The following spectral data were collected on a mixture of **29-Z** and **29-E**: R_f = 0.63; ^{1}H NMR ($CDCl_3$) δ 2.10–2.14 (m, *Z* + *E*), 2.26–2.35 (m, *Z* + *E*), 2.67 (s, 3H, *Z*), 2.79 (s, 3H, *E*), 3.45 (d, 2H, *J* = 6 Hz, *E*), 3.59–3.76 (m, 4H, *Z*), 4.46–4.61 (m, *Z* + *E*), 4.80–4.87 (m, 1H, *Z*), 7.29–7.32 (m, *Z* + *E*); ^{13}C NMR ($CDCl_3$) *Z* δ 22.54, 26.28, 41.52, 51.81, 70.07, 71.00, 73.47, 127.41, 127.61, 128.37, 137.31, 218.02, 223.37, 269.02; *E* δ 22.23, 28.08, 40.52, 60.43, 61.90, 69.62, 73.21, 127.75, 127.88, 128.49, 137.61, 218.13, 223.50, 270.51; IR (thin film) 2042 m, 1967 shoulder, 1910 s, 1891 s, 1487.

Standard Procedure for the Michael Reactions of Chiral Aminocarbene Complexes As Illustrated for the Reaction of (*S*)-Prolinol-Derived Carbene Complex 27 with 2-Cyclohexenone. A 2.5:1 mixture of *Z*- and *E*-rotamers of carbene complex **27** (0.204 g, 0.612 mmol) in 4 mL of THF was deprotonated at −78 °C by the addition of a hexane solution of *n*-butyllithium (0.38 mL, 1.6 M, 0.61 mmol). The solution was stirred for 15 min before 2-cyclohexenone (0.070 mL, 0.70 g, 0.72 mmol) was injected. The reaction was quenched after 20 min at −78 °C by the rapid addition of a saturated aqueous NH_4Cl solution. The mixture was diluted with ether, and the organic layer was washed with water and then brine. The organic layer was dried over anhydrous magnesium sulfate, filtered through a short plug of Celite, and concentrated. The crude reaction mixture was dissolved in 7 mL of dichloromethane, and trifluoromethanesulfonic acid (0.16 mL, 0.27 g, 1.80 mmol) was injected at 25 °C.[12b-d] After 5 min, a saturated solution of $NaHCO_3$ (aqueous) was added. The reaction mixture was diluted with ether, and the organic solution was washed sequentially with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered through Celite, and concentrated. The product was purified by silica gel chromatography (1:1, hexane/ethyl acetate) to give the known aldehyde **30**[21h] (50.0 mg, 0.36 mmol) in 59% yield based on starting carbene complex **27**. The yields for this reaction are variable (30–60%); all of the factors for this have not been identified, but the purity of complex **27** is important. The optical rotation of the product, $[\alpha]_D$ = +10.58° (*c* = 0.26, dichloromethane), corresponds to 65% ee based on the reported rotation for this compound.[21h] The optical purity of the product was checked by conversion to the known bis-dioxolane derivative **30a** prepared from (2*R*,3*R*)-(−)-2,3-butanediol (see procedure below) which also revealed an induction of 65% ee.[21h]

Control Experiment for Attempted Recovery of Chiral Auxiliary. The chiral auxiliary was not recovered from these reactions, and it was suspected that the auxiliary was destroyed during the triflic acid cleavage of the metal. This was confirmed in a control experiment. To a solution of (*S*)-(+)-2-(methoxymethyl)pyrrolidine (**26**) (75.5 μL, 70.5 mg, 0.612 mmol) in 7 mL of dichloromethane was added trifluoromethanesulfonic acid (108 μL, 183 mg, 1.22 mmol), the solution was stirred for 5 min. Analysis by capillary GC both before and after quenching with aqueous $NaHCO_3$ revealed that pyrrolidine **26** had been completely consumed by this procedure whereas the same treatment without the triflic acid did not consume it. The products of the reaction of pyrrolidine **26** with triflic acid were not determined.

Survey of Reaction Conditions for the Michael Reaction of (*S*)-Prolinol Complex 27 with 2-Cyclohexenone. With the exceptions that are noted, the following experiments were carried out with the procedure described above for the reaction of **27** with 2-cyclohexenone. All enantiomeric excesses were determined by conversion of aldehyde **30** to the known bis-dioxolane derivative **30a** (see procedure below) with (2*R*,3*R*)-(+)-2,3-butanediol.[21h]

Protolytic Cleavage with Trifluoroacetic Acid. The crude product mixture from the reaction of **27** (0.265 g, 0.795 mmol) with 2-cyclohexenone (0.099 g, 1.03 mmol) was treated with trifluoroacetic acid (0.50 mL, 0.74 g, 6.5 mmol) at 0 °C and then warmed to 23 °C for 30 min. After an aqueous workup, the product was purified by silica gel chromatography to give (*S*)-**30** (0.0460 g, 0.33 mmol) in 41% yield and 64% ee.

1.3:1 Rotameric Mixture of Starting Carbene Complex 27. A 1:1.3 (*Z*:*E*) rotameric mixture of **27** (0.344 g, 1.032 mmol) was deprotonated under standard conditions and reacted with 2-cyclohexenone (0.11 g, 1.14 mmol). Protolytic cleavage of the chromium pentacarbonyl by treatment of the crude reaction mixture with triflic acid (0.30 mL, 0.51 g, 3.4 mmol) and purification by chromatography led to the isolation of (*S*)-**30** (0.0571 g, 0.408 mmol) in 40% yield and 63% ee.

Excess Li Cation. Carbene complex **27** (0.224 g, 0.672 mmol) was added to a suspension of LiCl (0.30 g, 7.06 mmol) in 4 mL of THF, and the mixture was treated with a solution of *n*-butyllithium (0.42 mL, 1.6 M, 0.67 mmol) in hexane at −78 °C. After 1 h, 2-cyclohexenone (0.070 mL, 0.069 g, 0.73 mmol) was added and the resulting mixture was stirred for 20 min before the reaction was quenched. The crude reaction mixture was worked up in the typical fashion, and the metal pentacarbonyl was protolytically cleaved by the addition of triflic acid (0.18 mL, 0.31 g, 2.03

(40) (a) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445. (b) Senoff, C. V.; Lam, G. T.; Malkiewich, C. D. *Inorg. Synth.* **1978**, *17*, 95.

(41) It should be noted that the terms *Z* and *E* used here to describe the stereochemistry of the two rotamers about the carbene carbon–nitrogen bond are reversed from the usage employed by Fischer for this same purpose. (a) Moser, E.; Fischer, E. O. *J. Organomet. Chem.* **1969**, *16*, 275. (b) Fischer, E. O.; Leupold, M. *Chem. Ber.* **1972**, *105*, 599.

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

mmol) using standard conditions. The product was purified by silica gel chromatography and gave (*S*)-**30** (0.056 g, 0.40 mmol) in 60% yield and 66% ee.

Reaction Temperature of −100 °C. A solution of carbene complex **27** (0.275 g, 0.825 mmol) in 5 mL of THF was placed in a dry ice/anhydrous ether bath (−100 °C) and treated with a solution of *n*-butyllithium (0.52 mL, 1.6 M, 0.83 mmol) in hexanes. 2-Cyclohexenone (0.10 mL, 0.091 g, 0.95 mmol) was injected and the mixture stirred for 20 min before the reaction was quenched. Typical workup followed, and the crude reaction mixture was treated with triflic acid (0.22 mL, 0.37 g, 2.5 mmol) under standard conditions. Product (*S*)-**30** (0.0640 g, 0.457 mmol) was isolated in 55% yield and 61% ee.

Reaction Temperature of 5 °C. A solution of carbene complex **27** (0.252 g, 0.756 mmol) in 4.5 mL of THF was placed in an ice-water bath (5 °C) and treated with a solution of *n*-butyllithium (0.47 mL, 1.6 M, 0.75 mmol) in hexanes. 2-Cyclohexenone (0.090 mL, 0.089 g, 0.93 mmol) was injected and the mixture stirred for 20 min before the reaction was quenched. Typical workup followed, and the crude reaction mixture was treated with triflic acid (0.20 mL, 0.34 g, 2.3 mmol) under standard conditions. Product **30** (0.0272 g, 0.194 mmol) was isolated in 27% yield and 4% ee.

Reaction Temperature of −78 °C for 20 min, Then 0 °C for 20 min. A solution of carbene complex **27** (204 mg, 0.612 mmol) in 4 mL of THF was placed in a dry ice/acetone bath and treated with a solution of *n*-butyllithium (0.25 mL, 2.44 M, 0.610 mmol) in hexanes. 2-Cyclohexenone (0.070 mL, 0.069 mg, 0.720 mmol) was injected, and the mixture was stirred for 20 min at −78 °C and then moved to an ice bath and stirred for another 20 min before the reaction was quenched. Typical workup followed, and the reaction mixture was treated with triflic acid (0.16 mL, 0.271 mg, 1.80 mmol) under standard conditions. Product **30** (27 mg, 0.197 mmol) was isolated in 32% yield and 52% ee.

Reaction in Toluene. A solution of carbene complex **27** (0.4565 g, 1.37 mmol) in 8 mL of toluene was treated with a solution of *n*-butyllithium (0.86 mL, 1.55 M, 1.33 mmol) in hexanes at −78 °C under an argon atmosphere. After 15 min, 2-cyclohexenone was injected and the resulting mixture stirred for 30 min before the reaction was quenched. Only one organometallic compound was observed by TLC. Silica gel chromatography (1:1 hexane/ethyl acetate) led to the recovery of **27** (0.2938 g, 0.88 mmol) in 64% yield.

Michael Reaction of (*R*)-Prolinol-Derived Carbene Complex 28 with 2-Cyclohexenone. Following the procedure for complex **27**, the Michael adduct from this reaction was also cleaved in the same manner to give, after purification by silica gel chromatography (1:1 hexane/ethyl acetate), the known aldehyde (*R*)-**31** in 57% yield and 76% ee. The optical purity was determined from the ^{13}C NMR spectrum of the corresponding known bis-dioxolane derivative **21a** prepared from (2*R*,3*R*)-(−)-butanediol (see procedure below).[21h]

Michael Reaction of (*S*)-Benzyloxy-Protected Carbene Complex 29 with 2-Cyclohexenone. Following the procedure for complex **27**, the Michael adduct from this reaction was also cleaved in the same manner to give, after purification by silica gel chromatography (1:1 hexane/ethyl acetate), the known aldehyde (*S*)-**30** in 79% yield and 60% ee. The optical purity was determined from the ^{13}C NMR spectrum of the known bis-dioxolane derivative **30a** prepared from (2*R*,3*R*)-(+)-2,3-butanediol (see procedure below).[21h]

Michael Reaction of (*S*)-Prolinol-Derived Carbene Complex 27 with 2-Cyclohexenone. Following the procedure for complex **27**, the Michael adduct from this reaction was also cleaved in the same manner to give, after purification by silica gel chromatography (1:1 hexane/ethyl acetate), aldehyde **32** (38.0 mg, 0.302 mmol) in 46% yield and 64% ee. The optical purity was determined from the ^{13}C NMR spectrum of the known bis-dioxolane derivative **32a** prepared from (2*R*,3*R*)-(+)-2,3-butanediol (see procedure below).[21h]

Michael Reaction of (*S*)-Prolinol-Derived Carbene Complex 27 with 4,4-Dimethyl-2-cyclohexenone. Following the procedure for complex **27**, the Michael adduct from this reaction was also cleaved in the same manner to give, after purification by silica gel chromatography (1:1 hexane/ethyl acetate), aldehyde **33** in 51% yield and 95% ee. The optical purity was established from the ^{13}C NMR spectrum of the bis-dioxolane derivative **33a** (see procedure below). Spectral data for **33**: $[\alpha]_D = +7.4°$ ($c = 0.5$, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.02 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.67–1.76 (m, 2H), 2.10–2.41 (m, 6H), 2.61 (dd, 1H, $J = 18.5$, 1.9 Hz), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.78, 28.50, 32.26, 37.98, 39.55, 40.36, 43.49, 45.49, 201.04, 210.20; IR (thin film) 2960 m, 2925 m, 2718 w, 1721 s; mass spectrum, *m/e* (rel intensity) 168 M^+ (5), 153 (4), 140 (13), 125 (33), 112 (49), 97 (40), 81 (21), 69 (100), 55 (67); *m/e* calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1150.

General Procedure for the Preparation of Bis-dioxolane Derivatives As Illustrated for Aldehyde 33. Michael addition cleavage product **33** (0.0591 g, 0.352 mmol), (2*R*,3*R*)-(−)-2,3-butanediol (0.123 g, 1.36 mmol), and *p*-toluenesulfonic acid (6 mg, 0.032 mmol) were placed in a 25-mL round bottom flask and dissolved in 10 mL of dry benzene. The flask was fit with a Dean–Stark trap, and the mixture was refluxed for 12 h. The solution was concentrated, and a ^{13}C NMR spectrum was recorded. The product was purified by silica gel chromatography (1:1:4) to give bis-dioxalane **33a** (0.0979 g, 0.314 mmol) in 90% yield. This procedure was repeated with racemic aldehyde **33** which provided both diastereomers of bis-dioxalane **33a**. The optical purity of the aldehyde **33** obtained from the Michael addition reaction was determined to be 95% ee by integration of several corresponding absorptions of the two diastereomers of bis-dioxolane **33a** present in the ^{13}C NMR spectrum taken prior to purification. The 3*S* stereochemical assignment of the major diastereomer is consistent with the empirical rules that have been developed for assigning absolute configurations of chiral dioxolane derivatives of substituted cyclohexanones.[25] Spectral data for dioxolane **33a**: ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 0.82–0.91 (m, 2H), 0.91 (s, 3H), 1.28–1.34 (m, 12H), 1.34–1.42 (m, 2H), 1.53–1.87 (m, 5H), 3.55–3.60 (m, 4H), 5.01–5.03 (m, 1H); ^{13}C NMR ($CDCl_3$) (*S*)-**33a** δ 16.90 (CH_3), 17.00 (CH_3), 17.10 (CH_3), 18.45 (CH_3), 29.19 (CH_2), 29.55 (CH_2), 32.06 (CH_2), 33.10 (CH_2), 35.53 (CH_2), 38.12, 38.14, 39.19, 77.52 (CH), 77.59 (CH), 77.81 (CH), 79.60 (CH), 102.86 (CH), 108.11 (C); (*R*)-**33a** (determined from the racemic mixture) δ 16.98, 17.05, 17.18, 17.30, 18.48, 18.52, (CH_3 could not be unequivocally assigned to one diastereomer), 32.16, 32.36, 35.46, 38.61, 38.68 (i, 3-CH), 77.63 (i, CH), 77.93 (i, CH), 77.99 (i, CH), 79.37 (i, CH), 103.01 (i, CH), 108.20; the carbons were assigned by a proton-coupled spectrum and an ATP experiment; the pulse sequence results in methylenes and quaternary carbons resonating in the normal fashion and methyl and methine resonances to be inverted (indicated by "i"); IR (thin film) 2959 s, 2857 s, 1445, 1371 m, 1102 s; mass spectrum, *m/e* (rel intensity) 312 M^+ (2), 311 (9), 241 (19), 141 (22), 127 (69), 101 (100), 73 (23), 55 (38); *m/e* calcd for $C_{18}H_{32}O_4$ 312.2300, found 312.2302.

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