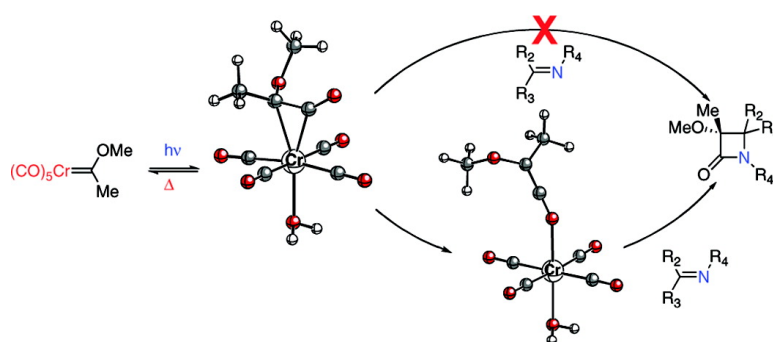## Article

Deeper Insight into the Mechanism of the Reaction of Photogenerated Metallaketenes and Imines

Israel Ferna#ndez, Miguel A. Sierra, Mari#a J. Manchen#o,
Mar Go#mez-Gallego, and Fernando P. Cossi#o

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Deeper Insight into the Mechanism of the Reaction of Photogenerated Metallaketenes and Imines

Israel Fernández,[†] Miguel A. Sierra,*,[†] María J. Mancheño,[†] Mar Gómez-Gallego,[†] and Fernando P. Cossío*,[‡]

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain, and Kimika Fakultatea, Euskal Herriko Unibertsitatea, P.K. 1072, 28080-San Sebastián Donostia, Spain

Received April 8, 2008; E-mail: sierraor@quim.ucm.es; fpcossio@ehu.es

Abstract: The reaction mechanism between Fischer carbene complexes and imines to produce β-lactams has been studied by a combination of computational (DFT) and experimental methodologies. After the photogeneration of metalla-cyclopropanone species, the reaction initiates by 1,3-migration of the metal fragment from the former carbene carbon atom to the oxygen in the S_o hypersurface. In spite of the endothermic nature of this rearrangement, it is biased by the more favorable HOMO(imine)-LUMO+1 interaction in the oxygen-coordinated ketene. This species reacts with the imine to yield metalla-zwitterions, which form the final products through a four electron conrotatory ring closure. The presence of the metal moiety during the whole reaction coordinate is demonstrated by the use of a chiral chromium(0) alkoxycarbene complex, which produces low but significant *ee* in the reaction with imines. The *cis*−*trans* stereoselection derives from 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 electrocyclation step leading to the final 2-azetidinones.

Introduction

Approaching the 50th anniversary in 2014 of the synthesis by Fischer and Maasböl of the first stable carbene complex,[1] the stoichiometric chemistry of these complexes is nowadays mature, but in no way senile. The thermal processes of group 6 Fischer carbene complexes have led to the discovery of an enormous array of different reactions,[2] the synthetic potential of most of them remaining to be fully deployed. During the last 10 years, the catalytic transmetalation of group 6 carbene complexes to late transition metal has opened alternative reactivity pathways,[3] while the single electron transfer reactions (SET) to these compounds are lately attracting the attention of different research groups.[4] In spite of the diverse and rich reactivity of this family of compounds, very little is known about the corresponding reaction mechanisms.[5] This is striking since few other chemicals offer a richer and more complex behavior than Fischer carbene complexes.

The photochemistry of these complexes relies on the highly efficient photocarbonylation of chromium(0) carbene complexes reported by McGuire and Hegedus 25 years ago.[6] An early mechanistic model for the photocarbonylation of chromium(0) carbene complexes was proposed by Hegedus.[7] According to this proposal, irradiation (visible light) of a chromium(0) carbene promotes the CO insertion into the metal-carbene bond to yield a ketene-like species. These species react with a wide variety of nucleophiles to produce ketene-derived products.[8] Despite the close parallelism of the ketenes derived from the irradiation of group 6 metal carbene complexes and free ketenes, the different efforts directed toward the detection of these elusive intermediates have met no success.[9] Recently, we reported a detailed experimental−computational study of the photocarbo-

[†] Universidad Complutense.

[‡] Kimika Fakultatea, Euskal Herriko Unibertsitatea.

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

(2) Selected reviews in the chemistry and synthetic applications of Fischer carbene complexes: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1983. (b) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1065. (c) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol 12, p 470. (d) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. (e) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163. (f) Alcaide, B.; Casarrubios, L.; Domínguez, G.; Sierra, M. A. *Curr. Org. Chem.* **1998**, *2*, 551. (g) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591. (h) Barluenga, J.; Fañanás, F. J. *Tetrahedron* **2000**, *56*, 4597.

(3) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44.

(4) Sierra, M. A.; Gómez-Gallego, M.; Martínez-Álvarez, R. *Chem.*−*Eur. J.* **2007**, *13*, 736.

(5) (a) Bernasconi, C. F. *Chem. Soc. Rev.* **1997**, *26*, 299. (b) Torrent, M.; Solá, M.; Frenking, G. *Chem. Rev.*, 2000, *100*, 439 and references therein.

(6) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *116*, 2680.

(7) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.

(8) Reviews: (a) Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143. (b) Hegedus, L. S. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 549. (d) Hegedus, L. S. *Acc. Chem. Res.* **1995**, *28*, 299. (e) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

(9) Gallager, M. L.; Greene, J. B.; Rooney, A. D. *Organometallics* **1997**, *16*, 5260 and the earlier attempts to trap the photogenerated ketenes from irradiation of chromium(0)carbenes referenced therein.

nylation process of group 6 carbene complexes.[10] According to our results, the carbonylation occurs by an intersystem crossing (ISC) from the lowest excited singlet state (S_1) to the lowest triplet state (T_1). Upon carbonylation, T_1 has a metalla-cyclopropanone structure with significant biradical character and evolves to the S_0 hypersurface by an additional ISC after coordination to a molecule of solvent. In the absence of nucleophiles, the latter species (which corresponds to a ketene species coordinated to chromium with a highly polarized Cr–C bond) reverts to the initial carbene complex by consecutive elimination of solvent followed by CO deinsertion (Figure 1). This is a strongly exothermic process that does not take place in the presence of nucleophiles. Moreover and according to our results, the photocarbonylation process occurs efficiently in chromium(0) complexes having a carbonyl ligand replaced by a σ-donor ligand such a phospine but not with alkoxypenta-carbonyltungsten(0) carbene complexes.
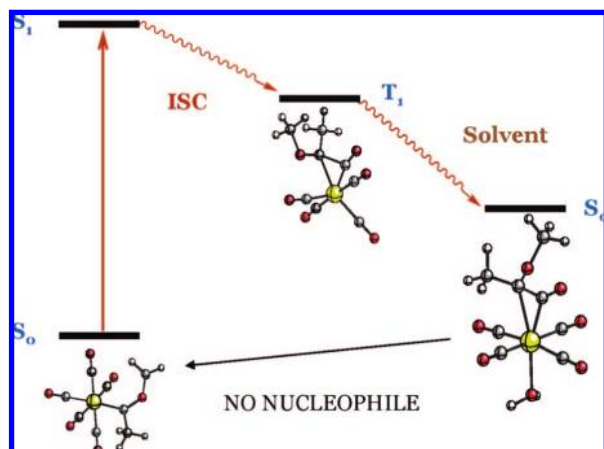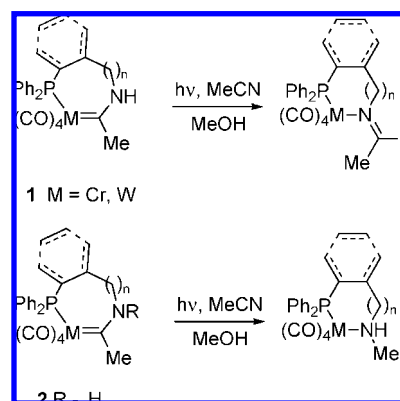

Figure 1. Schematic diagram of the photocarbonylation process for complex **3a**.

However, the photochemistry of group 6 metal carbene complexes is not limited to the carbonylation reaction. In fact, these compounds present a very rich and complex photoreactivity which strongly depends on the nature of the ligands. Thus, the carbonylation process competes or even may be completely inhibited for chelated complexes **1** and **2**, where stepwise metalla-dyotropic rearrangements of type I or cleavage of the N–C (former carbene carbon atom) bond[11] may occur, even for the traditionally considered "photoinert" tungsten(0) carbene complexes (Scheme 1).[12]

The photocarbonylation model discussed above and the photoreactivity discovered thereof collide with our previous observation about the decreased (or null) reactivity of triaryl and trialkylphosphine substituted chromium(0)carbene complexes and imines.[13] Thus, the ligands should not affect the photocarbonylation step but they should strongly influence the

(10) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *Chem.–Eur. J.* **2005**, *11*, 5988.
(11) Sierra, M. A.; Fernández, I.; Mancheño, M. J.; Gómez-Gallego, M.; Torres, M. R.; Cossío, F. P.; Arrieta, A.; Lecea, B.; Poveda, A.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2003**, *125*, 9572.
(12) (a) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 125. (b) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *Eur. J. Inorg. Chem.* **2008**, 2454.
(13) Arrieta, A.; Cossío, F. P.; Fernández, I.; Gómez-Gallego, M.; Lecea, B.; Mancheño, M. J.; Sierra, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 11509.

Scheme 1

further steps in the reaction with nucleophiles. This is not a trivial question, since our previous theoretical-experimental report did not show significant differences between the mechanism of the metal-mediated β-lactam formation[13] and the standard Staudinger reaction.[14] Reported herein is a full theoretical-experimental account of the factors determining the β-lactam formation from chromium(0) alkoxycarbene complexes and imines.

Results and Discussion

To understand the mechanism of the reaction of chromium(0) alkoxycarbene complexes and imines we first experimentally evaluated the effect of the ligand on the coordination sphere of the chromium in the formation of β-lactams using the reaction depicted in Scheme 2. Complexes **3a** having all CO ligands

Scheme 2
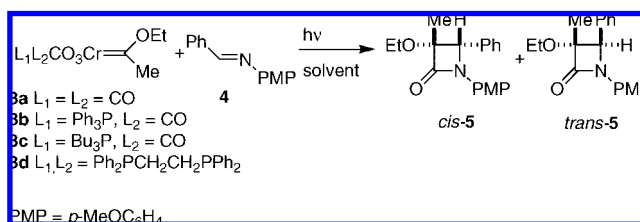
and **3b** having a PPh₃ ligand were irradiated (medium pressure Hg-lamp, Pyrex filter, and Pyrex well) in the presence of imine **4** for 6 h using MeCN as the solvent. The expected 2-azetidinones **5** were obtained in good conversions as *cis–trans* mixtures. Although the conversion for compound **3b** was slightly lower (73%) than that obtained for complex **3a** (81%), they are too close to consider any differences in reactivity based on ligand change. Complexes **3c** having a Bu₃P as ligand and **3d** having a bidentate phosphine were considerably less reactive (5 and 20% of conversion in the 2-azetidinone **5** after six hours). An analogous trend was observed for the reactions using THF as solvent (Table 1). Therefore, we discarded the bulk solvent

(14) Cossio, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925.
(15) To ensure that all experiments were effected under identical conditions, two different sets of four samples each (one sample for each complex) for each solvent were irradiated at 15 cm of the light source in a irradiation chamber maintained to 25° by forced air circulation.
(16) The effect of the solvent is, however, decisive in the carbonylation step as described in Figure 1. Coordinating solvents favor this step, while non-coordinating solvents hamper it. See ref 10 for a detailed discussion.

Table 1. Photochemical Reactions of Complexes **3a−d** and Imine **4** in Different Solvents

| entry	complex	conversion[a]	cis/trans[b]	solvent[c]
1	**3a**	81	2.8:1	MeCN
2	**3b**	73	7.3:1	MeCN
3	**3c**	5	3.6:1	MeCN
4	**3d**	20	4.5:1	MeCN
5	**3a**	79	1.4:1	THF
6	**3b**	71	2.5:1	THF
7	**3c**	10	2.3:1	THF
8	**3d**	30	1.3:1	THF

[a] Referred to unreacted imine (see ref 13). [b] Measured by integration of the signals corresponding to H4 of β-lactam ring in the ^{1}H NMR spectra of reaction mixtures. [c] All experiments were carried out by using a 10^{-2} M concentration of complex.

factor as decisive for the reactivity.[15,16] These sets of experiments allow to conclude that the substitution of a CO ligand by a soft σ-donor ligand like PPh₃ has little effect in the reaction of the carbene complex and imines (Table 1, entries 2 and 6). However, the presence of a strong σ-donor ligand in the coordination sphere of the metal such as PBu₃ practically inhibits the reaction (Table 1, entries 3 and 7).
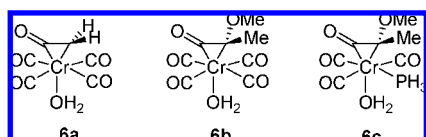
With these results in hand, we expanded our previously reported[13] theoretical mechanism for the reaction between the metallacyclopropanones obtained by irradiation of alkoxychromium(0) carbene complexes and imines. The reaction profile was calculated at the B3LYP/6-31G*&LanL2DZ level for complexes **6b** and **6c**. The first step, which is associated with the attack of the lone electron pair of the nitrogen atom of the imine to the carbonyl group of the metallaketene, was obviated due to its low contribution to the overall reaction profile.[13] Figure 2 compiles the computed reaction coordinates for these processes (the reported reaction profile for the model complex **6a**[13] has also been included for comparison). The essential features of these processes are the 1,3-chromium migration from the carbon atom to the oxygen (**INT2**→**INT3** transformation) and the conrotatory ring closure of the corresponding metalla-zwitterion (denoted as **INT3**) to the final β-lactams **5a−5c**. Strikingly, both barriers, which are associated with the 1,3-chromatropy through **TS2** and the zwitterions ring closure through **TS3** respectively, decrease by the incorporation of σ-donor ligands to the metallaketene. The straight conclusion is that the reaction of chromium(0) carbene complexes and imines to produce 2-azetidinones should be faster if the complex had strong σ-donor ligands, which is in complete opposition with the experimental data.

These contradictory results lead us to reconsider the presence of the metal moiety during the whole reaction coordinate. To ascertain the until now only hypothetical participation of the metal, the chiral complex **3e** was prepared by heating complex **3a** and the chiral phosphite **7** (Scheme 3). The irradiation of **3e** in the presence of imine **4** formed the mixture of *cis/trans-β*-lactams **5** (Scheme 2) in a 4.0:1 ratio with a 66% of conversion. Both diastereoisomers were separated by column chromatography and the *e.e.* for diastereomer *cis*-5 (14%) was measured
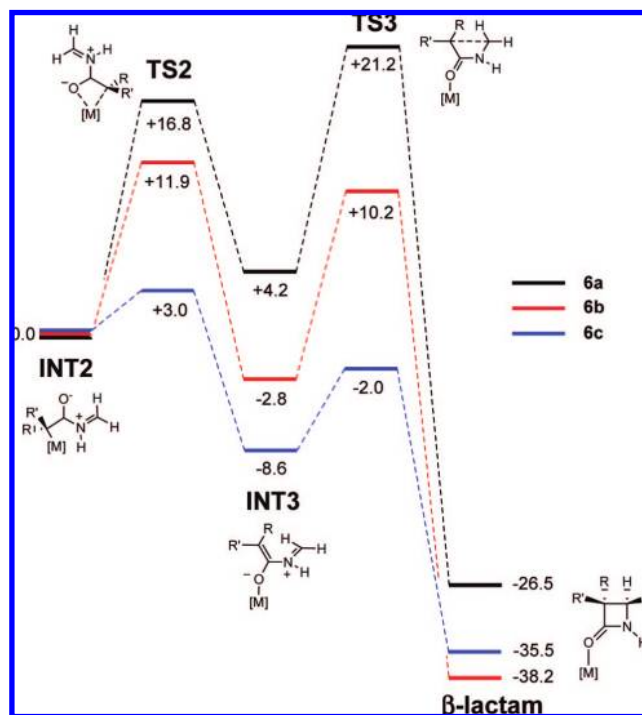
Figure 2. Reaction profiles for the reaction of complexes **6** and the model imine CH₂=NH. All data (in kcal/mol) have been calculated at the B3LYP/6-31G(d)&LanL2DZ+ΔZPVE level.

by ^{1}H NMR in the presence of Eu(hfc)₃.[17] Even with the observed low *e.e.*, due probably to the fact that the inducing center is placed 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-discrimination step, namely the conrotaroy ring closure of the zwitterion.[18] Nevertheless, there is a possibility of organocatalysis by the free chiral phosphine which would be the responsible for the observed *e.e.*

Scheme 3
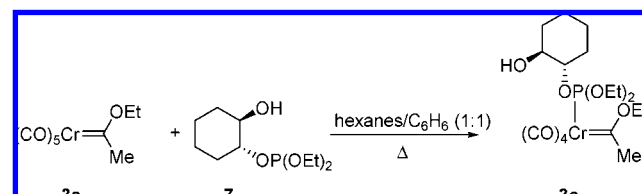
This fact emanates from the recent work in the asymmetric catalytic Staudinger reaction.[19] We ensured the removal of the metal-moiety from the reactive system by working under

(17) Sievers, R. E. *Nuclear Magnetic Resonance Shift Reagents*; New York: Academic Press, 1973.

(18) This enantio-discrimination observed in the conrotatory ring closure of the intermediate zwitterions in the formation of β-lactams is a case of asymmetric torquoselectivity. For a previous article in the asymmetric torquoselectivity of the Staudinger reaction, see: Cossío, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085.

(19) Examples: (a) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (b) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586. (c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T *J. Am. Chem. Soc.* **2002**, *124*, 6626. (d) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578. (e) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.

Scheme 4
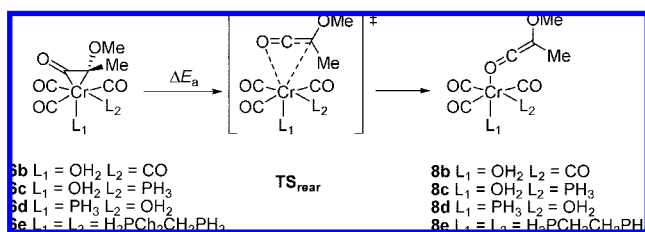
Table 2. Computed Activation Barriers and Reaction Energies (in kcal/mol) for the $6 \rightarrow 8$ Rearrangements[a]

entry	complex	ΔE_a	ΔE_R	r (Cr–C(=O))	Cr–C(=O) bond order
1	**6b**	+10.7	+6.4	2.071	0.52
2	**6c**	+8.3	+6.8	2.039	0.54
3	**6d**	+15.0	+13.9	1.969	0.62
4	**6e**	+21.8	+17.2	2.024	0.57

[a] Cr–C(=O) bond distances (in Å) and corresponding NBO-Wiberg Bond Orders (in a. u.) for complexes **6**. [a] All data have been computed at the B3LYP/6-31G(d)&LanL2DZ-ΔZPVE level.

moderate CO-pressures (90 psi). Thus, the irradiation of complex **3e** and imine **4** in MeCN under 90 psi of CO gave the mixture of *cis–trans-β*-lactams **5** in a 3.8:1 ratio and in 70% isolated yield. The isomers were separated and the compound *cis*-**5** was analyzed by ^{1}H NMR in the presence of Eu(hfc)$_3$. The *e.e.* was 0% within the experimental error, thus confirming that no asymmetric induction was obtained if the metal moiety is removed from the reactive system.

The similarity between the chromium(0) carbine-imine reaction and the classical Staudinger reaction makes difficult to explain the observed discrepancies between the above theoretical model and the experimental results on the basis of the zwitterions ring closure (**INT3**→**5** transformation in Figure 2). Once the presence of the metal during the whole reaction coordinated is clearly confirmed, the 1,3-C to O-chromatropy step, which obviously is not involved in the classical nonmetallic reaction, was re-evaluated (**INT2**→**INT3** transformation in Figure 2). Our previous work[13] assumed that the metallatropy occurred after the initial attack of the imine to the carbonyl of the metallaketene. However, due to the strong acyl-chromate character of species **6b−e**,[10] the 1,3-chromatropy may also occur *before* the imine attack, leading to truly oxygen coordinated ketenes **8b−e** through **TS$_{rear}$** (Scheme 4, Table 2).[20] Once the rearrangement has occurred, the remaining steps of the reaction mechanism should be identical to those proposed in Figure 2. Table 2 compiles the computed activation barriers (ΔE_a) and reaction energies (ΔE_R) for the rearrangement of **6b−e** to **8b−e**. Data in Table 2 show that the values for these rearrangements are similar for complexes **6b-c**, which are the model complexes for the reactive compounds **3a−b**, while the presence of a phosphine *trans-* to the group experiencing the metallatropy (complex **6d**) strongly increases both the activation barrier and the reaction energy ($\Delta\Delta E_a$ = 4.3 kcal/mol and $\Delta\Delta E_R$ = 7.5 kcal/mol respect to **6b**). This increase is even greater if two phosphine groups are present in the complex experiencing the rearrangement as in **6e** ($\Delta\Delta E_a$ = 11.3 kcal/mol and $\Delta\Delta E_R$ = 10.8 kcal/mol respect to **6b**). The computed activation barrier differences fully match the experimentally observed trend of

(20) Interestingly, all the efforts made (including solvent effects and different combinations of functionals/basis sets) to locate the corresponding TS's associated with the attack of imine **9** to **6b**, were fruitless.
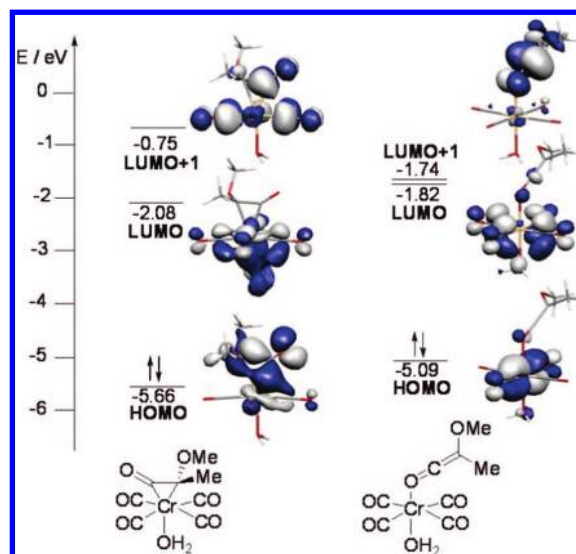

Figure 3. Frontier orbitals energies of complexes **6b** (left) and **8b** (right). All values (in eV) were computed at the B3LYP/LANL2DZ&6-31G(d) level of theory.

conversions of complexes **3** with imine **4** (Table 1). Moreover, this trend may be explained in terms of the strength of Cr−C(=O) bond in complexes **6**: the stronger Cr−C(=O) bond should lead to higher activation barriers. In fact, the computed NBO-Wiberg bond orders (Table 2) agree with this hypothesis. As instance, higher Cr−C(=O) bond orders (and therefore shorter Cr−C(=O) bond lengths) are computed for complexes **6d** and **6e** compared to **6b** and **6c**, which directly reflects the computed higher activation barriers.

From the data in Table 2, it is obvious that the rearrangement depicted in Scheme 4 is slightly endothermic ($\Delta G_{R,298}$ = +3.0 kcal/mol for **6b**→**8b**), therefore one can wonder why the imine reacts preferentially with the oxygen-coordinate **8** and not with the most stable acyl chromate complex **6**. Inspection of the frontier orbitals of both species gives a reasonable explanation for this apparent contradiction. As clearly seen in Figure 3, the HOMO of the imine (centered in the lone-pair of the nitrogen atom) should interact better with the LUMO+1 orbital of both species, which is mainly centered in the former carbene carbon atom and can be considered as the π^*(C=O) molecular orbital. Interestingly, the LUMO+1 of the oxygen−chromium coordinated ketene **8b**, which is practically degenerate to the metal-centered LUMO (ΔE = 0.08 eV), lies ca. 1 eV lower in energy than the reactive LUMO+1 of the acyl chromate **6b**. Therefore, the most favorable HOMO (imine)-LUMO+1 interaction occurs for the truly coordinate ketenes **8** and this constitutes the driving force for the rearrangement proposed in Scheme 4.[21]

Moreover, the NBO-charge analysis carried out on **6b** and **8b** also agrees with the above FMO discussion. As seen from the computed NBO charges (Figure 4), the carbon atom (former carbonyl ligand), which suffers the nucleophilic attack by the nitrogen atom of the imine, bears a more positive charge in **8b** than in **6b** (Δq = + 0.11 au) thus indicating a higher electrophilic character for the oxygen coordinated ketene **8b**.
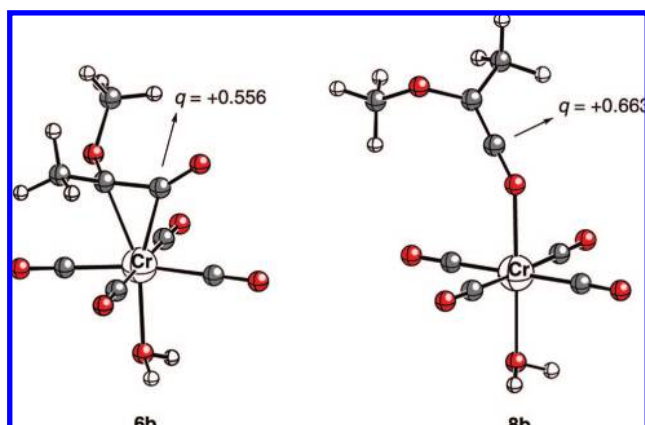
(21) (a) This situation contrasts with the thermally generated chromium(0)- and tungsten(0)ketene imines by the reaction with isonitriles. In this case, the reactive species toward nucleophiles are the corresponding metallacyclopropanoneimines and the 1,2-chromatropic rearrangement from these complexes to N-metal coordinated ketenimines is strongly exothermic. (b) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Organometallics* **2007**, *26*, 3010.

Scheme 5
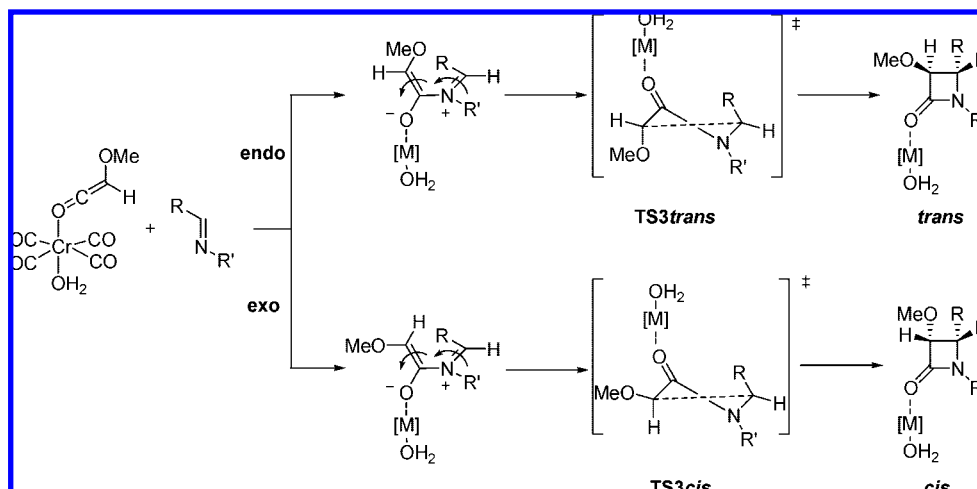
Should metal-coordinated ketenes **8** be the reactive species toward imines, a similar two-step reaction mechanism and identical distribution of products to that obtained with metal free ketenes would be expected. Moreover, the stereochemical outcome of reaction should be biased to the formation of *cis*-β-lactams since we are using the (*E*)-imine **4** and the *exo* approach should be favored. To check this point, we analyzed first the effect of the metal moiety in the four electron conrotatory electrocyclization, (which is subjected to torquoelectronic effects[22] and leads to the β-lactams from the corresponding zwitterions), comparing the process with the classical nonmetallic pathway (Scheme 5). From the computed energy differences between **TS**cis and **TS**trans (Table 3), which form the final *cis*- and *trans*-2-azetidinones respectively, it is obvious that there are not significant differences between metalla- and classical reaction pathways. Thus, the formation of the *cis*-β-lactams is strongly favored in both cases and therefore, it can be concluded that the metal moiety, even when a *cis*-CO ligand is replaced by a σ-donor ligand, has no effect in the outcome of the ring closure of the zwitterionic species.

The above results are not surprising based on the literature evidence.[14] However, our experimental results indicate that Fischer carbene complexes afford a significant amount of *trans*-β-lactams (even up to 1.4:1 *cis/trans* ratio, see entry 5 in Table 1). This fact seems to indicate that the stereochemical discrimination in the metallated reaction should occur in the nucleophilic

Table 3. Computed Energy Differences (in kcal/mol) between the *cis* and *trans* Transition States Leading to the Corresponding β-Lactams through a Conrotatory Ring Closure

| entry	R	R′	$\Delta\Delta E^{\ddagger a}$
	[M] = none		
1	H	H	+15.2
2	Me	Me	+14.4
3	Me	H	+10.8
4	Ph	Me	+12.5
	[M] = Cr(CO)₄		
5	H	H	+12.8
6	Me	Me	+14.3
7	Me	H	+13.7
8	Ph	Me	+13.8
	[M] = Cr(CO)₃L, L= PH₃*cis*		
9	H	H	+9.8
10	Me	H	+12.8

^{a} $\Delta\Delta E^{\ddagger}$ values, computed at the B3LYP/6-31G(d)&LanL2DZ level, have been computed as $\Delta\Delta E^{\ddagger} = E$ (**TS**trans) − E (**TS**cis).

Figure 4. Computed (B3LYP/LANL2DZ&6-31G(d)) NBO-charges of complexes **6b** (left) and **8b** (right).

addition of the imine nitrogen atom to the sp-hybridized carbon atom of the oxygen-coordinated ketene **8** (see Scheme 6). This addition leads to the same zwitterions originally proposed in the mechanism depicted in Figure 2. Thus, the *endo/exo* nucleophilic addition of (*E*)-imine **9** to the complex **8b** was finally computed. The results obtained are summarized in Scheme 6. **TS-***exo* (which is associated with the attack of the imine to the face of the ketene having the alkoxy group and leading to zwitterion **10-***exo*) is 1.48 kcal/mol more stable than TS-*endo*, which forms zwitterion **10-***endo*. This gas-phase free energy difference (computed at 298 K) corresponds to ca. 2.5:1 *exo/endo* ratio in the respective zwitterions and therefore is in nice agreement with the experimentally observed stereochemical outcome of the reaction (Table 1). However, it cannot be discarded that the *trans*-β-lactam is formed from the zwitterion **10-***exo* after isomerization to **10-***endo* followed by ring closure, as recently reported by Xu and co-workers.[23] Additionally, zwitterion **10-***exo,* leading to the corresponding *cis*-β-lactam,

(22) Jefford, C. W.; Bernardelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157.
(23) Jioa, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060.

Scheme 6. Chief Geometric Features of Transition Structures Associated with the Formation of the Two Possible Zwitterions in the Nucleophilic Addition of Imine **9** to Complex **8b**[a]
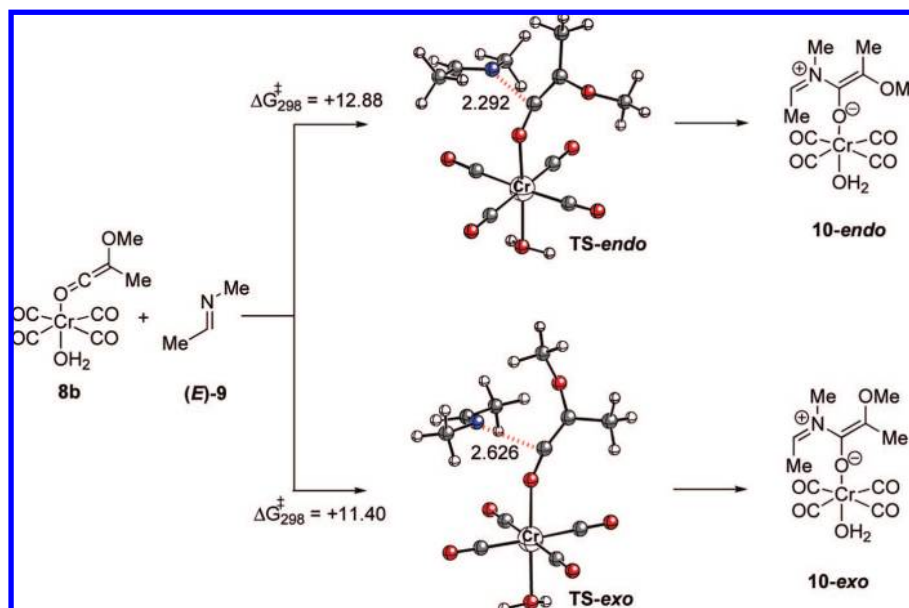
[a] Bond distances are given in Å and free energies (computed at 298 K) in kcal/mol. Unless otherwise stated, white, gray, red, and blue colors denote hydrogen, carbon, oxygen, and nitrogen atoms, respectively. All values were computed at the B3LYP/LANL2DZ&6-31G(d) level.

is 4.87 kcal/mol more stable than its counterpart **10-***endo,* which produces the respective *trans-β*-lactam.

Conclusions

The reaction between a photogenerated chromium—metallacyclopropanone and an imine to form a *β*-lactam occurs in the S$_o$ hypersurface by initial migration of the metal fragment from the former carbene carbon atom to the oxygen. This rearrangement is endothermic but it takes place due to a more favorable HOMO(imine)-LUMO+1(oxygen-coordinated ketene) interaction. The formed metallzwitterions lead to the final products through a four electron conrotatory ring closure (Figure 5). The use of a chiral chromium(0) alkoxycarbene complex produces a low but significant *ee* in the reaction with imines. This result is compatible with the presence of the metallic moiety during the steps leading to the formation of the two new chiral centers at the C3 and C4 positions of the *β*-lactam ring. 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 in the conrotatory electrocyclization step between the classical and the metallated processes leading to the final 2-azetidinones.

Computational Details

All the calculations reported in this paper were obtained with the GAUSSIAN 03 suite of programs.[24] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[25] and the standard 6-31G(d) basis set[26] for hydrogen, carbon, oxygen, nitrogen, and the Hay-Wadt small-core effective core potential (ECP) including a double-ξ valence basis

set[27] for the metal atoms (LanL2DZ keyword). Zero-point vibrational energy (ZPVE) corrections were computed at the B3LYP/LANL2DZ&6-31G(d) level and were not scaled. Reactants and cycloadducts were characterized by frequency calculations[28] and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.[29] The Wiberg bond indices[30] were computed using the natural bond orbital (NBO) method.[31]

Experimental Section

All reactions were carried under argon atmosphere, and all solvents used in this work were purified by distillation and were freshly distilled immediately before use. Tetrahydrofuran (THF) and diethylether (Et$_2$O) were distilled form sodium/benzophenone and dichloromethane (DCM) from calcium hydride. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. Silica gel for flash column cromatography purification of crude mixtures was purchased form Merck (230−400 mesh), and the identification of products was made by thin layer chromatography kieselgel 60F-254). UV light (λ = 254 nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates. NMR spectra were recorded at 22 °C in CDCl$_3$ on Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) or Bruker AM-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C). IR spectra were taken on a Brüker Tensor 27 (MIR 8000−400 cm^{-1}) spectrometer in CHCl$_3$ solution. UV measures were recorded on a Varian (Cary 50) spectrometer. All commercially available products were used without further purification. Complexes **3a**−**d** were prepared following the reported procedure.[13]

(24) Frisch, M. J. *Gaussian 03, Revision C.02*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
(25) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
(26) Hehre, W. J.; Radom, L.; Scheleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; p 76 andreferences therein.

(27) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
(28) McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.
(29) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.
(30) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.
(31) (a) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (b) Reed, A. E.; Weinhold, F. J. *J. Chem. Phys.* **1985**, *83*, 1736. (c) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (d) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
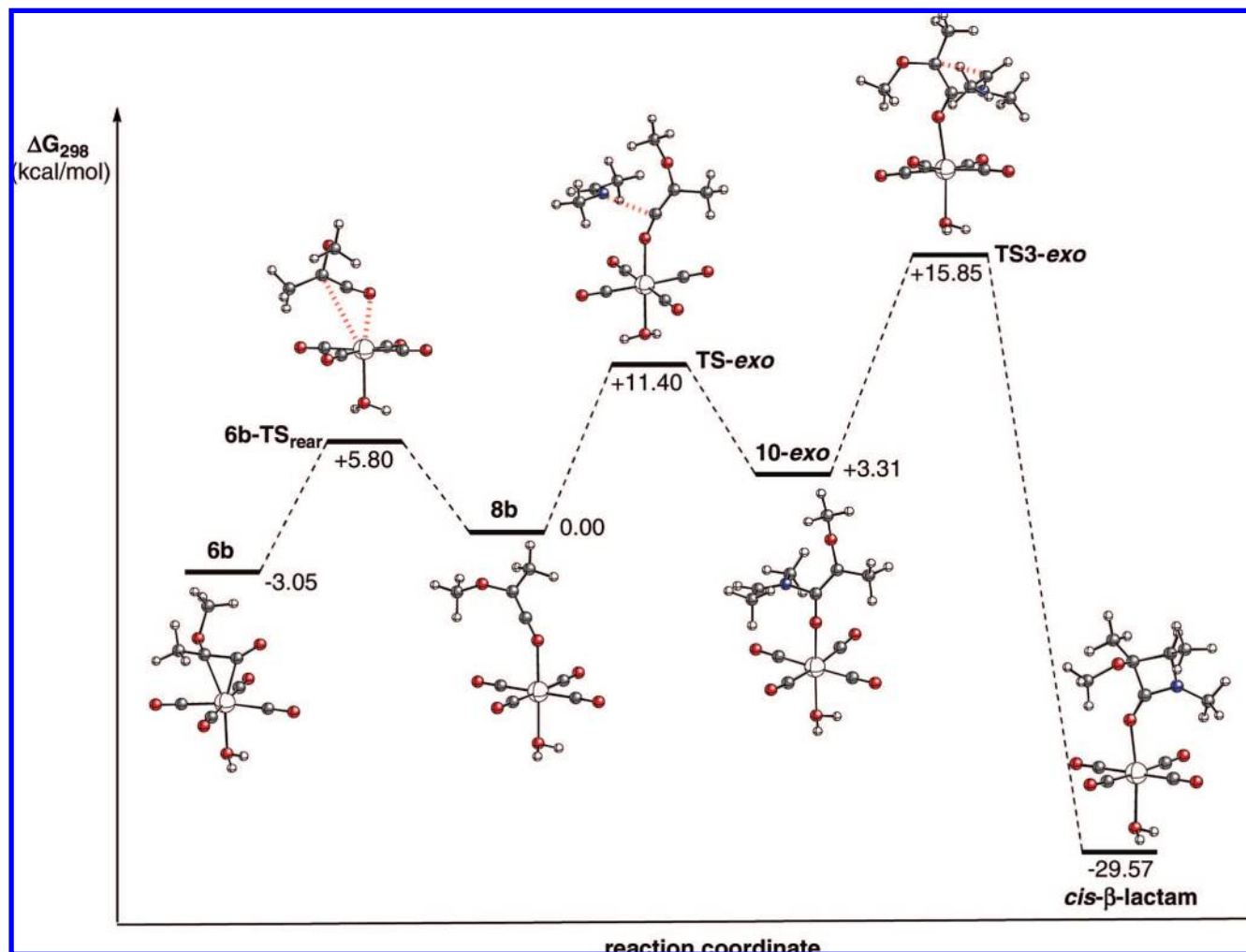
Figure 5. Favored reaction profile from the photochemically generated species **6b** to *cis*-β-lactam by reaction with imine **9**. Relative free energies (298 K) were computed at the B3LYP/LANL2DZ&6-31G(d) level.

Complex 3e. To a solution of 500 mg (4.3 mmol) of (+)-*trans*-(1S,2R)-cyclohexane-diol and 479 mg (4.7 mmol) of triethylamine in 30 mL of dry Et$_2$O at 0 °C were added dropwise 741 mg (4.7 mmol) of P(OEt)$_2$Cl for 15 min.[32] After stirring at this temperature for 15 h, the mixture was filtered on a short pad of Celite. Solvents were removed under reduced pressure and the residue was dissolved in 30 mL of benzene/hexane (1:1). To this solution, 1.14 g (4.3 mmol) of carbene complex **3a** was added and the mixture was heated at reflux overnight. The solvents were then removed under reduced pressure, and the residue was submitted to flash column chromatography (SiO$_2$, Hexane: AcOEt) under argon atmosphere to give 386 mg (19%) of pure **3e**. Spectral data for *cis*-**3e**: ^{1}H NMR (CDCl$_3$) δ: 1.26−1.61 (m, 14 H), 2.06 (m, 2 H), 2.23 (br s, 2 H), 2.93 (s, 3H), 3.68 (m, 2H), 3.94 (m, 4H), 4.89 (q, 2H, $J = 6.95$ Hz); ^{13}C NMR (CDCl$_3$) δ: 14.9, 16.1 (d, $J_{C-P} = 5.1$ Hz), 29.4 (d, $J_{C-P} = 5.9$ Hz), 29.6 (d, $J_{C-P} = 7.6$ Hz), 48.9, 61.4 (d, $J_{C-P} = 8.5$ Hz), 75.5, 81.5 (d, $J_{C-P} = 5.9$ Hz), 82.7 (d, $J_{C-P} = 5.9$ Hz), 219.7 (d, $J_{C-P} = 8.1$ Hz), 219.9 (d, $J_{C-P} = 7.7$ Hz), 223.7, 227.5 (d, $J_{C-P} = 19.3$ Hz), 358.1 (d, $J_{C-P} = 24.0$ Hz). IR (CCl$_4$) 3402 (br), 2071, 2019, 1907. C$_{18}$H$_{29}$CrO$_9$P (472.4), Calcd C, 45.77; H, 6.19; Found C, 45.59; H, 6.06.

Photochemical Reactions. General Procedure. All photochemical reactions were conducted by using a 450W-medium pressure mercury lamp through a Pyrex filter. All the reactions were carried out in the specified solvent, dry and degassed (vacuum-Ar, four

cycles) in a rubber septum-sealed Pyrex tube filled with argon. In a typical experiment a solution of 0.20 mmol of the carbene complex **3** and 42 mg (0.20 mmol) of imine **4** in 20 mL of the indicated solvent was irradiated for 6 h. The solvent was removed *in vacuo* and the residue was dissolved in a mixture of hexane/AcOEt (1:1) and exposed to direct sunlight until a clear solution was obtained. The solution was filtered through a short pad of celite, the solvent eliminated and the isomeric composition of the β-lactam mixture was checked by ^{1}H NMR (see Table 1 in text). The reaction conversion was estimated by integration of well-resolved signals of the imine proton at 8.4 ppm. The isomers ratio was determined by comparison of the signals at 4.85 and 5.01 ppm for compound **5**-*trans* and 4.78 and 5.03 ppm for **5**-*cis*, respectively.[13]

Irradiation of 3a. Following the general procedure a solution of carbene complex **3a** (53 mg, 0.20 mmol) and 42 mg (0.20 mmol) of imine **4** in 20 mL of the corresponding solvent was irradiated. The *cis/trans*-β-lactam **5** ratio was 2.8:1 in MeCN and 1.4:1 in THF.

Irradiation of 3b. Following the general procedure a solution of carbene complex **3b** (100 mg, 0.20 mmol) and 42 mg (0.20 mmol) of imine **4** in 20 mL of the corresponding solvent was irradiated. The *cis/trans*-β-lactam **5** ratio was 7.3:1 in MeCN and 2.5:1 in THF.

Irradiation of 3c. Following the general procedure a solution of carbene complex **3c** (121 mg, 0.20 mmol) and 42 mg (0.20 mmol) of imine **4** in 20 mL of the corresponding solvent was

(32) Cunningham, A. F.; Kuendig, E. P. *J. Org. Chem.* **1988**, *53*, 1823.

irradiated. The *cis/trans-β*-lactam **5** ratio was 3.6:1 in MeCN and 2.3:1 in THF.

Irradiation of 3d. Following the general procedure a solution of carbene complex **3d** (88 mg, 0.20 mmol) and 42 mg (0.20 mmol) of imine **4** in 20 mL of the corresponding solvent was irradiated. The *cis/trans-β*-lactam **5** ratio was 4.5:1 in MeCN and 1.3:1 in THF.

Irradiation of 3e. Following the general procedure a solution of carbene complex **3e** (95 mg, 0.20 mmol) and 42 mg (0.20 mmol) of imine **4** in 20 mL of CH₃CN was irradiated. The *cis/trans-β*-lactam **5** ratio was 4.0:1.

Supporting Information Available: Cartesian coordinates (in Å) and total energies (in a.u., noncorrected zero-point vibrational energies included) of all the stationary points discussed in the text. Complete ref 24. This material is available free of charge via the Internet at http://pubs.acs.org.

JA8024406