# Stereoselective aldol addition reactions of Fischer carbene complexes via electronic tuning of the metal center for enolate reactivity

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**Abstract**

The aldol reactions of tetracarbonyl(phosphine)methyl(methoxy)methylene chromium complexes and pentacarbonylmethyl(dialkylamino)methylene chromium complexes with aldehydes and ketones were examined. The reactions of the phosphine complexes give only aldol condensation products, but the desired aldol addition products can be isolated from the reactions of amino carbene complexes. This was attributed to the greater reactivity of the enolates of amino carbene complexes which is supported by a determination of the thermodynamic acidity of the dimethylamino complex **13** ($pK_a = 20.4$). The aldol reactions of amino complexes with $\alpha$-chiral aldehydes occur with very high facial selectivities rivaling the best methods that have been developed for facial selectivity in the aldol reaction. The aldol reactions of amino complexes can be considered as direct synthons for amides since amide functions can be obtained in the oxidative cleavage of the aldol adducts of these complexes. As illustrative of the versatility of carbene complexes, it is also demonstrated in a photo-induced carbon-homologative demetallation, that in combination with the aldol addition reaction the unique reactions of carbene complexes provide powerful and novel overall transformations.

*Key words:* Fischer carbene complexes; Aldol addition reactions; Stereoselectivity; Chromium complexes; Carbonyl complexes; Carbene complexes

## Introduction

The aldol reaction is one of the most powerful synthetic methods for the incorporation of 1,3-dioxygen functionality into organic compounds. Because this relationship occurs ubiquitously in natural products, considerable effort has been devoted to increasing the flexibility and stereocontrol of this reaction [1]. Nonetheless, the need for improved methods still exists. Toward this end, we became interested in studying the aldol reaction of Fischer-type transition metal carbene complexes [2–4]. A number of examples now exist where these readily available, air stable organometallics have been demonstrated to be synthons for carbonyl compounds since oxidative cleavage of the metal fragment leads to the corresponding carboxylate derivatives [5]. Our objectives were twofold: (i) to expand the scope of the established reactivity of carbene complexes to give the synthetically versatile $\beta$-hydroxy carbene complexes and (ii) to parlay the greater steric bulk of the enolate obtained by replacement of the carbonyl oxygen with the significantly larger metal pentacarbonyl group into increased stereocontrol in the aldol reaction.

Literature precedent at the outset indicated that only marginal success had been realized for nucleophilic reactions of the relative unreactive alkoxycarbene anions [6, 7]. While Casey found that the carbene complex anion **8a** fails to react with ketones, reactions with non-enolizable aldehydes can be realized, but the initial aldol addition products **6** cannot be isolated since they are rapidly converted to the aldol condensation product, the $\alpha,\beta$-unsaturated carbene complexes in 20–50% yields [7] (Scheme 1). This modest reactivity can be attributed to the uncommon stability of the extensively delocalized carbene anion **8** (Fig. 1). This is reflected in the thermodynamic acidity of the methyl(methoxy)pentacarbonyl chromium carbene complex **8** for which the $pK_a$ was determined to be approximately 8 by a study of the equilibration of the bis(triphenylphosphine)iminium (PPN) salt of **8** and various acidic phenols [6, 7k, 8]. The $pK_a$ of the lithium salt of **8** in THF was found to be 12. The disparity

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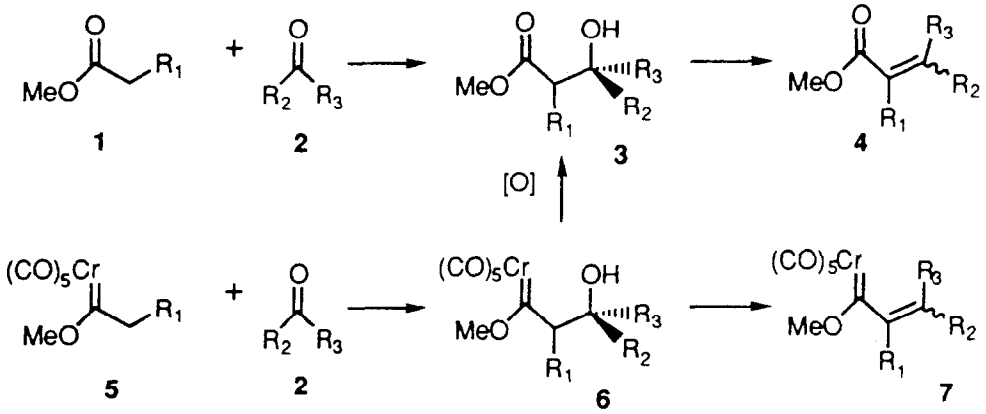


Scheme 1.

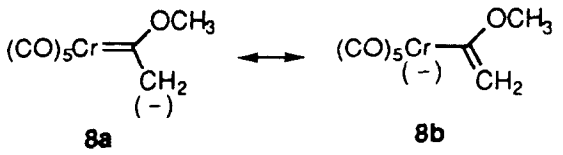
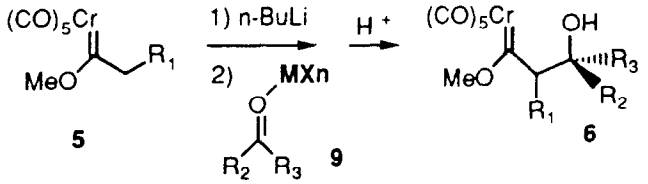


Fig. 1.



Scheme 2.

between these values is most likely due to ion-pairing effects of the phenoxide ions since spectral evidence suggests that the anion of **8** exists as a solvent separated carbene anion and the addition of HMPA to the lithium salt had a considerable effect on the $pK_a$ [6, 7k].

Our initial goal was to develop a synthetically useful method for accomplishing the aldol addition reaction of carbene complex anions to aldehydes and ketones and the isolation of $\beta$-hydroxy carbene complexes of type **6**. Since this reaction fails with most carbonyl compounds, the two most reasonable strategies to pursue involve either increasing the reactivity of the carbonyl compound or of the carbene complex anion. Our first efforts were with the former where substrate activation allowed the inherent stability of carbene complex anions to be circumvented. It was found that alkoxycarbene complex anions added to carbonyl compounds that were pre-complexed with Lewis acids to give the desired $\beta$-hydroxy carbene complexes in synthetically useful yields [2] (Scheme 2). This method proved effective for addition reactions with ketones, aldehydes and carbonyl equivalents including ketals and ortho esters. There were, however several limitations of this strategy. For example, the requisite Lewis acid precludes addition reactions with carbonyl compounds containing acid sensitive functionalities. In addition, the optimized reaction conditions require in many cases a large excess of the carbonyl–Lewis acid complex. These restrictions would necessarily limit the consideration of the application of this methodology.

Due to the limitations of the substrate activation strategy, we turned our attention to a complementary strategy which involved increasing the reactivity of the carbene complex anion. Within this strategy there are two choices for electronic tuning for increased reactivity of anion **A** and these involve substitutions for the heteroatom stabilizing substituent of the carbene carbon (XR) or for a ligand on the metal center (Fig. 2). In this work we will describe approaches where both types of substitution are examined and report in detail on the most successful approach involving the aldol reactions of amino carbene complexes.

## Aldol reactions of tetracarbonyl phosphine alkoxycarbene complexes

Our approach for accomplishing the aldol reaction of carbene complexes via increasing the reactivity of carbene complex anions required simple structural modification of the carbene complex that would destabilize its conjugate base. Our first modification was to replace one of the carbon monoxide ligands on the metal with a tributylphosphine to give the tetracarbonyl methoxy complex **10**. We have previously had success in alkylations of phosphine substituted carbene complexes of this type with alkyl halides that are normally unreactive

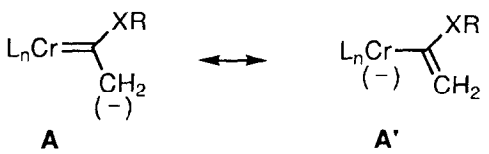
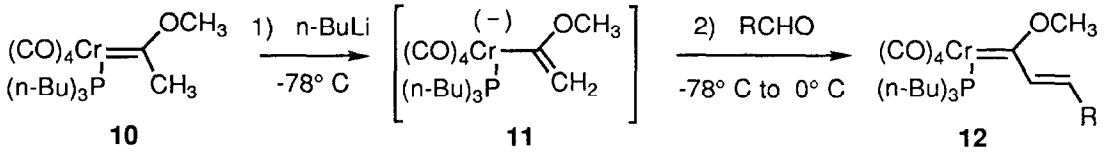


Fig. 2.




**10** **11** **12**

TABLE 1. Aldol reactions of the tetracarbonyl(tri-n-butylphophine) carbene complex **10**

| Entry | Aldehyde | Conditions | Product | R | Yield of **12** (%) |
|---|---|---|---|---|---|
| 1 | $(CH_3)_3CCHO$ | 0 °C, 5 h | **12a** | $(CH_3)_3C$ | 21 |
| 2 | PhCHO | 0 °C, 15 min | **12b** | Ph | 86 |
| 3 | $CH_3(CH_2)_2CHO$ | 0 °C, 1 h | **12c** | $CH_3(CH_2)_2$ | 21 |

with the anion of the methyl(methoxy)pentacarbonyl carbene complex **5** ($R_1$ = H) [9]. The extent of charge destabilization that this substitution of a trialkylphosphine for a strongly electron withdrawing carbon monoxide ligand affords is indicated by the p$K_a$ measured for the methyl(methoxy)tetracarbonyl(tributylphosphine)chromium carbene complex (**10**) (p$K_a$ = 18.8) which was found to be six orders of magnitude greater than the pentacarbonyl complex measured under similar conditions [9].

Results from the successful alkylation reactions prompted an investigation of the aldol reaction of the carbene complex anion **11**. Their reactions with carbonyl compounds, however, gave only the eliminated alkenyl carbene complexes **12** in yields very similar to those Casey reported for the pentacarbonyl carbene complex with the same aldehydes (Table 1). The trialkylphosphine substituent did have some influence on the reaction since a condensation product **12c** was isolated from the reaction with an enolizable aldehyde, albeit in low yield (entry 3). The attempted aldol reaction with acetone gives, under several conditions, the near quantitative recovery of carbene complex **10**. Deuterium labeling experiments demonstrated that deprotonation of acetone by the carbene anion **11** was a competing process [9]. Efforts to effect the aldol reaction with butyraldehyde employing conditions identical to those found optimal for the Lewis acid mediated reactions of pentacarbonyl carbene complexes [2] led to complicated product mixtures yielding only small amounts of the eliminated product.

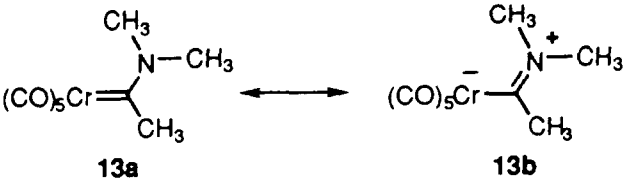
## Determination of the equilibrium acidity of an amino carbene complex

Upon consideration of other structural modifications that might result in even greater charge destabilization, our attention was drawn to the variability of the carbene heteroatom substituent. We thus began a study of (dialkylamino) carbene complexes [10]. These compounds are readily available, air stable complexes that are prepared in high yield simply by stirring the alkoxy complex with the unhindered mono or dialkylamines [11, 12]. A great deal of data suggests that electron donation of the heteroatom into the 'vacant' $p_z$ orbital of the carbene carbon **13b** is much more significant in aminocarbene complexes than alkoxycarbene complexes (Fig. 3) [13]. Competition for the $p_z$ orbital by electron donation from the heteroatom with anions generated at the $\alpha$-position should, therefore, result in a much less stable anion since delocalization into the metal pentacarbonyl is less favorable.

The p$K_a$ of the methyl(dimethylamino)chromium pentacarbonyl carbene complex (**13**) was measured in order to quantitatively support our anticipation of decreased anion stability. Attempts to determine the p$K_a$ under conditions similar to those reported for alkoxy carbene complexes [6, 7k, 9] in THF were unsuccessful due to decomposition of the aminocarbene complex. Alternatively, the spectrophotometric method of Bordwell and co-workers for determining relative equilibrium acidities of carbon acids in DMSO was employed [14]. This method benefits from the minimal interference from ion association effects and allows a direct comparison with a large number of carbon acids which have been similarly measured [15].

$$K_{equil} = \frac{[InH][(CO)_5CrC(NMe_2)CH_2^-]}{[In^-][(CO)_5CrC(NMe_2)CH_3]}$$

InH = 2-naphthylacetonitrile (p$K_a$ = 20.65)



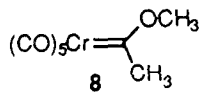
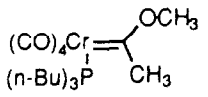
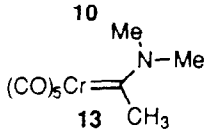

**13a** **13b**

Fig. 3.

The equilibrium was monitored by following the visible absorbance of the conjugate base of 2-naphthylacetonitrile ($pK_a = 20.65$) [16] in a measurement cell containing excess indicator acid to which aliquots of the carbene complex were added. The calculated equilibrium constant allowed the $pK_a$ of the carbene complex to be related to the known $pK_a$ of the indicator acid. From this relationship, the $pK_a$ of the methyl(dimethylamino)chromium carbene complex (**13**) was found to be approximately 20.4 (Table 2). The conditions used in the measurement were reproduced on a large, more concentrated scale which allowed recovery of carbene complex **13** in 83% after quenching. This, along with the stable absorbance readings recorded during the measurements, demonstrates the stability of the carbene complex and its anion to the measurement conditions and indicated that no side reactions significantly obscured the measurement. This was done from a consideration that DMSO will react with carbene complexes with an oxidative liberation of the carbene ligand [17]. In fact, DMSO can be used to oxidize amino carbene complexes (*vide infra*), however, this usually requires temperatures above room temperature or extended reaction times.

Equilibrium acidity measurements are extremely sensitive to the solvent, primarily as a result of ion pairing affects. The $pK_a$ value for **13** measured in DMSO is therefore most appropriately compared to the $pK_a$ value of the methyl(methoxy) carbene **8** established by equilibration with *p*-cyanophenol using the diffuse non-coordinating PPN(+) salt of the conjugate base ($pK_a = 8$) rather than the value of 12 determined for the lithium salt where ion pairing effects play an important role [6, 7k]. Substitution of the amino group has a dramatic effect when compared to the alkoxycarbene complex **8** and appears to be even somewhat less acidic than the tetracarbonyl tributylphosphine complex **10**. The aminocarbene complex **13** however remains much more acidic than the organic analog *N,N*-dimethylacetamide for which a $pK_a$ in DMSO has been estimated to be between 34 and 35 [18].

TABLE 2. $pK_a$ values of Fischer carbene complexes

| Complex | $pK_a$ | Reference |
|---|---|---|
|  **8** | 12[a]<br>8[b] | 6, 7k, 8 |
|  **10** | 18.8[c] | 9 |
|  **13** | 20.4[d] | this study |

[a]Lithium salt in THF. [b]$PPN^+$ salt in THF. [c]Lithium salt in THF. [d]Potassium salt in DMSO.

## Aldol addition reactions of amino carbene complexes

A significant charge destabilization of the conjugate base of amino carbene complexes, relative to alkoxy carbene complexes, would explain the observation that the anions of aminocarbene complexes have been shown to be efficient nucleophiles with a number of alkylating reagents [3, 19]. We have found that the anions of methyl(dialkylamino) carbene complexes also react cleanly and rapidly with aldehydes and ketones without the assistance of a Lewis acid to give the β-hydroxy carbene complexes in good to excellent yields (Table 3) [3]*. The reaction is procedurally simple, requiring no special precautions and the air stable aldol adducts can be easily isolated by silica gel chromatography. Alkyl aldehydes were found to react equally as well as non-enolizable aldehydes and both give high yields of the aldol addition product **17**. It is interesting that, whereas, the alkoxy carbene complexes fail to give aldol addition products unless the aldehyde or ketone is activated by precomplexation with a Lewis acid [2], the aldol reaction of amino carbene complexes fail only if the carbonyl is precomplexed with a Lewis acid. For example no aldol adduct was observed from the reaction of the anion of the amino complex **13** with benzaldehyde that had been precomplexed with $TiCl_4$ according to the procedure described for alkoxy complexes [2]. Other examples will be described for the reactions of amino carbene complexes with 2-methyl-3-phenylpropanal (*vide infra*).

Ketones also react with the amino carbene complex anions (entries 9–14), however, the yields of the aldol adducts are generally lower and they are accompanied with significant recovery of starting material. The ketone aldol adducts are notably less stable than aldehyde aldol products and some evidence suggests they are susceptible to a retro-aldol reaction. During purification by silica gel chromatography, the appearance of the easily separable starting carbene complex as a contaminant in aldol product **17i** indicated a retro-aldol reaction was facilitated by silica gel. It was found that rapid elution during chromatography was beneficial and in the case of the cyclohexanone adduct the yield for the clean aldol product **17i** can be increased to ~90% (entries 13–14). A reversible reaction was further illustrated by deprotonation of the acetone aldol adduct

*For related Peterson-type reactions of aminocarbene complexes see ref. 19a.

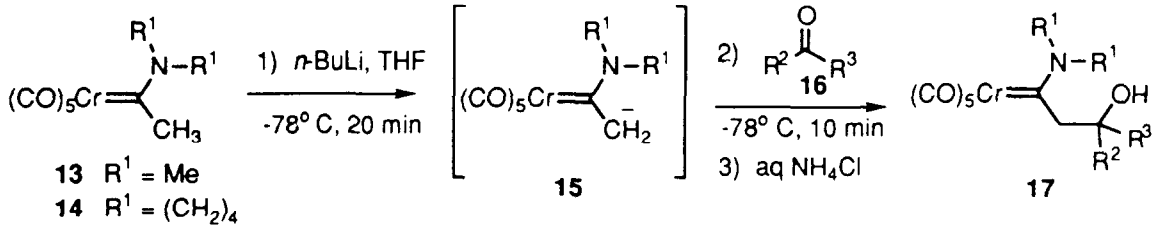



TABLE 3. Aldol reactions of amino carbene complexes

| Entry | Complex | Carbonyl **16** | | Equiv. **16** | Product | Yield of **17**[a] (%) | Recovery of **13** or **14** (%) |
|---|---|---|---|---|---|---|---|
| | | $R^2$ | $R^3$ | | | | |
| 1 | **13** | Ph | H | 5.6 | **17a** | 81 | 17 |
| 2 | | n-Pr | H | 1.7 | **17b** | 73 | 16 |
| 3 | | Me | H | 4.3 | **17c** | 81 | |
| 4 | **14** | Ph | H | 1.1 | **17d** | 96 | |
| 5 | | n-Pr | H | 2.0 | **17e** | 76 | 18 |
| 6 | | Me | H | 3.0 | **17f** | 79 | |
| 7 | | | | 10.0 | | 94 | |
| 8 | | i-Pr | H | 1.5 | **17g** | 81 | |
| 9 | | Me | Me | 1.7 | **17h** | 58 | 32 |
| 10 | | | | 1.0 | | 53 | 26 |
| 11 | | | | 1.7[b] | | 59 | 28 |
| 12 | | | | 1.7[c] | | 54 | 40 |
| 13 | | $-(CH_2)_5-$ | | 1.7 | **17i** | 66 | 24 |
| 14 | | | | 1.1 | | 89[d] | |

[a]Unless otherwise indicated, all yields are the average of at least two runs. [b]This reaction was quenched by addition of a solution of 0.2 ml of acetic acid (3.8 equiv) in 1.0 ml of THF which had been precooled to −78 °C. [c]0.33 M in **14**, all other reactions at 0.1 M. [d]Isolated by rapid chromatography on silica gel.

**17h** under the normal reaction conditions. After quenching the reaction, the crude $^1H$ NMR spectrum indicated a 3:1 mixture of the aldol adduct **17h** and the methyl(pyrrolidinyl) carbene complex **14**.

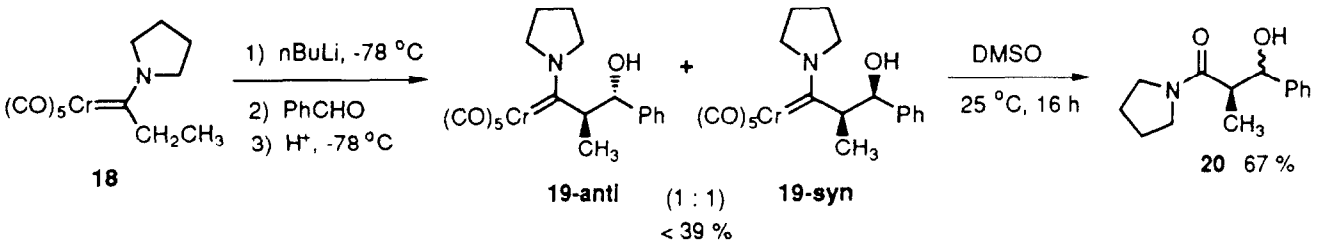
## Simple diastereoselectivity

The salient feature of the aldol reaction that has duly received the majority of recent attention has been the control of stereochemistry [1] and was therefore an important aspect of our investigation. Recent advances have distinguished the aldol reaction as one of the most synthetically useful stereoselective C–C bond forming methods available. Our initial investigation in this regard, began with a study of the simple diastereoselectivity resulting from the reaction of the prochiral anion of the ethyl carbene complex **18** with a simple aldehyde which could produce the racemic products having either *syn* or *anti* relative stereochemistry. (The diastereomers illustrated in Scheme 3 represent the structure as drawn and its enantiomer.)

The reaction of the ethyl (pyrrolidinyl)chromium carbene complex anion with benzaldehyde gives the relatively unstable aldol product **19** in low yield with no observable diastereoselectivity as determined from the unpurified reaction mixture by $^1H$ NMR. Some diastereomeric enrichment did occur during silica gel chromatography prior to oxidative conversion to the corresponding amide **20**. Because of the instability of the aldol adduct it was difficult to determine whether this was due to selective decomposition, isomerization or simply chromatographic enrichment. Oxidation of this mixture yielded an identical ratio of amide diastereomers. The low reactivity of $\alpha$-substituted amino carbene anions has been observed in the sluggish alkylations with other electrophiles [19a–c] and is most likely due to unfavorable steric affects. Solutions to the stereoselective aldol reactions of $\alpha$-substituted carbene complexes will first require the development of more reactive enolate species and then perhaps an examination of the stereochemistry of enolate formation.

## Diastereofacial selectivity

A more challenging synthetic task in the development of the aldol reaction has been the diastereofacially selective addition of $\alpha$-unsubstituted enolates to chiral aldehydes [1]. Concerns of controlling facial selectivity do not typically arise for reactions of substituted enolates since the phenomenon of double diastereoselectivity




Scheme 3.

can amplify modest intrinsic facial preferences to synthetically useful diastereomeric ratios [20]. The most successful solution for $\alpha$-unsubstituted nucleophiles has been the Lewis acid mediated addition of enolsilanes to chiral aldehydes which leads to remarkably improved diastereoselectivity with respect to typical metal enolates [21–23]. Heathcock proposes that the Lewis acid complex enhances facial selectivity by favoring approach of the nucleophile on a trajectory that brings it in greater proximity to the chiral substituent **21-B** than in the case of the uncomplexed aldehyde **21-A** (Fig. 4) [21, 24].

In light of the important controlling function of the Lewis acid suggested by this model, the high degree of the diastereofacial selectivity that is observed in the addition of the enolates of amino carbene complexes to uncomplexed $\alpha$-chiral aldehydes is dramatic. The anion of the dimethylamino carbene **13** reacts with 2-phenylpropionaldehyde with no Lewis acid present to give an 80% yield of the aldol adduct as a 40:1 (l:u) mixture of diastereomers* (Scheme 4). This can be compared to 3:1 (l:u) selectivity that has been reported for the addition of the lithium enolate of *N,N*-dimethylacetamide to the same aldehyde [21]. The ratio of diastereomers of the carbene complexes were determined by oxidation of the crude reaction mixtures with warm DMSO and analysis of the crude unpurified mixtures by capillary GC. The stereochemical assignments were confirmed spectroscopically and by GC with the co-injection of authentic samples of amides **23a** and **23b**. When the aldol product **22b** and the oxidation product **23b** were each purified by silica gel chromatography, a much cleaner GC trace was recorded and the ratio of l to u was found to be $\geqslant$200:1. The diastereofacial selectivity observed for the aminocarbene anion additions to 2-phenylpropionaldehyde is an order of magnitude greater than the additions of any $\alpha$-unsubstituted lithium enolates reported to date, and is equal to the highest selectivity reported for a Lewis acid mediated reaction of a enolsilane [21].

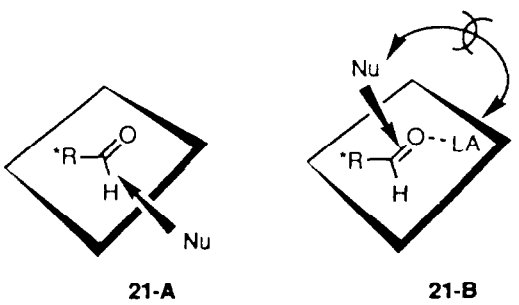
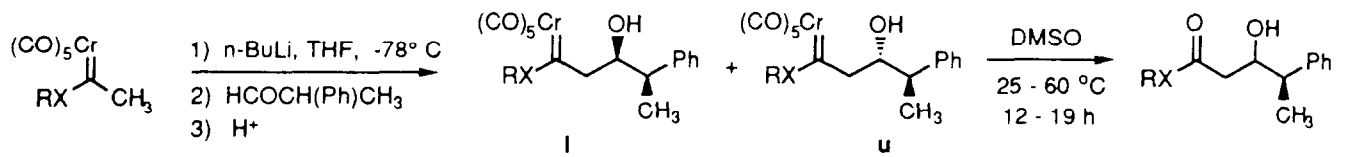



Fig. 4.

The highly stereoselective reaction of amino carbene complexes with 2-phenylpropanal was shown to be the result of a kinetically controlled addition. The carbene adduct **22a** was treated with one equivalent of n-butyllithium to generate the aldolate **24** and was then exposed to 1-deutero-2-phenylpropionaldehyde (**25**) under the typical reaction conditions (Scheme 5). The recovered adduct (65% isolated) was found not to have incorporated deuterium ($\leqslant$5% by crude $^1$H NMR). Additionally, the formation of **13** as a result of retro-aldolization could not be detected. Epimerization at the newly formed chiral center would necessarily involve equilibration by a reversible aldol reaction and would lead to deuterium incorporation at the carbinol position or to the appearance of **13**. Therefore, unlike the reactions with ketones (Table 3), the aldol additions

*The descriptors l and u are used as defined in ref. 25.



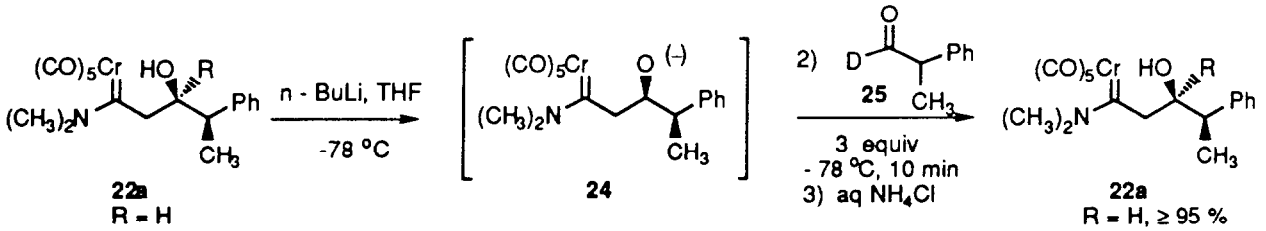

**13** XR = $NMe_2$
**14** XR = $N(CH_2)_4$

**22a** 80 % yield (≥ 40:1, l:u)
**22b** 94 % yield (≥ 36:1, l:u)

**23a** 65 % (≥ 40:1, l:u)
**23b** 71 % (≥ 36:1, l:u)

Scheme 4.

The highly stereoselective reaction of amino carbene complexes with 2-phenylpropanal was shown to be the result of a kinetically controlled addition. The carbene adduct **22a** was treated with one equivalent of n-butyllithium to generate the aldolate **24** and was then exposed to 1-deutero-2-phenylpropionaldehyde (**25**) under the typical reaction conditions (Scheme 5). The recovered adduct (65% isolated) was found not to have incorporated deuterium ($\leqslant$5% by crude $^1$H NMR). Additionally, the formation of **13** as a result of retro-aldolization could not be detected. Epimerization at the newly formed chiral center would necessarily involve equilibration by a reversible aldol reaction and would lead to deuterium incorporation at the carbinol position or to the appearance of **13**. Therefore, unlike the reactions with ketones (Table 3), the aldol additions




Scheme 5.

of the amino carbene complexes to aldehydes are irreversible.

A stereoselective reaction of amino carbene complex anions with dl-2-methyl-3-phenylpropionaldehyde requires the much more subtle facial discrimination between the adjacent methyl and benzyl groups. As indicated by the data in Table 4, the selectivity is markedly decreased (4:1) from that for the reaction with 2-phenylpropanal where the facial discrimination involves a methyl versus a phenyl group. Nonetheless, this level of selection is significant since other unsubstituted enolates give essentially 1:1 mixture with this aldehyde and silyl enol ethers give a 2.5:1 mixture (Table 4) [21, 26]. The carbene complex aldol adduct **27** was oxidized to the corresponding amide **28** in high yield without diastereomeric enrichment. The stereochemical assignment of the amides **28** was made by analogy to the published spectral data for related aldol adducts with this aldehyde [21]. The $^{1}H$ and $^{13}C$ resonances of the 4-methyl group and the 3-methine position are very diagnostic of the stereochemistry of the aldol adduct. In all reported cases with this aldehyde, the 4-methyl and the 3-methine protons of the l-diastereomers were shifted downfield with respect to the corresponding u-diastereomers. A brief study surveyed conditions that might influence the diastereofacial selectivity of this reaction (Table 4). Increasing the steric bulk of the nitrogen substituents had little influence (entry 2). No significant differences were observed when Li (hexamethyl) disilylamide (LiHMDS) was used for deprotonation instead of n-butyllithium. The influence of various counter ions was also examined with a moderate impact on the stereoselectivity and a more unsatisfactory effect on yield.

In order to determine whether the aldol reactions of aminocarbene complexes involve an open transition state, the addition reaction was studied in the absence of a coordinating counter-ion. The fluoride induced cleavage of the $\alpha$-silylmethyl carbene complex **29** in the presence of 2-phenylpropionaldehyde was attempted [27], however only the protodesilylated carbene complex **13** was isolated (85% yield). It has been reported that the fluoride initiated reaction of a silyl enol ether with 2-phenylpropionaldehyde fails [27b]. The fluoride induced reaction of **29** was successful with benzaldehyde but in this case the desired information regarding the transition state can not be translated into stereochemical information in the product (Scheme 6).

It was anticipated that precomplexation of the aldehyde would further increase the selectivity of the addition of carbene complex anions by influencing the trajectory of the nucleophile as proposed in the Heath-

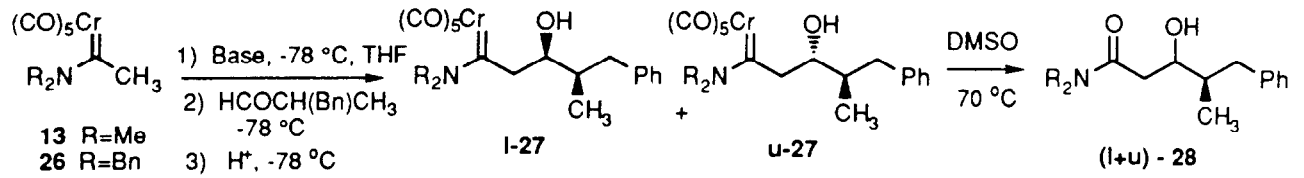
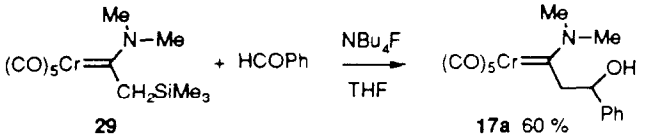



TABLE 4. Diastereofacial selectivities for aldol reaction with 2-methy-3-phenypropionaldehyde

| Entry | Carbene complex | Base | Product | Yield of 27 (%) (l:u) | Product | Yield of 28 (%) (l:u) |
|---|---|---|---|---|---|---|
| 1 | **13** | n-BuLi | **27a** | 78 (4.0:1.0) | **28a** | 89 (4.0:1.0) |
| 2 | **26** | n-BuLi | **27b** | | **28b** | 46 (3.0:1.0) |
| 3 | **13** | LiHMDS | **27a** | 27 (3.0:1.0) | **28a** | |
| 4 | **13** | NaHMDS | **27a** | 44 (4.0:1.0) | **28a** | |
| 5 | **13** | KHMDS | **27a** | 26 (2.0:1.0) | **28a** | |
| 6 | **13** | KHMDS (18-crown-6) | **27a** | 8 (2.4:1.0) | **28a** | |




Scheme 6.

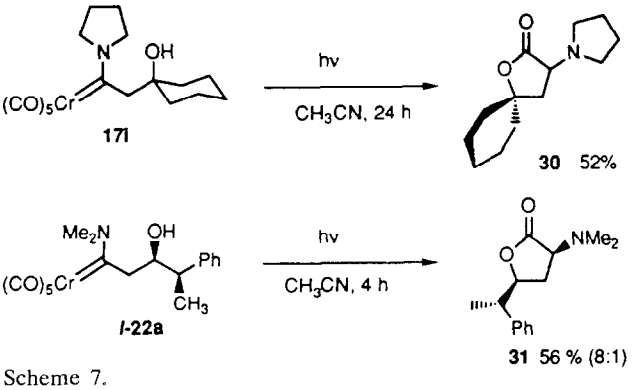
cock model (Fig. 4). However, in contrast to the alkoxycarbene anions [2]* all attempts to effect the reaction of the lithium amino carbene complex anions with the Lewis acid-complexed aldehydes failed. The reaction of carbene complex **13** with dl-2-methyl-3-phenylpropionaldehyde was unsuccessful with several Lewis acids ($TiCl_4$, $BF_3 \cdot Et_2O$ and $B(C_6H_5)_3$) and the only observable compounds in the reaction mixture after quenching were the starting carbene complex and the starting aldehyde.

The diastereofacial selectivity observed for the carbene addition reaction is the same that is qualitatively predicted by Cram [28] and Felkin [29] models for asymmetric induction. The degree of asymmetric induction that has been observed closely approaches the value that has been quantitatively predicted by molecular mechanics calculations of the selectivities of enolate additions to $\alpha$-chiral aldehydes (values were calculated for 2-phenylpropionaldehyde but not for 2-methyl-3-phenylpropionaldehyde) [30]. The calculations were done by locating minimum energy conformers of the aldehyde and modeling the nucleophilic attack from either face of the carbonyl at the Dunitz angle [31]. The modeled low energy face of the carbonyl was expected to be the preferred site of enolate attack. The predicted l:u ratio was calculated by assuming a Boltzmann's distribution among the stable conformers and summing over all conformers with the same facial preference for enolate attack. The reaction of the anion of the amino carbene complex **13** is the first addition reaction of a lithium anion with 2-phenylpropionaldehyde that approaches the selectivity that was quantitatively predicted from these molecular mechanics calculations (97:3 experimental versus 94:6 calculated) [30].

## Synthetic applications

The synthetic value of $\beta$-hydroxy carbene complexes transcend their synthetic applications as amide equivalents. Among the many methods that have been developed to liberate the organic fragment of carbene complexes [5], we demonstrate here a method of cleaving the organic fragment in a fashion which allows homologation of the carbon framework. Hegedus and

*The reaction of complex **8** with 2-phenylpropionaldehyde occurs with an 8:1 selectivity in the presence of a Lewis acid [2].




Scheme 7.

co-workers have recently reported the photolytic carbonylative cleavage of carbene complexes and have demonstrated the existence of an intermediate presumed to be a metal bound ketene [32]. Photolysis of the cyclohexanone aldol adduct **17i** allowed the intermediate ketene to be intramolecularly trapped and the ($\alpha$-amino)spirolactone **30** was isolated in 52% yield. Photolysis of the l-isomer of **22a** gave the lactone **31** as an 8:1 mixture of isomers (*cis*:*trans*) (Scheme 7). The stereochemistry of **31** was assigned by comparison of diagnostic vicinal coupling constants and chemical shifts of similar 2,4-disubstituted lactones [33]. Most characteristic is the large $J_{3',4}$ (10.3 Hz) for the *cis* isomer of **31** versus the smaller $J_{3',4}$ (4.8 Hz) of the *trans* isomer. These values and the resulting assignments are consistent with similarly substituted butyrolactones and theoretical predictions [33]. Derivatives of 2-amino-$\gamma$-butyrolactones have interesting biological properties and have been used as intermediates in prostaglandin synthesis [33b, 34].

## Conclusions

The $pK_a$ of a dialkylamino carbene complex has been measured and found to be several orders of magnitude less acidic than its corresponding alkoxycarbene complex. The concomitant destabilization of the derived aminocarbene complex anion was sufficient to allow aldol addition reactions with a number of carbonyl compounds to give synthetically useful yields of $\beta$-hydroxy carbene complexes. The method developed here provides a complementary strategy to earlier aldol reactions of carbene complexes in which substrates were activated with Lewis acids. Although no simple diastereoselectivity was observed with simple aldehydes, the diastereofacial selectivities involving the reactions of $\alpha$-unsubstituted aminocarbene complex anions with chiral aldehydes were extremely high. Only Lewis acid mediated Mukiayama-type aldol reactions lead to similarly high facially selective addition reactions. The

aminocarbene complexes were shown to be synthons for the corresponding amide enolates since oxidative cleavage under mild conditions was demonstrated. The metal fragment was also cleaved in a photolytic reactions that resulted in the homologation of the carbon framework and the production of functionally elaborate butyrolactones. The unique stereocontrol of the aldol reactions of aminocarbene complexes and the productive metal cleavage reactions make these complexes powerful reagents for organic synthesis.

## Experimental

*General*

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. For $pK_a$ measurements, dimethyl sulfoxide (DMSO) was distilled from $CaH_2$ under reduced pressure at 50 °C and the fraction collected following several milliliters of forerun was degassed by stirring under vacuum (0.2 Torr) until no bubbling was observed. 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 unless otherwise noted. Gas chromatography was performed on a Carlo Erba Fractovap 2900 series dual column instrument fit with a 15 m×0.32 mm glass carbowax coated column and interfaced with a Spectra-Physics SP4270 integrator. The on-column injection method (Grob-type injector) was employed with hydrogen as the carrier gas (flow rate, 0.5). Other experimental procedures including additional instrumentation have appeared elsewhere [35]. The preparations of the carbene complexes **13** [36] and **14** [37] were effected as described in the literature.

*$pK_a$ measurement of dimethylamino(methyl) carbene complex **13***

Experimental procedures for the $pK_a$ measurement employing this method have been described in detail elsewhere [14]. The measurements were made using rigorously dried glassware and reagents under an argon atmosphere at 23 °C. Stable absorbance readings (479 nm) for each run were recorded at 5 equilibrium positions. The known $pK_a$ of 2-naphthylacetonitrile (20.65) [16] was related to the $pK_a$ of the carbene complex from the equilibrium constant determined from these measurements. $pK_a$ values of 20.46, 20.42, 20.43 and 20.31 measured from four runs were determined. A $pK_a$ value of 20.4 for **13** was estimated from the average of the four measurements.

*Recovery of carbene complex **13** from $pK_a$ measurement conditions*

To a tarred, flame dried, argon filled round bottom flask containing a teflon coated stir bar, fit with a rubber septum, was added potassium hydride (0.040 g, 35 wt.% dispersion in mineral oil, Aldrich) while the flask was flushed with argon. The mineral oil was removed with 3 pentane washings. After the final wash, the residual pentane was removed under high vacuum and the flask was slowly backfilled with argon. The flask containing the potassium hydride (0.0124 g, 0.30 mmol) was cooled to −78 °C and 1.5 ml of dimethyl sulfoxide was added. The flask was warmed to room temperature under dynamic high vacuum which was maintained by a needle connection. The potassium dimsyl/dimethyl sulfoxide solution was stirred for 1 h at room temperature and a solution of 2-naphthylacetonitrile (0.0625 g, 0.374 mmol) in 0.7 ml of dimethyl sulfoxide (0.5 M) was slowly injected. After 10 min, a solution of carbene complex **13** (0.068 g, 0.259 mmol) in 0.5 ml of dimethyl sulfoxide (0.5 M) was added. The resulting mixture stirred for 20 min with no changes in the deep red–orange color. A saturated aqueous solution of $NH_4Cl$ was added and the mixture was extracted with three portions of ether. The ethereal extracts were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. TLC of this mixture indicated the presence of only two major components which co-spotted with 2-naphthylacetonitrile and **13**. Silica gel chromatography (3:1, hexane–ethyl acetate) led to recovery of **13** (0.057 g, 0.22 mmol) in 84%.

*Aldol reaction of cis-phosphine complex **10** with pivalaldehyde*

To a solution of *cis*-**10** (114.1 mg, 0.269 mmol) in 5 ml of THF was added 0.21 ml of n-butyllithium (1.3 M, 0.270 mmol) at −78 °C under argon atmosphere. After 10 min, pivalaldehyde (0.07 ml, 55.5 mg, 0.664 mmol) was then introduced at −78 °C by syringe. The reaction mixture was warmed to 0 °C and stirred for 5 h. After 5 ml of buffer solution (pH=7) and 15 ml of ether were added, the organic layer was washed with brine and water, dried over $MgSO_4$. Upon evaporation of the volatiles, the product was purified by chromatography on silica gel to give **12a** as a mixture of *cis* and *trans* isomers as a red oil (27.5 mg, 0.056 mmol, *cis*/*trans*=5:1, 21%). The following data were obtained on the 5:1 mixture of *cis* and *trans* **12a**: $^1H$ NMR ($CDCl_3$, *cis*-**12a**): $\delta$ 0.80–1.00 (m, 9H), 1.08 (s, 9H), 1.29–1.49 (m, 12H), 1.55–1.65 (m, 6H), 4.62 (s,

3H), 5.94 (d, 1H, $J=15$ Hz), 7.24 (d, 1H, $J=15$ Hz); $^1$H NMR ($CDCl_3$, *trans*-**12a**): $\delta$ 0.80–1.00 (m, 9H), 1.07 (s, 9H), 1.29–1.49 (m, 12H), 1.55–1.65 (m, 6H), 4.67 (s, 3H), 5.89 (d, 1H, $J=15$ Hz), 7.30 (d, 1H, $J=15$ Hz); IR (neat): 2910s, 2040w, 2000s, 1890vs, 1450s, 1200s cm$^{-1}$.

The assignment of the stereochemistry of the products from all of the reactions of complex *cis*-**10** are made on the basis that it is generally observed that methoxyl absorption for the *cis*-isomer of a tetracarbonyl-(phosphine) Fischer carbene complex in the $^1$H NMR is upfield from that for the *trans*-isomer [9].

*Aldol reaction of cis-phosphine complex **10** with benzaldehyde*

With the procedure described for pivalaldehyde, this reaction was quenched after 15 min at 0 °C to give **12b** as a purple oil in 86% yield as a mixture of *cis* and *trans* isomers (117.8 mg, 0.230 mmol; *cis*/*trans* = 8:1; *cis*, $R_f=0.32$; *trans*, $R_f=0.42$) and recovered starting material *cis*-**10** in 3.4% yield. The following spectral data were taken from the mixture of isomers: $^1$H NMR ($CDCl_3$, *cis*-**12b**): $\delta$ 0.82–0.98 (m, 9H), 1.25–1.50 (m, 12H), 1.60–1.80 (m, 6H), 4.69 (s, 3H), 6.61 (d, 1H, $J=17$ Hz), 7.30–7.38 (m, 3H), 7.45–7.50 (m, 2H), 7.97 (d, 1H, $J=17$ Hz); $^1$H NMR ($CDCl_3$, *trans*-**12b**): $\delta$ 0.84–0.89 (m, 9H), 1.25–1.50 (m, 12H), 1.55–1.80 (m, 6H), 4.73 (s, 3H), 6.61 (d, 1H, $J=17$ Hz), 7.30–7.38 (m, 3H), 7.45–7.50 (m, 2H), 7.97 (d, 1H, $J=17$ Hz).

*Aldol reaction of cis-phosphine complex **10** with butyraldehyde*

With the procedure described for pivalaldehyde, this reaction was quenched after 60 min at 0 °C to give **12c** as a red oil in 21% yield as a mixture of *cis* and *trans* isomers (24.2 mg, 0.051 mmol, *cis*/*trans* = 4:1). The following spectral data were obtained on the 4:1 mixture of *cis* and *trans* isomers: $^1$H NMR ($CDCl_3$, *cis*-**12c**): $\delta$ 0.89–0.97 (m, 12H), 1.30–1.48 (m, 14H), 1.52–1.78 (m, 6H), 2.04–2.10 (m, 2H), 4.57 (s, 3H), 5.97 (m, 1H), 7.25 (d, 1H, $J=17$ Hz); $^1$H NMR ($CDCl_3$, *trans*-**12c**): $\delta$ 0.81–0.97 (m, 12H), 1.30–1.48 (m, 14H), 1.52–1.78 (m, 6H), 2.04–2.11 (m, 2H), 4.65 (s, 3H), 5.89 (m, 1H), 7.33 (d, 1H, $J=17$ Hz).

*Aldol reactions of aminocarbene complexes; general procedure*

A flame dried round bottom flask containing a teflon coated stir bar was charged with carbene complex **13** or **14** and fitted with a rubber septum. A 0.15–0.2 M solution was prepared by syringe addition of THF under an argon atmosphere. The solution was cooled to −78 °C and 1 equiv. of n-butyllithium in hexane (1.6 M) was injected. After 20 min, the aldehyde or ketone was added in one portion (see Table 3). The mixture was stirred for 10–30 min and then 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 ethereal extract was dried over anhydrous magnesium sulfate, filtered through a short plug of celite, and concentrated. The residual oil was purified by flash silica gel chromatography in air with a 1:1:4 mixture of ether/$CH_2Cl_2$/hexanes as eluent.

**17a**: $^1$H NMR ($CDCl_3$): $\delta$ 1.83 (bs, 1H, OH), 3.40–3.44 (m, 5H, $NCH_3$, $CH_{2\alpha}$), 3.87 (s, 3H, $NCH_3$), 5.42–5.48 (m, 1H, C*H*OH), 7.29–7.41 (m, 5H, ArH). $^{13}$C NMR ($CDCl_3$): $\delta$ 44.66, 54.23, 60.21, 72.53, 125.42, 128.08, 128.77, 144.06, 218.27, 222.93, 272.27: IR (thin film): 3591br w, 3443br w, 3062w, 3020w, 2950w, 2051s, 1902vs, 1534m cm$^{-1}$. *Anal.* Calc. for $C_{16}H_{15}O_6CrN$: C, 52.03; H, 4.09; N, 3.79. Found: C, 52.54; H, 4.27; N, 3.69%.

**17b**: $^1$H NMR ($CDCl_3$): $\delta$ 0.98 (t, 3H, $J=7.3$ Hz, $CH_2CH_3$), 1.39–1.63 (m, 5H, $CH_2CH_2$, OH), 3.15 (dd, 1H, $J=12.5$, 10.2 Hz, $CH_\alpha$), 3.26 (dd, 1H, $J=12.4$, 2.4 Hz, $CH_\alpha$), 3.45 (s, 3H, $NCH_3$), 3.87 (s, 3H, $NCH_3$), 4.32–4.35 (m, 1H, C*H*OH). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.86, 18.74, 40.81, 44.62, 54.15, 58.37, 70.19, 218.22, 223.05, 273.40: IR (thin film): 3611br m, 3456br m, 2963m, 2936m, 2865w, 2051s, 1900vs, 1537s, 1401m, 674s, 661s cm$^{-1}$. *Anal.* Calc. for $C_{13}H_{17}O_6CrN$: C, 46.57; H, 5.11; N, 4.20. Found: C, 46.62; H, 5.27; N, 4.22%.

**17c**: $^1$H NMR ($CDCl_3$): $\delta$ 1.36 (d, 3H, $J=6.1$ Hz, $CH_3$), 3.16 (dd, 1H, $J=13.2$, 12.6 Hz, $CH_\alpha$), 3.27 (dd, 1H, $J=12.6$, 3.0 Hz, $CH_\alpha$), 3.45 (s, 3H, $NCH_3$), 3.85 (s, 3H, $NCH_3$), 4.46–4.50 (m, 1H, C*H*OH). $^{13}$C NMR ($CDCl_3$): $\delta$ 24.90, 44.64, 54.15, 59.78, 66.83, 218.18, 223.01, 273.54. IR (thin film): 3408br m, 2976m, 2929m, 2051s, 1893s, 1908m, shoulder, 1537m, 674s, 660s cm$^{-1}$.

**17d**: $^1$H NMR ($CDCl_3$): $\delta$ 1.58 (br s, 1H, OH, exchangeable with $D_2O$), 2.01–2.12 (m, 4H, $CH_2CH_2$), 3.30–3.32 (m, 2H, $CH_{2\alpha}$), 3.49–3.54 (m, 1H, NCH), 4.08–4.23 (m, 3H, $NCH_2$, NCH), 5.55–5.58 (m, 1H, C*H*OH), 7.26–7.41 (m, 5H, ArH). $^{13}$C NMR ($CDCl_3$): $\delta$ 25.04, 25.36, 54.46, 61.40, 62.01, 72.84, 125.34, 127.93, 128.66, 144.22, 218.83, 223.03, 266.85. IR (thin film): 3607br w, 3421br w, 2958w, 2935w, 2877w, 2050s, 1961 shoulder, 1903s, 1507m, 1450m, 702m, 676s, 661s cm$^{-1}$. *Anal.* Calc. for $C_{18}H_{17}O_6CrN$: C, 54.69; H, 4.33; N, 3.54. Found: C, 54.24; H, 4.44; N, 3.34%.

**17e**: $^1$H NMR ($CDCl_3$): $\delta$ 0.98 (t, 3H, $J=7.3$ Hz, $CH_3$), 1.40–1.62 (m, 5H, $CH_2CH_2CH_3$, OH), 2.07–2.12 (m, 4H, $CH_2CH_2$), 3.02–3.06 (m, 1H, $CH_\alpha$), 3.16 (dd, 1H, $J=12.0$, 1.5 Hz, $CH_\alpha$), 3.66–3.70 (m, 1H, NCH), 4.05–4.15 (m, 3H, $NCH_2$, NCH), 4.47–4.52 (m, 1H, C*H*OH). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.90, 18.76, 25.09, 25.40, 40.73, 54.44, 59.40, 61.89, 70.58, 218.82, 223.13, 268.01. IR (thin film) 3617br m, 3450br m, 3961m, 2976m, 2049s, 1960 shoulder, 1901s, 1509m 1450m, 676s, 660s

$cm^{-1}$. *Anal.* Calc. for $C_{15}H_{19}O_6CrN$: C, 49.86; H, 5.30; N, 3.88. Found: C, 50.23; H, 5.51; N, 3.90%.

**17f**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.36 (d, 3H, $J=6.1$ Hz, $CH_3$), 1.45 (br s, 1H, OH), 2.04–2.12 (m, 4H, $CH_2CH_2$), 3.06 (dd, 1H, $J=12.2$, 10.1, $CH_a$), 3.16 (dd, 1H, $J=12.4$, 2.5 Hz, $CH_a$), 3.67–3.72 (m, 1H, NCH), 4.04–4.16 (m, 3H, $NCH_2$, NCH), 4.64–4.66 (m, 1H, *C*HOH). $^{13}C$ NMR ($CDCl_3$): $\delta$ 24.64, 25.02, 25.36, 54.44, 60.87, 61.89, 67.18, 218.69, 223.16, 267.78. IR (thin film): 3605br m, 3444br m, 2976m, 2880m, 2050s, 1957 shoulder, 1894s, 1508m, 1451s, 675s, 660s $cm^{-1}$. *Anal.* Calc. for $C_{13}H_{15}O_6CrN$: C, 46.85; H, 4.54; N, 4.20. Found: C, 46.85; H, 4.69; N, 4.38%.

**17g**: $^1H$ NMR ($CDCl_3$): $\delta$ 0.97 (d, 6H, $J=6.8$ Hz, 2 $CH_3$), 1.47 (d, 1H, $J=3.6$ Hz, OH), 1.74–1.82 (m, 1H, $CH(CH_3)_2$), 2.0–2.10 (m, 4H, $CH_2CH_2$), 3.02 (m, 1H, $CH_\alpha$), 3.13 (dd, 1H, $J=12.1$, 2.4 Hz, $CH_a$), 3.62–3.68 (m, 1H, NCH), 4.02–4.28 (m, 4H, NCH, $NCH_2$, *C*HOH). $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.38, 18.55, 25.08, 25.38, 35.04, 54.34, 56.16, 61.89, 75.12, 218.87, 223.15, 268.25. IR (thin film): 3619m, 3470br m, 2966m, 2879m, 2049s, 1901vs, 1507m, 1451m, 676s, 662 $cm^{-1}$. *Anal.* Calc. for $C_{15}H_{19}O_6CrN$: C, 49.86; H, 5.30; N, 3.88. Found: C, 49.93; H, 5.47; N, 3.76%.

**17h**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.43 (s, 6H, 2 $CH_3$), 2.06–2.10 (m, 4H, $CH_2CH_2$), 3.41 (s, 2H, $CH_{2\alpha}$), 3.98 (t, 2H, $J=7$ Hz, $NCH_2$), 4.16 (t, 2H, $J=7$ Hz, $NCH_2$). $^{13}C$ NMR ($C_6D_6$): $\delta$ 24.72, 25.02, 31.62, 55.10, 62.34, 64.18, 72.40, 219.48, 223.80, 270.78. IR (thin film): 3500br m, 2927m, 1996w, 1963 shoulder, 1897s, 1865s, 1809s, 1450m $cm^{-1}$. This compound was not suitably stable to give an acceptable combustion analysis.

**17i**: $R_f=0.58$; m.p. 79 °C decomp. $^1H$ NMR ($CDCl_3$): $\delta$ 1.28–1.76 (m, 10H, $-(CH_2)_5-$), 2.05–2.13 (m, 4H, $-(CH_2)_2-$), 3.36 (s, 2H, $CH_{2\alpha}$), 3.95 (t, 2H, $J=6.5$ Hz, $NCH_2$), 4.14 (t, 2H, $J=6.5$ Hz, $NCH_2$). $^{13}C$ NMR ($C_6D_6$): $\delta$ 22.11, 24.31, 25.13, 25.38, 39.26, 55.28, 62.32, 65.70, 73.51, 219.56, 223.80, 270.73. IR (thin film) 3429bw, 2925w, 2861w, 2049m, 1961 shoulder, 1987vs, 1574w, 1496w, 1439w, 675m, 659m $cm^{-1}$.

*Retroaldol reaction of acetone adduct 17h*

To a solution of the carbene complex **17h** (0.161 g, 0.437 mmol) in 4 ml THF at −78 °C under argon, was added an n-butyllithium solution (0.29 ml, 1.6 M, 0.46 mmol) in hexanes. The solution was stirred for 10 min and was then quenched and worked up under the standard conditions. The $^1H$ NMR of the unpurified mixture indicated the presence of **14** in a 1:3 ratio with the aldol adduct **17h**. Purification of the products on silica gel led to the recovery of **17h** (0.066 g, 0.19 mmol) in 44% yield and the isolation of **14** (29 mg, 0.101 mmol) in 22% yield.

*Reaction of the ethyl substituted carbene complex 18*

A solution of carbene complex **18** (0.264 g, 0.870 mmol) in 5 ml of THF at −78 °C was treated with n-butyllithium (0.56 ml, 1.55 M, 0.87 mmol) in hexanes. Benzaldehyde (0.10 ml, 100 mg, 0.985 mmol) was injected and the resulting mixture was stirred 10 min before the reaction was quenched. The $^1H$ NMR of the crude reaction mixture indicated a 1:1 (*anti*/*syn*) mixture of diastereomeric aldol products **19**. Silica gel chromatography (1:1:4) with rapid elution led to the recovery of **18** as a mixture with benzaldehyde and to the isolation of the viscous yellow aldol adduct **19** (0.141 g, 0.345 mmol) in less than 39% yield. The moderately stable product could not be isolated in completely pure form and was enriched in the *anti* diastereomer (2:1, *anti*:*syn*). Spectral data for **19** was collected on the mixture: $^1H$ NMR ($CDCl_3$): $\delta$ 0.87 (d, 3H, $J=7.1$ Hz, *anti*), 0.89 (d, 3H, $J=7.3$ Hz, *syn*), 1.25–1.35 (m, mixture), 1.51 (br s, mixture), 1.68–1.97 (m, mixture), 2.01–2.20 (m, mixture), 3.15–3.17 (m, 1H, *anti*), 3.69–3.75 (m, mixture), 3.98–4.04 (m, mixture), 4.18–4.28 (m, mixture), 4.63–4.65 (m, 1H, *anti*), 5.17 (br d, 1H, $J=7.9$ Hz, *syn*), 5.35 (br d, 1H, $J=9.5$, *anti*), 7.2–7.4 (m, mixture); IR (thin film): 3584br w, 3399br m, 2955m, 2931m, 2875w, 2048s, 1960 shoulder, 1902vs, 1483m, 1440m $cm^{-1}$.

A 2:1 (*anti*:*syn*) mixture of diastereomers of the carbene complex **19** (0.123 g, 0.301 mmol) was placed in a 10 ml round bottom flask and 0.63 ml of dimethyl sulfoxide was added. A small portion (~0.5 ml) of ether was added to enable mixing and was then stirred at room temperature for 16 h. The residue was loaded on a short silica gel column and the product was eluted (1:1, hexane:ethyl acetate) to give the amide **20** (46 mg) in 67% yield as a 2:1 (*anti*:syn) mixture. The diastereomeric amides **20** were found to be identical to samples prepared from the published route [38].

*Aldol reaction of complex 13 with 2-phenylpropionaldehyde*

A solution of carbene complex **13** (0.0640 g, 0.244 mmol) in 3 ml of THF at −78 °C was treated with a solution of n-butyllithium (0.15 ml, 1.6 M, 0.24 mmol) in hexanes. 2-Phenylpropionaldehyde (0.070 ml, 71 mg, 0.53 mmol) in 1 ml of THF was injected and the resulting mixture was stirred 15 min before the reaction was quenched. Silica gel chromatography (1:1:5) led to the recovery of **13** (10 mg, 0.04 mmol) in 15% yield and to the isolation of a single diastereomer of the viscous yellow aldol adduct **22a** (80.0 mg, 0.202 mmol) in 80% yield. The selectivity of the reaction was quantified by conversion to the corresponding amide. Spectral data for **22a–l**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.34 (d, 3H, $J=7.1$ Hz, $CH_3$), 1.41 (br s, 1H, OH), 2.97–3.01 (m, 1H, $CHCH_3$), 3.16 (dd, 2H, $J=8.1$, 3.4 Hz, $CH_{2\alpha}$), 3.35 (s, 3H, $NCH_3$), 3.81 (s, 3H, $NCH_3$), 4.30–4.34 (m, 1H,

CHOH), 7.20–7.34 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.73, 44.54, 46.15, 54.13, 55.95, 74.15, 126.92, 127.76, 128.71, 143.34, 218.19, 222.97, 273.21; IR (thin film): 3559br m, 3450br m, 2973m, 2949m 2896m, 2051s, 1964 shoulder, 1901s, 1538m, 600m cm$^{-1}$. The structural assignment was confirmed by conversion to the known $\beta$-hydroxy amide [21] **23a–l** as described below.

Carbene complex **22a** (66.5 mg, 0.167 mmol) was placed in a round bottom flask and 5 ml dimethyl sulfoxide was added. The resulting solution was stirred open to air for 19 h. The mixture was diluted with ether and washed with water (3×) and brine. The organic solution was dried over anhydrous magnesium sulfate and passed through a short plug of silica gel and concentrated. The product **23a–l** (24 mg) was isolated in 65% yield. The selectivity of the aldol reaction of **13** with 2-phenylpropionaldehyde was determined in a separate reaction run under identical conditions. Neither the carbene complex **22a** nor the oxidized product **23a** were purified by chromatography prior to analysis. An average l:u ratio of $\geqslant$40:1 was determined by GC. Column temperature was increased from 130 to 200 °C at (10 °C/min). The retention times of the l and u diastereomers were 6.86 and 7.11 min, respectively. Peak assignments were confirmed by co-injection with an authentic sample of a (3:1, u:l) diastereomeric mixture of the known amide **23a** [21].

*Aldol reaction of complex **14** with 2-phenylpropionaldehyde*

A solution of carbene complex **14** (0.386 g, 1.33 mmol) in 8 ml of THF at −78 °C was treated with a solution of n-butyllithium (0.83 ml, 1.6 M, 1.33 mmol) in hexanes. 2-Phenylpropionaldehyde was injected and the resulting mixture was stirred 10 min before the reaction was quenched. Silica gel chromatography (1:1:5) led to the isolation of a single diastereomer of the aldol adduct **22b** (0.527 g, 1.25 mmol) as a very viscous light yellow oil in 94% yield. The selectivity of the aldol reaction was quantified by conversion to the corresponding amide **23b–l**. Spectral data for **22b–l**: $^1$H NMR ($CDCl_3$): $\delta$ 1.36 (d, 3H, $J$=7.0 Hz, $CH_3$), 1.44 (d, 1H, $J$=3.7 Hz, OH, exchangeable with $D_2O$), 2.02–2.05 (m, 4H, $CH_2CH_2$), 2.97–3.0 (m, 1H, $CHCH_3$), 3.05 (d, 2H, $J$=6.7 Hz, $CH_{2\alpha}$) 3.57–3.60 (m, 1H, NCH), 4.01–4.12 (m, 3H, NCH, $NCH_2$), 4.47–4.48 (m, 1H, CHOH), 7.20–7.39 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.17, 25.03, 25.33, 46.23, 54.24, 57.02, 61.81, 74.59, 126.82, 127.75, 128.62, 143.39, 218.72, 223.04, 267.75; IR (thin film): 3592br m, 3451br m, 2975m, 2880m, 2049s, 1961 shoulder, 1900s, 1509m, 1451m, 677s, 659s cm$^{-1}$.

Carbene complex **22b–l** (0.190 g, 0.450 mmol) was placed in a 10 ml round bottom flask and 0.5 ml of dimethyl sulfoxide was added along with 2 ml of a 1:1 hexane–ethyl acetate solution to ensure mixing. The flask was placed, open to air, in an oil bath maintained at 70 °C for 2 h. The reaction mixture was loaded directly onto a short silica gel column and eluted with a 2:1 hexane–ethyl acetate solution. The product **23b** (79.4 mg, 0.321 mmol) was isolated in 71% yield as a clear colorless oil which was spectroscopically identical to an authentic sample prepared as described below. The diastereofacial selectivity was determined as described above for **22a** and the GC analysis of a separate run which involved no purifications indicated a $\geqslant$36:1 ratio of l to u isomers. The GC retention times of the l and u diastereomers were 13.47 and 14.42 min, respectively. The peak assignments were confirmed by co-injection with an authentic sample of a (4:1, u:l) diastereomeric mixture of the amide **23b**. Analysis of the oxidation product **23b** isolated by silica gel chromatography (71%) from a chromatographically purified carbene complex **22c**, gave a much cleaner GC trace and the ratio of **23b–l**:**23b–u** could be set at $\geqslant$200:1.

*Independent synthesis of amides **23b***

Diisopropylamine (1.0 ml, 0.72 g, 7.14 mmol) was dissolved in 15 ml of THF. This solution was cooled to 0 °C under an argon atmosphere and a solution of n-butyllithium (4.46 ml, 1.6 M, 7.14 mmol) in hexane was injected. The solution was stirred for 15 min and then cooled to −78 °C. *N*-Pyrrolidinylacetamide (0.747 g, 6.61 mmol) was injected over a 3 min period with the assistance of 0.5 ml THF. The resulting solution stirred for 10 min and then 2-phenylpropionaldehyde (0.878 g, 6.614 mmol) was injected in one portion. The reaction was quenched after 1 min by the addition of a saturated aq. solution of $NH_4Cl$. The solution was extracted (3×) with ether. The organics were combined, dried over $MgSO_4$, filtered through celite and concentrated by rotary evaporation to give **23b** as a 4:1 (l:u) mixture of diastereomers in quantitative yield. Stereochemical assignments were made by analogy to $^1$H and $^{13}$C NMR data of known aldol adducts with this aldehyde [19]. Spectral data for the u-diastereomer was collected from a 4:1 (l:u) mixture of diastereomers. Spectral data for **23b**: $^1$H NMR ($CDCl_3$): (**23b-l**) $\delta$ 1.40 (d, 3H, $J$=6.9 Hz, $CH_3$), 1.77–1.89 (m, 4H, $-(CH_2)_2-$), 2.11 (dd, 1H, $J$=16.3, 8.4 Hz, $CH_\alpha$), 2.23 (dd, 1H, $J$=16.3, 2.7 Hz, $CH_{\alpha'}$), 2.76–2.82 (m, 1H, $CHCH_3$), 3.07 (t, 2H, $J$=6 Hz, $NCH_2$), 3.42 (t, 2H, $J$=6 Hz, $NCH_2$), 4.06 (ddd, 1H, $J$=11.3, 8.5, 2.8 Hz, CHOH), 4.75 (br s, 1H, OH), 7.2–7.3 (m, 5H, ArH); (**23b-u**): $\delta$ 1.33 (d, 3H, $J$=7.1 Hz, $CH_3$), 1.74–1.96 (m, 4H, $-(CH_2)_2-$), 2.37 (dd, 1H, $J$=16, 1.9 Hz, $CH_\alpha$), 2.90 (m, 1H, $CHCH_3$), 3.05 (m, 2H), 3.2–3.45 (m, 3H), 4.23 (ddd, 1H, $J$=8.5, 5.6, 2.5 Hz, CHOH), 4.3 (bs, 1H, OH), 7.1–7.9 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): (**23b–l**) $\delta$ 18.39, 24.21, 25.71, 38.25, 45.36, 45.81, 46.32, 72.99, 126.40, 127.57, 128.45,

144.44, 171.35; (**23b-u**) $\delta$ 16.73, 24.07, 25.65, 37.52, 44.57, 45.34, 46.36, 71.93, 126.16, 127.43, 128.01, 143.23, 171.20; IR (thin film): 3402br s, 2968m, 2931m, 2875m, 1620s, 1493 shoulder, 1452s, 1020m, 703m $cm^{-1}$; mass spectrum, *m/z*, (GC/MS) (% relative intensity): 229, $M^+ - 18$ [$-H_2O$] (5), 159 (1), 142 (100), 98 (98), 70 (17). *Anal.* Calc. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.67; H, 8.28; N, 4.95%.

*Preparation of 1-deutero-2-phenylpropionaldehyde (25)*

Lithium aluminum deuteride (2.50 g, 59.54 mmol, Aldrich) was suspended in 100 ml of THF and cooled to 0 °C under a dry nitrogen purge. 2-Phenylpropionic acid (3.82 g, 25.46 mmol) was added slowly and the resulting mixture was warmed to room temperature for 1.5 h then refluxed for 4 h. The solution was cooled to 0 °C and quenched by the sequential slow addition of 2.5 ml of water, 2.5 ml of 15% NaOH (aq.) and 7.5 ml of water. The mixture was refluxed an additional 15 min and then the cooled solution was filtered through a glass frit. The filter cake was washed with THF and the combined organics were concentrated by rotary evaporation. The residue was redissolved in (1:1) ether–dichloromethane, washed with saturated aq. $NaHCO_3$ and brine and then dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated to give 1,1-dideuterio-2-phenylpropanol (**32**) (3.41 g, 24.68 mmol) as a clear colorless oil in 97% yield. Spectral data for **32**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.26 (d, 3H, $J = 7.0$ Hz, $CH_3$), 1.36 (br s, 1H, OH). 2.92 (q, 1H, $J = 7.0$ Hz, CH), 7.18–7.29 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.41, 41.95 (5 line resonance), 66.87, 67.15, 67.44, 67.73, 68.02, 126.27, 127.25, 128.27, 143.74; IR (thin film): 3350br s, 3023m, 2956m, 1490s, 1446s, 1089m, 960s, 750s $cm^{-1}$; mass spectrum, *m/z* (% relative intensity): 138 (10) $M^+$, 106 (27), 103 (7), 91 (8), 79 (12), 77 (10). *Anal.* Calc. for $C_9H_{10}D_2O$: C, 77.10; H, 8.82. Found: C, 77.28; H, 8.75%.

The deuterated alcohol **32** (3.114 g, 22.53 mmol) in 5 ml of dichloromethane was slowly added to a suspension of pyridinium dichlorochromate (PCC) in 45 ml of dichloromethane. The resulting mixture was stirred at room temperature for 2 h. Ether was added to precipitate the chromium salts and the mixture was filtered through florisil and concentrated to give a yellow–brown oil. The reaction mixture contained the desired product **25** as well as side products including acetophenone. The mixture was chromatographed (1:1, hexane:ethyl acetate) twice to yield the aldehyde **25** (0.914 g, 6.77 mmol) in 29% yield. Spectral data for **25**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.43 (d, 3H, $J = 7$ Hz, $CH_3$), 3.61 (q, 1H, $J = 7$ Hz, CH), 7.1–7.4 (m, 5H, ArH); mass spectrum, *m/z* (% relative intensity): 136 (10) $M^+ + 1$, 135 (23) $M^+$, 120 (23), 106 (21), 105 (100), 92 (18), 79 (32), 77 (31).

*Kinetic selectivity in the aldol addition of carbene complex 13 to 2-phenylpropionaldehyde*

Carbene complex **22a-l** (0.284 g, 0.715 mmol) was dissolved in 4.5 ml of THF and cooled to −78 °C under an argon atmosphere. A solution of n-butyllithium (0.44 ml, 1.6 M, 0.71 mmol) in hexanes was injected and stirred for 5 min. The deuterated aldehyde **25** (0.303 g, 2.24 mmol) was injected and the resulting solution stirred for 10 min. The reaction was quenched by the rapid addition of a saturated aq. $NH_4Cl$ solution and followed by an aqueous workup. The $^1H$ NMR spectrum of the crude reaction mixture indicated that **13** was not present nor was any n-butyllithium addition product observed. The 1.0:3.0 integration ratio of the carbinol resonance (4.30–4.34 ppm) with respect to the $NCH_3$ resonances (3.35 and 3.81 ppm) indicated that no deuterium had been incorporated. Silica gel chromatography (1:1:4) led to the recovery of **22a-l** (0.185 g, 0.466 mmol) in 65% yield.

*Preparation of 2-methyl-3-phenylpropionaldehyde*

Diisopropylamine (9.0 ml, 6.5 g, 64 mmol) was dissolved in 250 ml of THF and cooled to −78 °C under an argon atmosphere. A solution of n-butyllithium (40.13 ml, 1.6 M, 64.2 mmol) in hexane was injected and the resulting solution stirred for 15 min. Propionitrile (4.56 ml, 3.52 g, 64.5 mmol) was slowly injected and stirred for 15 min and then at 0 °C for 25 min. The solution was transferred via cannula to a solution of benzyl bromide (14.17 g, 82.9 mmol) in 100 ml of THF maintained at −78 °C over a 30 min period. The solution was stirred an additional 15 min at −78 °C and then for 30 min at 0 °C. The reaction was quenched by the addition of a saturated solution of $NH_4Cl$ (aq.). The mixture was diluted with ether, washed with a pH 4 buffer and the organic solution was dried over anhydrous magnesium sulfate. After filtration through celite and concentration, the product was isolated from the residue by silica gel chromatography (1:1:5, $R_f = 0.53$) to give 1-phenyl-2-cyanopropane (**33**) (8.98 g, 62.0 mmol) in 97% yield as an oil which solidifies to a clear colorless crystalline solid (m.p. $\leqslant 22$ °C) upon standing in the freezer. Spectral data for nitrile **33**: $^1H$ NMR ($CDCl_3$): $\delta$ 1.32 (d, 3H, $J = 6.7$ Hz, $CH_3$), 2.80–2.95 (m, 3H, CH, $CH_2$), 7.21–7.38 (m, 5H, ArH); $^{13}C$ NMR ($CDCl_3$): $\delta$ 16.93, 26.81, 39.13, 121.98, 126.55, 128.03, 128.50, 136.47; IR (thin film): 3070w, 3030m, 2983m, 2940m, 2239m, 1496s, 1454s, 1083w, 739, 700s $cm^{-1}$; mass spectrum, *m/z* (% relative intensity) 145 (10) $M^+$, 92 (5), 91 (100), 77 (2), 65 (9). *Anal.* Calc. for $C_{10}H_{11}N$: C, 82.70; H, 7.65; N, 9.64. Found: C, 82.73; H, 7.48; N, 9.63%.

The nitrile **33** (7.44 g, 51.3 mmol) was dissolved in 450 ml of hexanes and cooled to −78 °C under an argon atmosphere. A solution of diisobutylaluminum hydride (10.2 ml, 1.0 M, 10.2 mmol) in hexane was

injected and the resulting cloudy mixture was stirred for 45 min and then warmed to room temperature for 15 h. Ethyl formate (8.2 ml) was injected and the clear solution was stirred 1 h. The mixture was poured into 150 ml of a saturated $NH_4Cl$ (aq.) solution and stirred 30 min. An aqueous $H_2SO_4$ solution was added and the solution was extracted with several portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, filtered through Celite and concentrated. The residual oil was vacuum distilled (90 °C/5 mm) to give the known aldehyde [39] (4.03 g, 31.9 mmol) as a clear colorless oil in 62% yield.

*General procedure for the aldol reaction of 13 with 2-methyl-3-phenylpropionaldehyde illustrated for the anion generated with n-BuLi*

A solution of carbene complex **13** (0.8 mmol) in 5 ml of THF was treated with a solution of the indicated base (nBuLi, 0.8 mmol) (Table 4) at −78 °C. 2-Methyl-3-phenylpropionaldehyde (0.16 g, 1.1 mmol) was injected and the resulting mixture was stirred 10 min before the reaction was quenched with saturated aq. $NH_4Cl$. The residue was loaded onto a silica gel column and eluted with a 1:1:5 solvent mixture to give a 10% recovery of **13** (21 mg, 0.08 mmol) and a 78% yield of the aldol adducts **27a** (l+u) as a very viscous light yellow oil and as an inseparable (4:1) mixture of diastereomers. The following spectral data were collected on the mixture of isomers of **27a**: $^1$H NMR ($CDCl_3$): (**27a-l**) $\delta$ 0.95 (d, 3H, $J$=6.8 Hz, $CH_3$), 1.38 (br s, 1H, OH), 1.98–2.02 (m, 1H, C*H*$CH_3$), 2.5 (dd, 1H, $J$=13, 8.9 Hz, CHPh), 2.79 (dd, 1H, $J$=13, 6.1 Hz, CHPh), 3.15 (dd, 1H, $J$=13.2, 1.6 Hz, HC$H_a$), 3.26 (dd, 1H, $J$=12.2, 11.2 Hz, $H_\alpha$CH), 3.40 (s, 3H, $NCH_3$), 3.85 (s, 3H, $NCH_3$), 4.22–4.25 (m, 1H, CH), 7.1–7.3 (m, 5H, ArH); (**27a-u**) $\delta$ 0.92 (d, 3H, $J$=6.7 Hz, $CH_3$), 1.98–2.02 (m, 1H, C*H*$CH_3$), 2.35–2.43 (m, 1H), 2.93–3.02 (m, 1H), 3.1–3.3 (m, 2H, $CH_{2\alpha}$), 3.41 (s, 3H, $NCH_3$), 3.86 (s, 3H, $NCH_3$), 4.24–4.25 (m, 1H, C*H*OH), 7.11–7.27 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): (**27a-l**) $\delta$ 13.17, 39.94, 41.75, 44.55, 54.16, 55.65, 72.53, 126.11, 128.42, 128.97, 140.17, 218.16, 223.04, 273.63; (**27a-u**) $\delta$ 15.42, 22.62, 31.54, 38.41, 42.34, 55.11, 74.02, 126.03, 128.37, 129.06, 140.41, 218.27, 223.04, 273.63; IR (thin film) 3598br m, 3457br m, 2965m, 2936m, 2873w, 2050s, 1964 shoulder, 1900vs, 1538m, 1454m, 1400m, 675m, 661m cm$^{-1}$.

The stereochemistry was assigned by the oxidative conversion to the corresponding amides **28a**. A mixture of the carbene complexes **27a** (l+u) (0.111 g, 0.26 mmol) was dissolved in ~1 ml of dimethyl sulfoxide with the assistance of a minimal amount of a hexane–ethyl acetate (1:1) solution. The mixture was stirred at room temperature for 12 h and then at 70 °C for 1 h. The residue was loaded onto a silica gel column and eluted with a 1:1 mixture of hexane–ethyl acetate to give the corresponding amide **28a** (l+u) (56.4 mg, 0.24 mmol) in 89% yield with no diastereomeric enrichment. The amides obtained from the oxidation of **27a** proved to be identical with the amides obtained by the independent synthesis described below.

*Independent synthesis of the amides 28a (l+u)*

Diisopropylamine (0.31 ml, 0.22 g, 2.2 mmol) was dissolved in 6 ml of THF and cooled to 0 °C under an argon atmosphere and a solution of n-butyllithium (1.25 ml, 1.6 M, 2.0 mmol) in hexanes was injected. After 10 min the solution was cooled to −78 °C and *N*,*N*-dimethylacetamide (0.185 ml, 0.173 g, 1.99 mmol) was injected and stirred for 10 min. 2-Methyl-3-phenylpropionaldehyde (0.302 g, 2.04 mmol) was added directly to the mixture. The reaction was quenched after 1 min by the rapid addition of saturated aq. $NH_4Cl$. The mixture was extracted (3×) with ether and the combined extracts were dried over anhydrous magnesium sulfate. The solution was filtered through Celite and concentrated by rotary evaporation. The $^1$H NMR of the crude product indicated the presence of a 1.0:1.1 (l+u) mixture of diastereomers. Purification of the product on silica gel (2:1, hexane:ethyl acetate) led to the isolation of the aldol adduct **28a** (0.247 g, 0.106 mmol) as a clear colorless oil in 53% yield without diastereomeric enrichment. The stereochemical assignments for the isomeric amides **28a** were made by correlating the $^1$H NMR shifts of the vicinal methyl group and the carbinol methine hydrogen with those of known u and l aldol adducts with this aldehyde [21]. Spectral data collected on the mixture of isomers of **28a** (l+u): $^1$H NMR ($CDCl_3$): (**28a-l**) $\delta$ 0.92 (d, 3H, $J$=6.8 Hz, $CH_3$), 1.81–1.82 (m, 1H, C*H*$CH_3$), 2.39–2.47 (m, 3H, C$H_2$Ph, $CH_\alpha$), 2.88 (dd, 1H, $J$=13.3, 6.3 Hz, $CH_\alpha$), 2.93 (s, 3H, $NCH_3$), 2.95 (s, 3H, $NCH_3$), 3.95–3.97 (m, 1H, C*H*OH), 4.2 (s, 1H, OH), 7.13–7.24 (m, 5H, ArH); (**28a-u**) $\delta$ 0.84 (d, 3H, $J$=6.8 Hz, $CH_3$), 1.60–1.67 (m, 1H, C*H*$CH_3$), 2.32–2.47 (m, 2H, C$H_2$Ph), 2.51 (dd, 1H, $J$=16.4, 1.8 Hz, $CH_\alpha$), 2.95 (s, 3H, $NCH_3$), 2.98 (s, 3H, $NCH_3$), 2.98–3.02 (m, 1H, $CH_\alpha$) 3.86–3.86 (m, 1H, C*H*OH), 4.4 (s, 1H, OH), 7.13–7.24 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): (**28a-l**) $\delta$ 13.88, 35.08, 36.67, 39.51, 39.98, 40.86, 69.84, 125.62, 128.09, 129.07, 140.95, 172.72; (**28a-u**) $\delta$ 15.07, 35.12, 35.96, 37.01, 38.52, 39.86, 71.41, 125.62, 128.09, 129.08, 140.71, 172.72; IR (thin film): 3419br s, 2961s, 2932s, 2879s, 1628vs, 1495s, 1400s, 1148m, 1059m, 743, 702 cm$^{-1}$; mass spectrum, *m/z* (% relative intensity): 235 (24) $M^+$, 217 (27), 173 (8), 144 (9), 131 (18), 116 (100), 91 (58), 87 (22), 72 (61). *Anal.* Calc. for $C_{14}H_{21}O_2N$: C, 71.45; H, 8.99; N, 5.95. Found: C, 71.78; H, 8.44; N, 5.53%.

*Aldol reaction of **26** with 2-methyl-3-phenylpropionaldehyde*

Under the standard reaction conditions, a solution of carbene complex **26** [40] (0.209 g, 0.504 mmol) in 3 ml of THF was treated with n-butyllithium (0.31 ml, 1.6 M, 0.50 mmol) in hexanes. 2-Methyl-3-phenylpropionaldehyde (76.4 mg, 0.52 mmol) was injected and the resulting mixture was stirred 10 min before the reaction was quenched. Repeated attempts in previous experiments indicated that **27b** was difficult to purify by silica gel chromatography, so the reaction mixture was oxidized directly without purification. The crude aldol reaction mixture containing a 3:1 mixture of diastereomeric aldol adducts **27b** along with starting carbene complex was dissolved in 0.5 ml dimethyl sulfoxide and warmed, open to air, for 12 h at 60 °C. The oxidation mixture was loaded onto a short silica gel column and eluted with a (1:1) hexane–ethyl acetate solution which led to the isolation of the aldol adduct **28b** (86 mg, 0.232 mmol) as a clear colorless oil (3:1, l:u) in 46% yield and *N,N*-dibenzyl acetamide ($R_f$=0.43, 19 mg, 0.079 mmol) in 16% yield based on starting carbene complex **26**. Spectral data for amides **28b** taken on the mixture of diastereomers: $R_f$=0.75; $^1$H NMR ($CDCl_3$): $\delta$ 0.78 (d, 3H, $J$=6.8 Hz, $CH_3$, u), 0.86 (d, 3H, $J$=6.8 Hz, $CH_3$, l), 1.73–1.82 (m, 1H, l), 1.87–1.95 (m, 1H, u), 2.31–2.63 (m, mixture), 2.85 (dd, 1H, $J$=13.2, 6.0 Hz, l), 2.90 (dd, 1H, $J$=13.5, 4.5 Hz, u), 3.89–3.92 (m, 1H, u), 4.01–4.05 (m, 1H, l), 4.17 (br s, 1H, l), 4.32–4.53 (m, mixture), 4.67–4.71 (m, 1H, l; 1H, u), 7.05–7.40 (m, mixture); $^{13}$C NMR ($CDCl_3$): (**28b-l**) $\delta$ 13.95, 36.91, 39.59, 40.08, 48.18, 49.88, 70.33, 136.33, 140.26, 141.05, 173.69; (**28b-u**) 15.15, 36.13, 38.61, 39.90, 48.29, 49.94, 71.64, 135.91, 140.76, 141.05, 173.69; (**28b-u** + **28b-l**) the following aryl carbons could not be unambiguously assigned: 125.76, 126.34, 127.56, 127.79, 128.16, 128.69, 129.07, 129.18, 129.25; IR (thin film) 3442br m, 3024m, 2963m, 2921m, 1629vs, 1487m, 1463m, 1451s, 1415m, 1203m cm$^{-1}$. *Anal.* Calc. for $C_{26}H_{29}O_2N$: C, 80.58; H, 7.54; N, 3.60. Found: C, 80.58; H, 7.69; N, 3.47%.

*Attempted Lewis acid mediated aldol reactions of **13** with 2-methyl-3-phenylpropionaldehyde*

Carbene complex **13** (77.0 mg, 0.293 mmol) in 5 ml of ether was treated with n-butyllithium (0.183 ml, 1.6 M, 0.29 mmol) in hexanes at −78 °C under an argon atmosphere. This solution was transferred via cannula at −78 °C into a solution of 2-methyl-3-phenylpropionaldehyde (0.107 g, 0.722 mmol) and $BF_3$-etherate (0.89 ml, 0.10 g, 0.72 mmol) in 10 ml ether. The solution was stirred 15 min and then warmed to 0 °C for 30 min and finally warmed to room temperature for 1 h. The reaction was quenched by the addition of a pH 7 buffer, diluted with ether and followed by an aqueous workup. Silica gel chromatography of the reaction mixture led to the recovery of the aldehyde (41 mg, 0.28 mmol) in 39% yield and the starting carbene complex **13** (47.7 mg, 0.181 mmol) in 62% yield. Attempt reactions under similar conditions with $TiCl_4$ and triphenylborine as Lewis acids led only to recovered starting material.

*Preparation of the trimethylsilylmethyl carbene complex **29****

Carbene complex **13** (0.189 g, 0.718 mmol) was dissolved in 10 ml of THF and cooled to −78 °C under an argon atmosphere. A solution of n-butyllithium (0.45 ml, 1.6 M, 0.72 mmol) in hexane was injected. After 20 min trimethylsilyl chloride (0.12 ml, 0.10 g, 0.95 mmol) was injected and the solution stirred 30 min. The reaction was concentrated and chromatographed on silica gel (1:1:4) to yield the desired complex **29** (0.082 g, 0.24 mmol) in 34% yield. Spectral data for **29**: $R_f$=0.56; $^1$H NMR ($CDCl_3$): $\delta$ 0.22 (s, 9H, $Si(CH_3)_3$), 3.14 (s, 2H, $CH_2$), 3.25 (s, 3H, $NCH_3$), 3.82 (s, 3H, $NCH_3$); $^{13}$C NMR ($CDCl_3$): $\delta$ 0.54, 42.95, 48.42, 53.02, 218.10, 223.15, 273.97; IR (thin film) 2953w, 2897w, 2050m, 1921s, 1896s, 1898s, 1872s, 845m, 661m cm$^{-1}$; mass spectrum, *m/z* (% relative intensity) 335 (2) $M^+$, 307 (12), 279 (7), 223 (16), 195 (100), 143 (35), 128 (90), 102 (89), 75 (91).

*Reaction of the trimethylsilyl carbene complex **29** with benzaldehyde*

To a solution of carbene complex **29** (31.4 mg, 0.0937 mmol) and benzaldehyde (79.6 mg, 0.751 mmol) in 1 ml of THF was added a solution of tetrabutylammonium fluoride (0.094 ml, 1.0 M, 0.094 mmol) in THF at −78 °C. The reaction was quenched after 25 min by the rapid addition of saturated aq. $NH_4Cl$. The mixture was diluted with ether, washed with water and brine and the organic layer was dried over anhydrous magnesium sulfate. The solution was filtered through Celite, concentrated by rotary evaporation and the product was purified by silica gel chromatography to give the protodesilylated carbene complex **13** (5 mg, 0.019 mmol) in 20% yield and the aldol adduct **17a** (22.1 mg, 0.0599 mmol) in 64% yield.

*Photolysis of carbene complex **17i***

A solution of carbene complex **17i** (0.127 g, 0.329 mmol) in 25 ml of acetonitrile (0.01 M) was prepared in a 25 ml flask with a screw cap high vacuum seal. The solution was deoxygenated by the freeze–thaw method and backfilled with an argon atmosphere. The flask was placed in a large dewar containing a water cooled, medium pressure mercury arc lamp, covered

*This complex was prepared by a procedure similar to that published for the analogous tungsten complex [19a].

with aluminum foil and irradiated for 24 h. The yellow solution was transferred in air to a 100 ml round bottom flask, concentrated by rotary evaporation and redissolved in 25 ml of ethyl acetate. The solution was oxidized by stirring in air for 24 h and was then filtered through celite and concentrated. The product was purified by silica gel chromatography (1:1:4 then 3:3:1) to give the butyrolactone **30** as a white solid in 52% yield. Spectral data for **30**: m.p. 52–53 °C; $^1$H NMR ($CDCl_3$): $\delta$ 1.37–1.80 (m, 14H), 1.95 (dd, 1H, $J$=12, 11 Hz, HC*H*), 2.28 (dd, 1H, $J$=12, 9 Hz), 2.60 (m, 2H, $NCH_2$), 2.94 (m, 2H, $NCH_2$), 3.61 (dd, 1H, $J$=11, 9 Hz, NCH); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.45, 22.57, 23.55, 24.91, 36.45, 37.97, 38.23, 50.91, 60.96, 82.91, 174.96; IR (thin film): 2935s, 2861m, 1770s, 1201m cm$^{-1}$. *Anal.* Calc. for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.48; N, 6.27. Found C, 69.98; H, 9.56; N, 6.10%.

*Photolysis of carbene complex 22a-l*

A solution of carbene complex **22a-l** (0.242 g, 0.609 mmol) in 55 ml of acetonitrile (0.01 M) was prepared in a 50 ml flask with a screw cap high vacuum seal. The solution was deoxygenated by the freeze–thaw method and backfilled with an argon atmosphere. The flask was placed in a large dewar containing a water cooled, medium pressure mercury arc lamp, covered with aluminum foil and irradiated for 4 h. The yellow solution was transferred in air to a 250 ml round bottom flask and concentrated by rotary evaporation. The residue was redissolved in ethyl acetate and the flask was fit with an upright condensor. The solution was irradiated in a Rayonet reactor with 6 fluorescent lamps for 12 h. Irradiation failed to completely oxidize the residual organometallic species and the resulting brown solution was allowed to air oxidize an additional 24 h at room temperature. The resulting solution was filtered through Celite and concentrated. The $^1$H NMR of this mixture indicated an 8.4:1 (*cis*:*trans*) mixture of the butyrolactones **31**. Silica gel chromatography (1:1:4 then 3:3:1) led to the isolation of two fractions as clear colorless oils. The first fraction (66.0 mg) contained a 6:1 (*cis*:*trans*) mixture of the product and the second fraction (14.0 mg) contained only the *cis* product for a combined yield (80.0 mg, 0.343 mmol) of 56%. Spectral data for **31**-*cis*: $^1$H NMR ($CDCl_3$): $\delta$ 1.43 (d, 3H, $J$=6.9 Hz, $CH_3$), 1.79 (m, 1H, *H*CH), 1.96 (m, 1H, *H*CH), 2.31 (s, 6H, $N(CH_3)_2$), 2.91 (pent, 1H, $J$=7.7 Hz, CH), 3.54 (dd, 1H, $J$=12.0, 8.4 Hz, C*H*N$(CH_3)_2$), 4.36 (ddd, 1H, $J$=10.3, 8.1, 5.5 Hz, OCH), 7.20–7.36 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.03, 28.11, 41.70, 45.23, 64.53, 80.77, 127.19, 127.77, 128.71, 141.13, 174.76; IR (thin film) 2965m, 2935m, 2873m, 1776s, 1454m, 1197m, 1171s, 1008m cm$^{-1}$; mass spectrum, *m/z* (% relative intensity) 233 (4) $M^+$, 205 (6), 129 (5), 105 (11), 102 (28), 100 (42), 85 (18), 84 (100), 72 (19), 71 (34). Spectral data for **31**-*trans*: $^1$H NMR ($CDCl_3$): $\delta$ 1.39 (d, 3H, $J$=6.9 Hz, $CH_3$), 1.90–2.13 (m, 2H, *HCH*), 2.31 (s, 6H, $N(CH_3)_2$), 2.91 (pent, 1H, $J$=7.23 Hz, C*H*$CH_3$), 3.14 (dd, 1H, $J$=9.2, 7.5 Hz, C*H*N$(CH_3)_2$), 4.59 (ddd, 1H, $J$=7.9, 4.8, 4.8 Hz, OCH), 7.22–7.37 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$): $\delta$ 17.76, 27.20, 41.80, 44.87, 62.75, 82.00, 127.25, 127.83, 128.81, 141.20, carbonyl carbon not located; IR (thin film): 2965m, 2936m, 1774vs cm$^{-1}$; mass spectrum, *m/z* (% relative intensity) 233 (26) $M^+$, 205 (4), 188 (17), 174 (12), 128 (16), 115 (17), 105 (66), 103 (24), 102 (100), 100 (99), 98 (10); calc. for $C_{14}H_{19}O_2N$ *m/z* 233.1415; found *m/z* 233.1408.

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