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Chromium aminocarbene complexes in organic synthesis *

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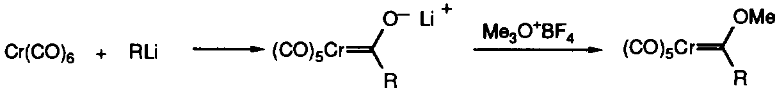
Abstract

The synthesis, the physical and spectroscopic properties, and the thermal and photochemical reactions of chromium aminocarbene complexes are reviewed, with an emphasis on the authors' research in the area.

Heteroatom stabilized pentacarbonylchromium carbene complexes (**1**) were first synthesized by the Fischer group in the 1960's [1] by the reaction of organolithium reagents with chromium hexacarbonyl followed by *O*-alkylation of the resulting acyl complex (eq. 1). The chemistry of the metal–carbon double bond in these complexes has fascinated chemists since their discovery [2]. Until recently, most studies focussed on alkoxycarbene complexes. Increasing interest in the chemistry of aminocarbene complexes has prompted this review.



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(Eq. 1)

Synthesis of aminocarbene chromium complexes

Aminocarbene complexes were first prepared by exchange of amines with alkoxycarbene chromium complexes (eq. 2) [3]. These are normally prepared by the original Fischer procedure which restricts the functionality of the alkyl group to those available from organolithium reagents. The amine exchange process is restricted to primary amines or nonhindered secondary amines. Sterically hindered amines such as dibenzyl or diisopropylamine do not exchange with the (methyl)methoxy carbene complex although the less hindered isoindoline does, producing the corresponding aminocarbene complex (eq. 3) [4].

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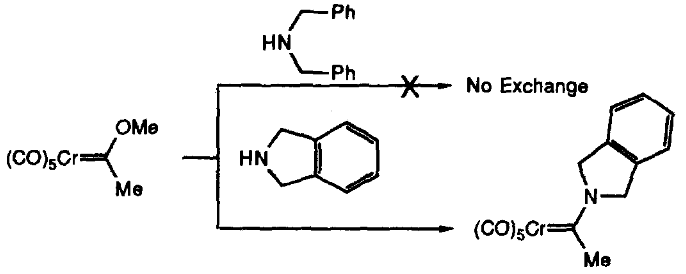
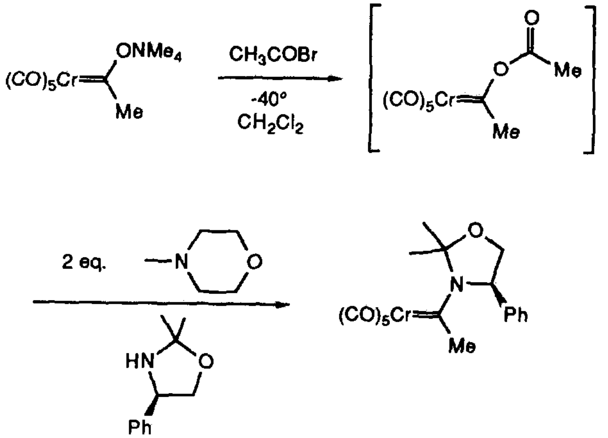
* Dedicated to Professor Peter Pauson on the occasion of his retirement.

(Eq. 2)



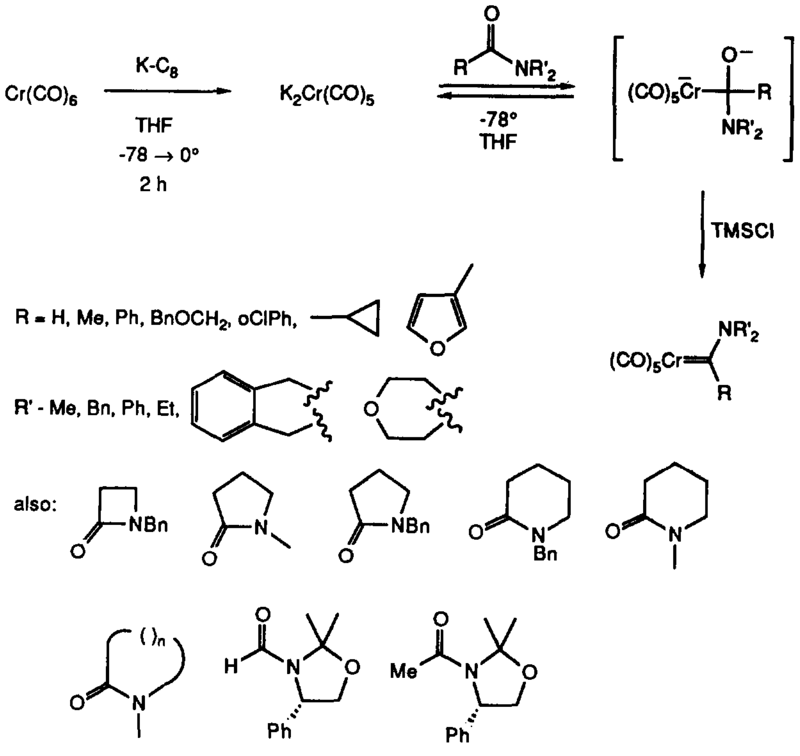
(Eq. 3)

The amine exchange process can be enhanced by using activated oxo leaving groups in place of alkoxy groups. Tetramethylammonium (but not lithium) salts of chromium acylate complexes undergo *O*-acylation by acid halides to produce highly reactive *O*-acyl carbene complexes, organometallic analogs of organic mixed anhydrides [5]. Use of acetyl bromide as the acylating agent permitted us to synthesize the sterically hindered, optically active aminocarbene complex **2** (eq. 4) [6] by exchange.



(Eq. 4)

Aminocarbene complexes having hydrogen on the carbene carbon cannot be prepared by exchange procedures since the corresponding formyl complexes are strong hydride donors and cannot be *O*-alkylated or *O*-acylated. Simple aminocarbene complexes of this type had been prepared by the reaction of Vilsmeier's salts of formamides with $Na_2Cr(CO)_5$ [7]. However the procedure was cumbersome, and of limited scope. A more convenient and much more general approach to a wide range of aminocarbene complexes was developed in our laboratories [8], and consists of producing $K_2Cr(CO)_5$ by the reduction of chromium hexacarbonyl with

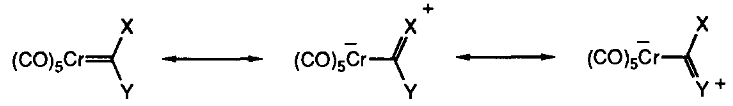


(Eq. 5)

potassium-graphite (K-C$_8$) followed by treatment with tertiary formamides, alkyl and aryl amides, or lactams, and trimethylsilyl chloride (eq. 5). This procedure makes a wide range of structurally varied aminocarbene complexes readily available for use in synthetic studies.

Physical and spectroscopic properties of aminocarbene chromium complexes

In chromium carbene complexes, the three groups attached to the sp^2-hybridized carbene carbon—the metal, the heteroatom, X, and the other group, Y—are all potentially engaged in π-bonding with the carbene carbon. Depending on the relative π-donor abilities of these groups, the appropriate description of the bonding lies somewhere between the three extremes shown in eq. 6. For aminocarbene complexes (X = N) structure II is a major contributor, as evidenced by a shortened C–N bond length (1.31 Å), similar to that in amides such as acetanilide, and a large rotational barrier about the carbene C–N bond (25 kcal) [9]. Because of this large barrier, rotameric isomers of unsymmetrical aminocarbene complexes are stable and isolable. As the X group becomes a better donor, the carbene carbon becomes a weaker π-acceptor of the metal's electron density, resulting in increased π-back-bonding from the metal to the CO groups, and shortening of the *trans* Cr–CO bond length is predicted and observed [10]. This is reflected in a shift to lower frequency of 10–20 cm^{-1} for the infrared absorption of the *trans* CO group, relative to that of alkoxycarbene complexes. Chromium carbene complexes are characterized by a long-wavelength absorption band in the electronic spectrum assignable to a π–π^* transition. This band shifts to longer wavelength with changes in the heteroatom in the order $N < O < S$ [11], and these carbenes range in color from pale yellow to deep red. This absorption has been assigned as a metal-to-ligand-charge-transfer band (MLCT) [12] and corresponds to the excitation of an electron from the metal-centered HOMO to the carbene-carbon p^* centered LUMO.



I II III

(Cr π-donor) (X-π-donor) (Y-π-donor)

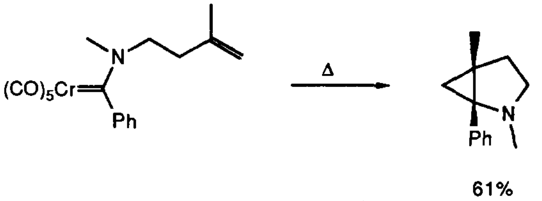
The ^{13}C NMR chemical shift of the carbene carbon in these complexes spans a range over 150 ppm, with those of aminocarbene complexes varying from δ 285 to 250 ppm. Although this is in the chemical shift range of organic carbocation values [13], the analogy cannot be considered reliable. In contrast to ^{1}H NMR chemical shifts, the observed ^{13}C chemical shift is the sum of local and nonlocal contributions of a diamagnetic shielding term as well as a paramagnetic shielding term [4]. Since the nonlocal contributions depend on all of the substituents on the carbene carbon —the chromium, the heteroatom and the other substituent—direct correlation of $\delta(^{13}C)$ with the degree of shielding or deshielding experienced by the carbene carbon is difficult.

In our laboratories [4], ^{53}Cr NMR spectroscopy was developed to provide detailed information about the efficiency of π-overlap of the carbene carbon with its substituents and the sensitivity of this π-overlap to steric crowding about the carbene carbon. A downfield shift (deshielding) of the ^{53}Cr signal in the carbene complex (relative to $Cr(CO)_6$) occurred with an increase in steric bulk of the amine group, and was attributed to the steric inhibition of the parallel orientation of *p*-orbitals required for efficient π-overlap of the heteroatom with the carbene carbon. The ^{53}Cr chemical shifts correlated well with the donor–acceptor properties of the carbene ligand and were quite sensitive to steric influence on the efficiency of the π-overlap of the nitrogen with the carbene carbon. ^{53}Cr NMR spectroscopy provides the most direct information concerning the electron density at the metal center, and its use to rationalize and perhaps even predict reactivity is currently under study.

Use of aminocarbene chromium complexes in organic synthesis

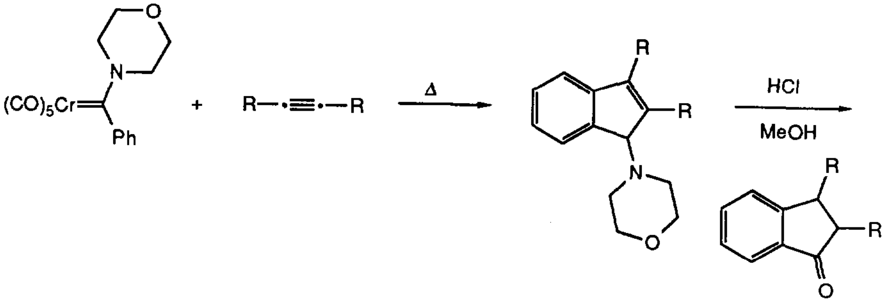
Aminocarbene complexes are generally more stable than alkoxycarbene complexes, and only recently has their use in organic synthesis been developed. The two most common thermal reactions of alkoxycarbene complexes—cyclopropanation of electron deficient olefins, and benzannulation reactions with alkynes—take a somewhat different route with aminocarbene complexes. Neither alkoxy- nor aminocarbene complexes cyclopropanate .unactivated olefins in intermolecular reactions.

However, we have shown that the intramolecular version is facile and efficient (eq. 6) [14].

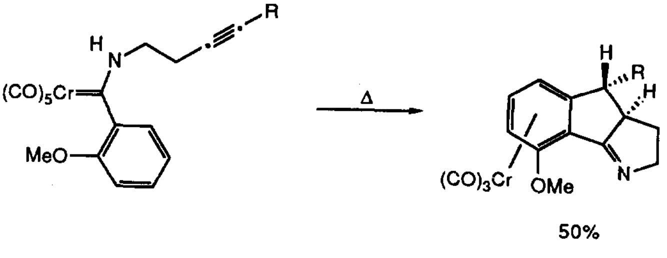


(Eq. 6)

While the benzannulation of alkynes with unsaturated alkoxycarbene complexes almost invariably results in the production of hydroquinone derivatives via a CO insertion-produced vinyl ketene intermediate [2d] (see below), aminocarbene complexes produce primarily indenones via intermediates not derived from CO insertion processes (eq. 7 [15], eq. 8 [16]).

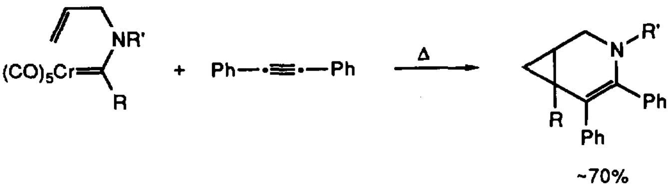


(Eq. 7)



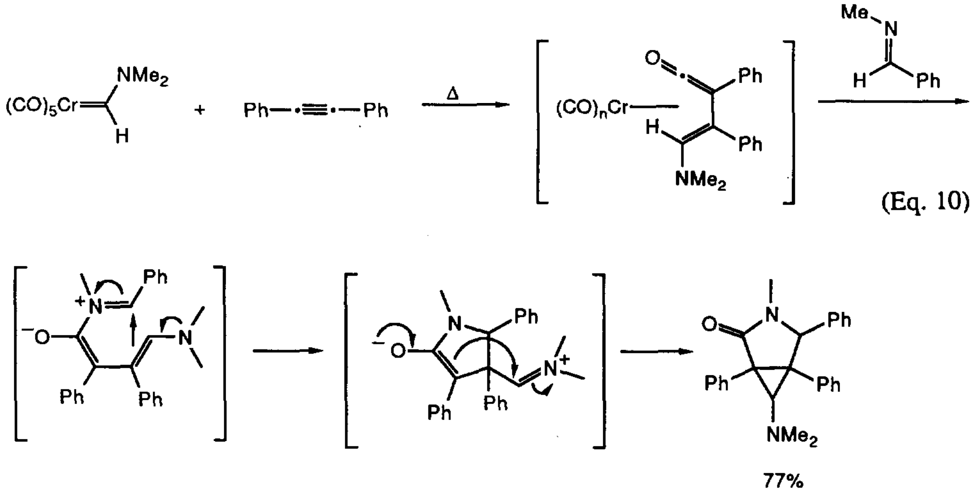
(Eq. 8)

When olefinic unsaturation is present in the amino side chain rather than the alkyl side chain, alkyne insertion/cyclopropanation results (eq. 9) [17]. With cyclic and acyclic unsaturated amino groups, unusual rearrangements occur, with incorporation of CO [18]. The reaction of simple aminocarbenes with enynes results in polycyclic compounds produced by a complex cascade of cycloaddition, metathesis, cycloaddition, and reductive elimination [19].



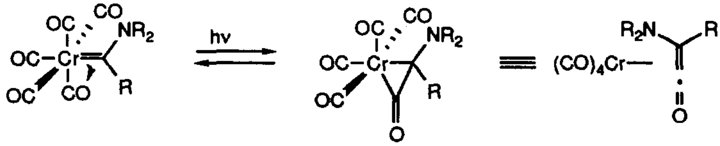
(Eq. 9)

Although a majority of the above reactions do not incorporate CO, the reaction of aminocarbene complexes with alkynes can indeed produce vinylketene intermediates, as evidenced by results from our laboratories (eq. 10) [20]. The production of enaminoketenes such as this has recently been confirmed by X-ray crystallography [21].



(Eq. 10)

For the past 10 years, research in our laboratories has focussed on the development of photochemical reactions of alkoxy- and aminocarbene complexes for use in organic synthesis. Photolysis of chromium carbene complexes with visible light (350–450 nm, MLCT) is thought to photochemically drive a reversible insertion of one of the four *cis* CO groups into the metal carbon double bond, producing a metallacyclopropanone or metal-bound ketene (eq. 11) [22,23]. Free ketenes are unlikely, and photolysis in the absence of reactive substrates results in recovery of the carbene complex, even after several days irradiation. However irradiation in the presence of reactive substrates, such as imines or nucleophiles, results in consumption of the carbene complexes, and production of ketene derived product, usually in good yield, within 12 h.

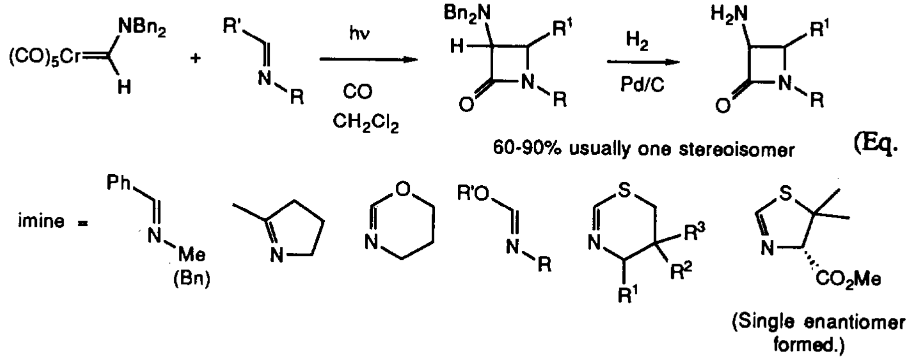


(Eq. 11)

This procedure for the generation of species having aminoketene-like reactivity has several synthetic advantages over classical methods for ketene generation and utilization. A wide range of structurally complex aminocarbene complexes are easily synthesized from readily available starting materials such as amides (eq. 5) or alkoxycarbene complexes (eq. 4). Primary (NH_2), secondary (NHR), and tertiary (NR_2) aminocarbenes are stable, and protection of the N functionality as the amide or imide is not necessary. The metal-bound ketene is generated under very mild conditions (visible light, solvents ranging from hexane to DMF, no external base) and in low concentration, suppressing ketene–ketene reactions and multiple ketene incorporations.

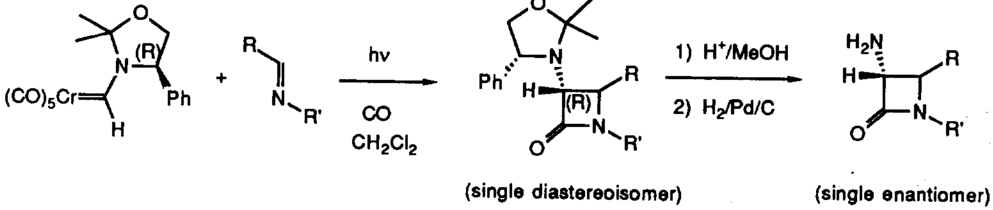
In contrast, ketenes are conventionally generated *in situ* from the reaction of acid chlorides with tertiary amines at low temperatures. Since α-amino acid chlorides are not stable, precursors to aminoketenes must have the nitrogen protected as the amide, imide, or azide. Since the ketene is generated all at once, these reactions often suffer from side reactions of this highly reactive intermediate. Finally, the structural variety of classic aminoketene precursors is somewhat limited.

Our research has focussed on the synthesis of biologically active β-lactams by the photolytic reaction of aminocarbene complexes with imines. With the simple dibenzylaminocarbene complex, a wide variety of cyclic and acyclic imines were converted to amino β-lactams in excellent yield and with high diastereoselectivity (eq. 12) [24]. With imines of formaldehyde (as cyclic trimers) monobactams (monocyclic β-lactams) were prepared [25]. Optically active aminocarbene complexes were prepared from optically active formamides derived from L-valine, and (R)-phenyl glycine. These underwent photochemical reaction with imines to produce β-lactams in high chemical yield and with $\geqslant 97\%$ diastereoselectivity, in most cases. The absolute stereochemistry of the chiral center adjacent to the amino group was the same as that of the chiral auxiliary, while that of the second chiral carbon was determined by the imine (eq. 13) [26].

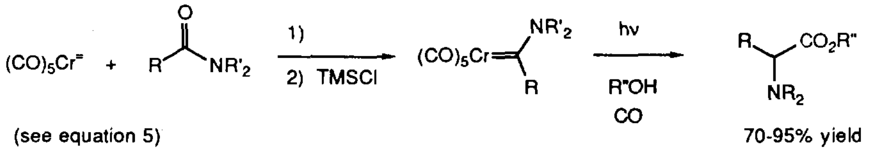


(Eq. 12)

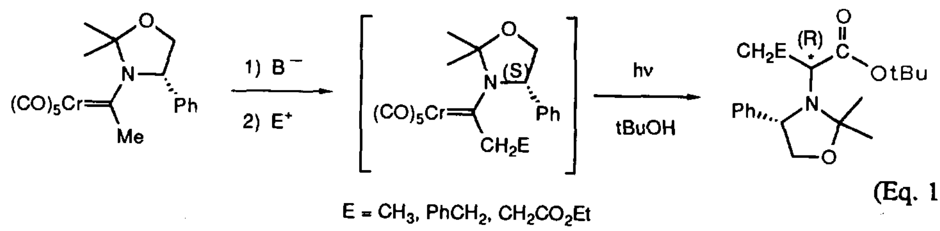
(Eq. 13)



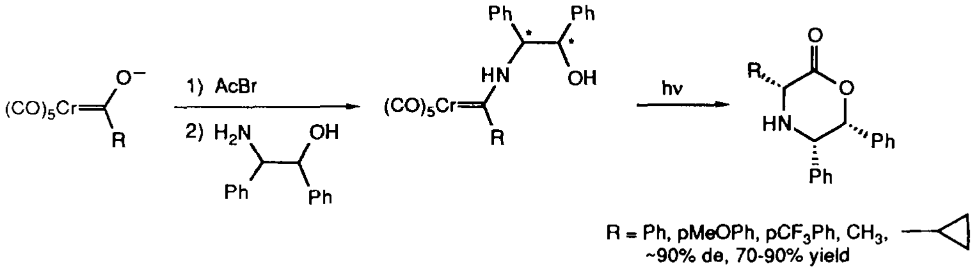
Photolysis of aminocarbene complexes in the presence of alcohols produced excellent yields of α-amino acid esters. Since aminocarbene complexes are prepared from amides, this is an efficient, two step conversion of amides to α-amino acids (eq. 14) [6]. With optically active aminocarbene complexes, optically active amino acid esters having the absolute configuration opposite that of the chiral auxiliary were produced in excellent yield and with $\geqslant 97\%$ diastereoselectivity. The α-protons on methyl carbene complexes are acidic and the resulting anion can be alkylated [27]. Utilizing this aspect of reactivity, the optically active (methyl)aminocarbene was homologated and photolyzed without purification, to give the homologated α-amino acid ester. Thus, the aminocarbene complex in eq. 15 is an alanine homoenolate equivalent. Optically active amino acids were also prepared by the photolysis of aminocarbene complexes made from an optically active amino alcohol (eq. 16) [22].



(Eq. 14)



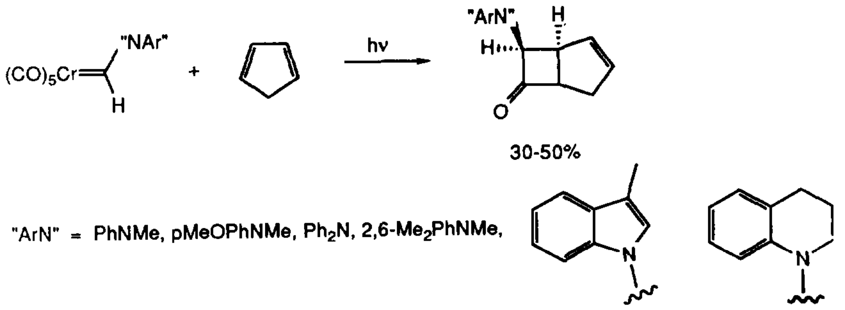
(Eq. 15)



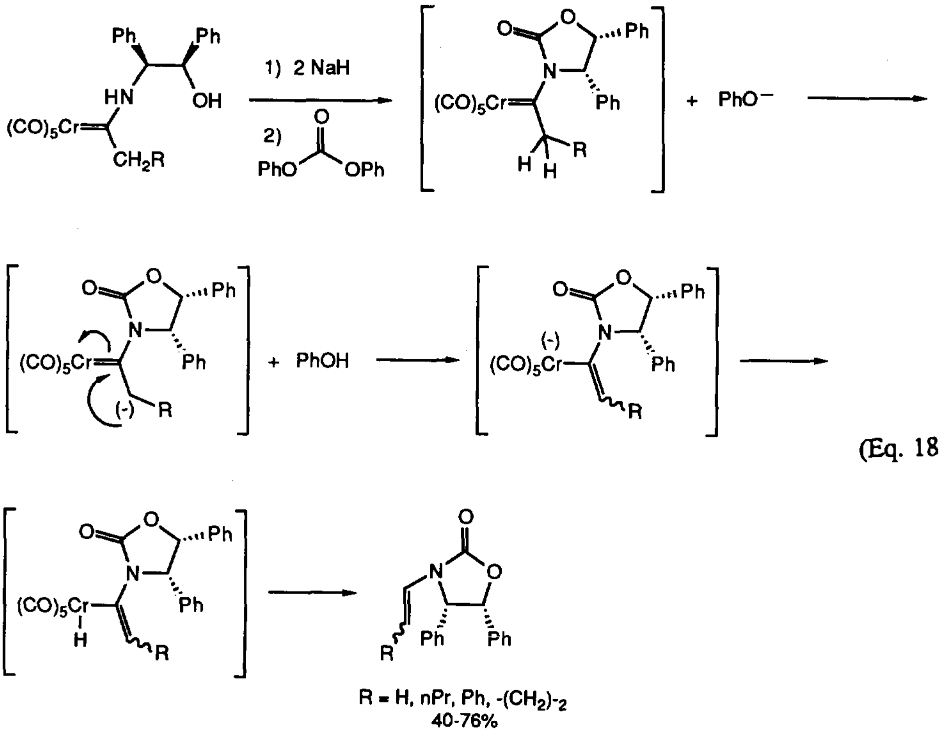
(Eq. 16)

Photolysis of alkoxy carbene complexes in the presence of olefins produced cyclobutanones in excellent yield [28]. However, normal aminocarbene complexes failed to undergo this reaction, probably because of the relatively high basicity of the amino group. However, carbene complexes of the much less basic aryl amines did participate in this cycloaddition reaction (eq. 17) [29].

Finally, in an effort to prepare optically active oxazolidinone carbene complexes, cyclization of an amino alcohol derived carbene was attempted (eq. 18) [30]. Although the carbene formed, it was very unstable, and decomposed to give optically active ene carbamates in good yield, by an α-deprotonation/metal protonation/reductive elimination sequence [31]. These compounds have found use in the Pd-assisted synthesis of thienamycin and of optically active cyclobutanones [32].



(Eq. 17)



(Eq. 18)

Acknowledgements

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