β-Lactams from Fischer Carbene Complexes: Scope, Limitations, and Reaction Mechanism

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Abstract The irradiation (visible light) of Fischer carbene complexes promotes the reversible insertion of a cis-carbonyl ligand into the metal–carbene carbon bond in a process known as photocarbonylation. This reaction gives rise to the formation of ketene-like complexes which are able to react with nucleophiles to yield a great variety of reaction products. When the nucleophile is an imine, β-lactams are formed in good to excellent yields and with high diastereoselectivities. The scope and limitations of this synthetically useful transformation as well as its reaction mechanism are considered herein.

Keywords Fischer Carbene complexes · β-lactams · Photochemistry · Reaction mechanisms · Metallocenes · DFT calculations

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1 Introduction

The chemistry of Fischer carbene complexes has been largely developed since the first synthesis of the pentacarbonyl[methoxy(methyl)carbene] tungsten(0) complex by Fischer and Maasböl in 1964 [1]. Due to their special electronic features and multifunctional structure, most of the investigations performed so far have mainly focused on their applications in organic synthesis (selected reviews on the chemistry of Fischer carbenes [2–10]). Nowadays, Fischer carbene complexes have shown themselves to be very efficient and versatile starting materials to carry out a wide variety of organic transformations under mild reaction conditions.

Representative examples of the rich and versatile chemistry of this family of organometallic complexes are the useful Dötz-benzannulation reaction [11], which produces substituted phenols by reaction with alkynes and carbon monoxide, cycloaddition reactions such as cyclopropanation [12–15], Diels–Alder reaction ([16–19]; for a recent computational study, see [20]) or dipolar cycloadditions ([21–24]; for a recent computational study, see [25]), and the catalytic transmetallation to late transition metals [26, 27], which enhances the reactivity of the carbene complexes leading to a great number of different reaction products.

The discovery by Hegedus and McGuire at the beginning of the 1980s that alkoxychromium(0) carbene complexes can be transformed into β-lactams when irradiated (visible light) in the presence of imines marked the beginning of a key reaction in organometallic chemistry [28]. This reaction, which is known as photocarbonylation, gives rise to ketene-like intermediates which show all the advantages of ketenes without their shortcomings, i.e., dimerization, formation of undesired adducts, and so forth. Depending on the nucleophile added to the reaction medium, this process allows the easy and efficient access to a wide variety of compounds such as β-lactams, cyclobutanones, amino acids and peptides, poly-nuclear hydrocarbons, or β-lactones [29] (Scheme 1). This synthetically powerful photoreactivity has no parallel in the photochemistry of any other class of organometallic compounds and competes in efficiency and exceeds in versatility with many well-established and synthetically useful photochemical organic reactions [30–32].

Herein, the scope, limitations, and mechanism of the photocarbonylation reaction of group 6 Fischer carbene complexes in the presence of imines to produce β-lactams are summarized [33].

2 Synthesis of β-Lactams from Fischer Carbene Complexes

2.1 Scope and Limitations

The irradiation of group 6 Fischer metal–carbene complexes with visible light in the presence of a wide range of imines (including heterocyclic imines) produces β-lactams in good to excellent yields [28, 34–36]. In contrast to the analogous
Staudinger process, the photoreaction of these organometallic compounds is free of the typical by-products formed when ketenes derived from acyl chlorides are involved. Moreover, the transformation is highly diastereoselective, usually giving rise to a single diastereoisomer (Scheme 2).

The usefulness of this process toward the synthesis of new $\beta$-lactams is clearly demonstrated in the reactions depicted in Schemes 3 and 4. Thus, the family of $\beta$-lactams azapenams [37–39] and bis-azapenams [40] are easily produced by the reaction of mono- or bis-alkoxycarbene complexes with N-protected imidizolines followed by deprotection of the Cbz group.

Nevertheless, most biologically active $\beta$-lactams lack an alkyl and an alkoxy group $\alpha$ to the carbonyl group of the 2-azetidinone ring, but rather they possess an amino group and a hydrogen atom. Therefore, aminocarbene complexes must be used to produce such $\beta$-lactams. Usually, complexes where $R^1 = H$, which are readily prepared by the reaction of $M_2\text{Cr(CO)}_5$ with iminium chlorides [41] or with amides with the addition of trimethylsilyl chloride [42, 43] can undergo an efficient photoreaction with a wide range of imines to produce $\alpha$-amino $\beta$-lactams in good to excellent yields and with high diastereoselectivity [44] (Scheme 5). However, aminocarbene complexes with $R^1 = \text{alkyl}$ or $\text{aryl}$ formed $\beta$-lactams in only low yields.

Attempts to induce asymmetry into the reaction of chromium alkoxycarbene complexes with imines met with mixed results. In most cases chiral auxiliaries attached
to the nitrogen of the imine were ineffective, resulting in low to moderate diastereoselectivity [35]. However, when rigid, cyclic imines such as thiazolines (Scheme 6) [35] and imidazolines [37] were used, very high (essentially 100%) d.e. were observed.

Although the formed β-lactams were not of biological interest, they provided chiral templates for the synthesis of highly functionalized quaternary systems (Scheme 7) [45].
Chiral auxiliary oxazolidine was also directly attached to the carbene ligand \([46]\). The photochemically produced oxazolidine metal–ketene complex gave excellent chemical yields of single diastereoisomers of \(\beta\)-lactams with imidates, oxazines, thiazines, and cyclic and acyclic aliphatic imines, but only modest yields of mixtures of \(\text{cis}\) and \(\text{trans}\) diastereoisomers of \(\beta\)-lactams with imines derived from benzaldehyde and cinnamaldehyde (Scheme 8). In sharp contrast, the related nonorgano-metallic oxazolidinone ketene gave excellent chemical yields of single \(\text{cis}\) diastereoisomers of \(\beta\)-lactams with imines of benzaldehyde and cinnamaldehyde, but very low yields of \(\beta\)-lactams with other imines. This different behavior clearly exemplifies the dramatically different albeit complementary reactivity of these closely related intermediates ([47]; for the related oxazolidinone ketene see [48]).

Finally, there is a single example of the intramolecular cyclization of chromium (0) carbene complex bearing imino tethers \([49]\). The preparation of these complexes is achieved in two-steps from simple chromium(0) complexes and their cyclization.
yields bicyclic anti-Bredt $\gamma$-lactams instead of the expected $\beta$-lactams. This is probably due to the opening of these unstable intermediates or, alternatively, by a competitive evolution of the intermediate zwitterion. This zwitterion is derived from the intramolecular attack of the imine nitrogen on the photogenerated ketene (Scheme 9).

2.2 Synthesis of $\beta$-Lactams from Chromium(0) Carbene Complexes and Subsequent Manipulation of the Four-Membered Ring

The use of appropriate imine substrates in the chromium(0) carbene-mediated photocycloaddition allows for ulterior manipulation of the four-membered ring.
Thus, malonoimides have been prepared by reaction of iminodithiocarbonates and chromium(0) carbene complexes followed by oxidation with N-bromosuccinimide (NBS) [50] (Scheme 10).

\[
\begin{align*}
\text{(CO)}_2\text{Cr} & \quad \underset{\text{MeCN, hv}}{\rightarrow} \quad \text{MeCN, hv} \\
\text{R}^1\text{N} & \quad \underset{\text{NBS, MeCN/H}_2\text{O}}{\rightarrow} \\
\text{SMe} & \\
\text{SMe} & \\
\end{align*}
\]

\( R^1 = \text{PMP, Ph, 2-Me-3-ClC_6H_4, Bn, allyl} \)
\( R^2 = \text{OMe, OBn, OPr', NBn_2} \)
\( R^3 = \text{H, Me, Ph, cyclopropyl} \)

**Scheme 10** The two-step synthesis of malonoimides from iminodithiocarbonates

These iminodithiocarbonates also behave as formaldehyde imine equivalents using the sequence chromium(0) carbene photocycloaddition-nickel boride desulfuration [51]. This sequence allows the preparation of either chiral or racemic 4-unsubstituted-2-azetidinones in two steps and highly overall yields (Scheme 11).

\[
\begin{align*}
\text{(CO)}_2\text{Cr} & \quad \underset{\text{Et}_2\text{O, hv}}{\rightarrow} \\
\text{R}_3\text{N} & \quad \underset{\text{Ni-Boride}}{\rightarrow} \\
& \quad ( > 95:5 ) \\
\text{SMe} & \\
\text{SMe} & \\
\end{align*}
\]

\( R^3 = \text{Bn, PMP} \)
\( \text{PMP} = \rho\text{-MeO-C}_6\text{H}_4 \)

**Scheme 11** The synthesis of chiral 4-unsubstituted-\(\beta\)-lactams from chiral aminocarbene chromium(0) complexes and iminodithiocarbonates

Alternatively, the chromium(0) carbene moiety can be incorporated in a preformed 2-azetidinone ring. This methodology based mainly on solvolysis reactions of chromium(0) alkoxycarbene complexes have been used in the preparation of peptide containing 2-azetidinones, including penicillin and cephalosporin derivatives [52] (Scheme 12).

### 2.3 Synthesis of Metallocenyl-\(\beta\)-Lactams from Bimetallic Carbenes

The synthesis of novel \(\beta\)-lactams which incorporate organometallic moieties in their structures has attracted much attention in the recent years due to their novel and
interesting biological properties ([53–62]). As instance, almost all of the ferrocenyl-penicillins and cephalosporins exhibited antibiotic activity, some being highly active, while others proved to be potent β-lactamase inhibitors. Despite that, 2-azetidinones having organometallic fragments attached to the four-membered ring are scarce. The use of Fischer carbene complexes is a useful alternative toward the synthesis of new organometallic β-lactams.

We pioneered the use of the photocarbonylation reaction to access novel ferrocenyl-β-lactams [63]. Thus, alkoxychromium(0) carbene complexes react smoothly with ferrocene imines to place ferrocene substituents at the N1, C4, or simultaneously at N1 and C4 positions of the β-lactam ring (Scheme 13). Interestingly, when the ferrocene unit was introduced in the carbene ligand, the reaction yield dramatically decreases to 23% for aminoferrocenyl-chromium(0) complex or no reaction is observed when the ferrocenyl substituent is directly attached to the carbene carbon atom (Scheme 14).

In contrast, the analogues mono- or bis-ruthenocyl-carbene complexes are photoreactive and readily produce the expected β-lactams [64] (Scheme 15). To our knowledge, these are the unique examples of a 2-azetidinone bearing a metallocene directly attached to the C3 of the four-membered ring. Reasons for the differential behavior of ruthenocenyl- vs. ferrocenyl-substituted carbene complexes are found in the structure of the corresponding excited states formed upon irradiation (see below). Using this useful methodology, the preparation of the first 6-ruthenocenyl-substituted penicillin by reaction of ruthenocenyl-substituted carbene complex and thiazoline was achieved [64] (Scheme 15). This metallapeenicillin might exhibit potential biological activity.
3 Reaction Mechanism

It is well established that not all carbene complexes can undergo the photocarbonylation reaction and produce metallaketenes able to react with imines to yield β-lactams. In fact, those group 6 Fischer carbenes complexes based on tungsten(0) instead of chromium(0) or molybdenum(0) do not photocarbonylate. This is mainly due to the higher back-donation of tungsten(0) compared to its group 6 congeners.

Scheme 13 Ferrocenyl-substituted β-lactams

Scheme 14 The anomalous behavior of ferrocene-substituted chromium(0) carbene complexes
which makes the metal–carbene and metal–carbonyl bonds stronger inhibiting the photoinsertion of the cis-CO into the metal–carbene bond (see below). Similarly, chromium(0) complexes bearing σ-donating ligands (i.e., PBu₃ or diphos) are not photoreactive either [65]. In contrast, soft σ-donor ligands (like PPh₃ or phosphites) can form β-lactams in moderate to good yields [65, 66].

As stated above, the nature of the substituents attached to carbene carbon atom has a strong influence on the photoreactivity of Fischer carbenes. Thus, alkoxy carbenes with alkenyl or alkynyl groups attached to the carbene or aminocarbenes, where the R¹ substituent is different from hydrogen (see above), are not photoactive at all or lead to very low conversions [28]. Therefore, it seems that the electronic properties of the carbene ligand (mainly, the occupation of the “empty” pₓ-atomic orbital of the carbene carbon atom) is the main factor controlling the photoreactivity of Fischer carbene complexes. By the proper selection of the ligands surrounding the metal center and the substituents at the carbene ligand, the photoreactivity of the complexes can be indeed modulated and processes different to the photocarbonylation reaction such us stepwise 1,2-dyotropic rearrangements, ([67, 68]; for a recent review on dyotropic rearrangements, see [69]), α-fragmentations [70] or photoslippage [71] can occur [33].
3.1 The Photocarbonylation Process

The photocarbonylation process relies on the reversible insertion of a \textit{cis}-CO ligand into the M=C bond to yield metal-coordinated ketenes or metallacyclop propane species. This mechanism was proposed by Hegedus in 1988 [72] (Scheme 16). Despite the close parallelism of the ketenes derived from the irradiation of group 6 metal–carbene complexes and free ketenes (for a recent review in the state of the art of the research on the mechanism of the Staudinger reaction, see [73]), all the efforts directed toward the isolation or detection of these elusive intermediates have been fruitless so far.

By means of a combination of experimental and computational tools [65, 74], it was found that the irradiation of alkoxychromium(0) carbene complexes, either in the LF band followed by relaxation to the MLCT band, or directly in the MLCT band, results in the excitation of these complexes to the $S_1$ excited state, which readily decays to the triplet $T_1$ state by intersystem crossing (ISC) due to spin–orbit coupling (this is a general phenomenon in group 6 metal carbonyl complexes; see [32] and [75].) These triplet species ($1(T_1)$) have a chromacyclop propane structure whose unpaired electrons are mainly localized in the metal fragment and in the former carbene carbon atom and therefore corresponds with the chomacyclo propane proposed by Hegedus and co-workers to explain the reaction products obtained in the photochemical reaction of chromium(0) carbene complexes [28, 72]. These coordinatively unsaturated complexes change their multiplicity prior to evolving the ketene-derived products. This is accomplished by filling the corresponding free coordination site with a molecule of a coordinating solvent in the apical position to form $2(S_0)$ complex (Fig. 1). To experimentally
confirm this theoretical prediction, the photolysis of pentacarbonyl[ethoxymethyl] carbene-chromium(0) complex with the imine PhCH=N(p-OMeC₆H₄) was carried out in solvents with different coordinative ability. It was found that the higher the donor number of the solvent (i.e., tetrahydrofuran or acetonitrile) the higher were the conversions of complex 1 into the corresponding β-lactam [74].

The geometrical features and the Natural Bond Orbital (NBO) analyses carried out on these newly formed species (2(S₀)) show that they possess a structure which corresponds to a ketene species coordinated to chromium with a highly polarized Cr–C (former carbene carbon atom) bond. Therefore, complexes 2(S₀) can be viewed as acylchromate complexes from which ketene-derived products can now be formed in the presence of nucleophiles on the S₀ hypersurface, while in their absence, these species revert to the starting carbene complex in a highly exothermic process (Fig. 1).

The solvent-induced T₁–S₀ crossing of chromoketene 1(T₁) to the acylchromate 2(S₀) was further analyzed in detail (for a recent example on Lewis-base-induced triplet-singlet crossing in organometallic compounds, see [76]; for a review on this problem, see [77]). Relaxed scans of this complex at different Cr–OH₂ distances, where the OH₂ ligand models an ethereal solvent (Fig. 2), showed that the T₁ state exhibits a very shallow Morse-like curve, whose minimum is located at r = 3.746 Å, r being the Cr–OH₂ distance (Fig. 2). The harmonic analysis of this structure shows two low-frequency vibrations associated with stretching of the Cr–O interaction and symmetrical bending of two carbonyls to achieve the octahedral coordination. This result, together with the negligible energy difference between both

![Fig. 1 The computed mechanism for the photocarbonylation of chromium(0) carbene complexes](image)
states at long Cr–OH₂ distances, indicates that the available thermal energy is enough for the molecule to go from the T₁ to the S₀ potential energy surface. This radiationless ISC does not take place through a narrow conical intersection (a photochemical funnel) but occurs at r-values larger than 4.0 Å along an energy plateau shared by both spin states. This process, which is called the Loose-Bolt effect in organic chemistry [32], has no known precedents in the photochemistry of metal complexes.

The formation of the metallacyclopropanone complex in the triplet state is decisive for the production of β-lactams in the presence of imines. DFT calculations clearly show that the most stable triplet species of the analogous tungsten(0) alkoxy carbene complex does not have the required metallacyclopropanone structure. Thus, the computed bond lengths between the carbene carbon atom and the nearest C(=O) groups are 2.716 Å and 2.567 Å, respectively, without any measurable bond order between both atom pairs [74]. Therefore, no ketene-like species are formed by excitation of an alkoxy-pentacarbonyltungsten(0) carbene complex which is in good accord with the experimentally observed lack of photochemical reactivity of tungsten(0) carbene complexes.

Similarly, the computational data show the coexistence of a very low-energy noncarbonylated triplet for ferrocenyl-substituted carbene complex (T₁) and a high-energy metallacyclopropanone triplet (T₂, Fig. 3a). This implies that irradiation of this complex leads to the formation of a triplet species, which does not possess the structure required to react with nucleophiles [64]. In sharp contrast, two nearly degenerated triplet states coexist in its ruthenocenyl counterpart (Fig. 3b).

**Fig. 2** The Loose-Bolt mechanism for the ISC in chromium(0) carbene photochemistry
Simple visual inspection of the corresponding SOMOs of $T_1$ species (Fig. 3) indicates clear differences in the electronic structures of ferrocenyl- and ruthenocenyl-substituted carbenes, which are translated into a differential photoreactivity (see above). One of these two triplets is a carbonylated metallacyclopropanone species (similar to $I(T_1)$ in Fig. 1), which can react with imines to form the observed $\beta$-lactams [64] (Schemes 14 and 15).

### 3.2 The Reaction with Imines to Yield $\beta$-Lactams

Having established a reasonable model for the photocarbonylation step of chromium(0) carbene complexes, the addition of an imine to the coordinated ketene was
studied next. As above-mentioned, this reaction forms 2-azetidinones in good yields and it is usually free of by-products [28]. The reaction is highly diastereoselective since Fischer carbene complexes form β-lactams where the larger substituent of the ketene is placed cis to the anti-substituent of the imine. This contrasteric bias has been claimed to be due to the presence of the metal moiety during the cycloaddition [28].

The participation of the metal in the transformation of the chromium complex into the final products and not only in the first carbonylation step was experimentally confirmed by irradiating the chiral complex depicted in Scheme 17 in the presence of an imine. This reaction yielded a mixture of the corresponding cis/trans-β-lactams in a 4.0:1 ratio with a 66% of conversion [66]. After separation of both diastereoisomers, a 14% e.e. for cis-diastereomer was measured by 1H NMR in the presence of Eu(hfc)₃. Even with the observed low e.e., which can be very likely ascribed to the fact that the inducing center is located far away from the emerging chiral centers, the formation of chiral products is compatible with a mechanism in which the metal is present in the enantio-discriminating step, namely the conrotatory ring closure of the zwitterion ([73]). Nevertheless, there is a possibility of organocatalysis by the free chiral phosphine which would be responsible for the observed e.e. (related examples [78–80]). To safely disregard this process, the removal of the metal-moiety from the reactive system was ensured by working under moderate CO-pressures (90 psi). Thus, the irradiation of the same chiral complex and imine in MeCN under 90 psi of CO gave the mixture of the corresponding cis/trans-β-lactams in a 3.8:1 ratio and in 70% isolated yield (Scheme 17). Similarly, the isomers were separated and the cis-isomer was analyzed again by 1H NMR in the presence of Eu(hfc)₃. The e.e. was 0% within

![Scheme 17 The enantioselection in the reaction of chromium(0) carbene complexes having chiral ligands as a probe for the β-lactam formation mechanism](image)
the experimental error, thus confirming that no asymmetric induction was obtained if the metal moiety is removed from the reactive system.

Two related reaction mechanisms can be envisaged for this transformation: (1) the nucleophilic attack of the lone-pair of the nitrogen atom of the imine to the carbonyl group of the acyl-chromate \(2(S_0)\) followed by a 1,3-metallatropic process forming a chromium enolate–iminium zwitterionic complex which produces the final cycloadduct through a conrotatory ring closure, or alternatively, (2) the 1,3-metallatropic process can occur first from the acyl-chromate to produce the corresponding O-coordinated ketene, which produces the final cycloadduct after nucleophilic attack of the imine and subsequent four electron conrotatory electrocyclation, following the standard mechanism for the Staudinger reaction (see [73]) (Scheme 18).

Scheme 18  Pausible reaction pathways in the reaction between chromium(0) Fischer carbene complexes and imines
It has been suggested that the 1,3-metallatropy must occur before the nucleophilic attack of the imine [66]. This rearrangement, albeit slightly endergonic (see Fig. 4), takes place due to a more favorable HOMO(imine)–LUMO+1(oxygen-coordinated ketene) interaction which constitutes the driving force of the transformation. Moreover, the NBO-charge analyses carried out on both key intermediates show that the carbon atom (former carbonyl ligand), which suffers the nucleophilic attack by the nitrogen atom of the imine, bears a more positive charge in the oxygen coordinated ketene ($\Delta q = +0.11$ au) thus indicating a higher electrophilic character for this species (Fig. 4).

Finally, it was also found that the cis–trans stereoselection is produced during the nucleophilic addition of the nitrogen atom of the imine to the oxygen-coordinated ketene, since there are no significant differences between the classical and the metallated processes in the four-electron conrotatory electrocyclization step leading to the final 2-azetidinones [66]. The complete reaction profile for the reaction of complex 1 and MeHC=NM to form the final $\beta$-lactam is shown in Fig. 5.

Fig. 4 Molecular orbitals of the metallacyclopropanone (left) and oxygen-coordinated ketene (right) complexes.
4 Conclusions

In this chapter, we have shown that the photocarbonylation reaction of Fischer carbene complexes in the presence of imines is a powerful tool toward the synthesis of \(\beta\)-lactams. This process allows the easy access to 2-azetidinones, which are difficult to obtain using standard methodologies with very good reaction yields and excellent diastereoselectivities. From a reaction mechanism point of view, the irradiation of Fischer carbene complexes promotes the insertion of a cis-carbonyl ligand into the metal–carbene bond to form a metallacyclopropanone intermediate in the triplet excited state which produces ketenes coordinated to metal. From the latter species and in the singlet hypersurface, the reaction with imines occurs. Different to the closely related Staudinger reaction between ketenes and imines, the \textit{cis–trans} stereoselection is produced during the nucleophilic addition of the nitrogen atom of the imine to the oxygen-coordinated ketene, since there are no significant differences between the classical and the metallated processes in the final four-electron conrotatory electrocyclization step leading to the final \(\beta\)-lactams.
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