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Cycloaddition Reactions

The Photochemical Reaction of Vinylaziridines and Vinylazetidines with Chromium(0) and Molybdenum(0) (Fischer) Carbene Complexes

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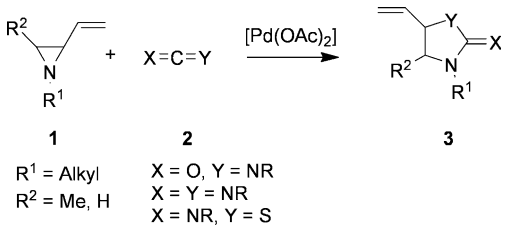
Abstract: The [5+2] and [6+2] cycloaddition reactions of vinylaziridines and vinylazetidines with ketenes generated photochemically from chromium(0) and molybdenum(0) Fischer carbene complexes have been investigated. These processes constitute a straightforward and efficient route to azepanones and azocinones, respectively. The peculiar electronic properties of the metalated ketenes allow for the introduction of electron-rich substituents in the final cycloadducts, a difficult task using conventional organic chemistry procedures. The versatility of the process is demonstrated by using Cr^0 Fischer bis(carbene) complexes as metalated bis(ketene) precursors. These species produce tethered bis(azepanone)s in a single step under mild reaction conditions. Density functional theory calculations point to a stepwise reaction pathway through the initial nucleophilic attack of the nitrogen atom of the aziridine on the metalated ketene, followed by ring closure of the zwitterionic intermediate formed.

Introduction

The ring-opening reaction of vinyl-substituted three- and four-membered nitrogen heterocycles with cumulenes has been little studied despite their potential to produce medium-sized rings in an easy and efficient manner.[1] This contrasts with the use of the strained nature of these cyclic amines to prepare other classes of compounds in reactions involving the cleavage of the C–N bond.[2] For example, Alper and co-workers reported the first examples of a reaction involving 2-vinylaziridines and isocyanates, isothiocyanates, and carbodiimides.[3] Thus, the reactions of a series of vinylaziridines **1** with cumulenes **2** under Pd catalysis yielded the corresponding five-membered heterocycles **3** in acceptable to excellent yields (Scheme 1). Aggarwal and co-workers have reported a similar transformation[4] in the Pd-catalyzed insertion of CO_2 into a vinylaziridine. However, it should be noted that in both cases the double bond is not incorporated into the final five-membered ring.[5]

The simultaneous participation of the double bond of a vinylaziridine with the concomitant three-membered ring opening has been used to develop synthetically useful routes to the azepane skeleton. For instance, the reaction of these substrates with electron-poor alkynes leads to a seven-membered ring through a divinylcyclopropane–cycloheptadiene-type rearrangement.[6] Moreover, phenyl isothiocyanate and very recently sulfonyl isocyanates have been employed as C2 units in formal [5+2] cycloaddition reactions with 2-vinylaziridines to smoothly produce 1,3-thiazepine derivates[7] and various cyclic ureas,[8] respectively (Scheme 2a and b). It is remarkable that in these cases the cycloaddition processes occurred at 0 °C and in the absence of metal catalysts. A similar methodology was previously reported by the same authors in the ring-expansion reaction of vinylazetidines with electron-deficient isocyanates (in a formal [6+2] cycloaddition reaction).[9]



Scheme 1. The reactions of vinylaziridines and cumulenes under Pd catalysis.

Despite the efficiency of the aforementioned processes, the cycloaddition reaction with vinylaziridines or vinylazetidines is restricted to electron-deficient cumulenes, limiting the scope of this synthetically valuable transformation. Therefore, the use of substrates with electron-donor substituents in their structures is an unfulfilled challenge. At this point, we turned our attention to the ability of Group 6 Cr^0 and Mo^0 Fischer-type carbene complexes to form electron-rich metalated ketenes when irradiated in the presence of visible light.[10] These species are able to produce a wide variety of reaction products in the presence of nucleophiles, avoiding the main shortcomings

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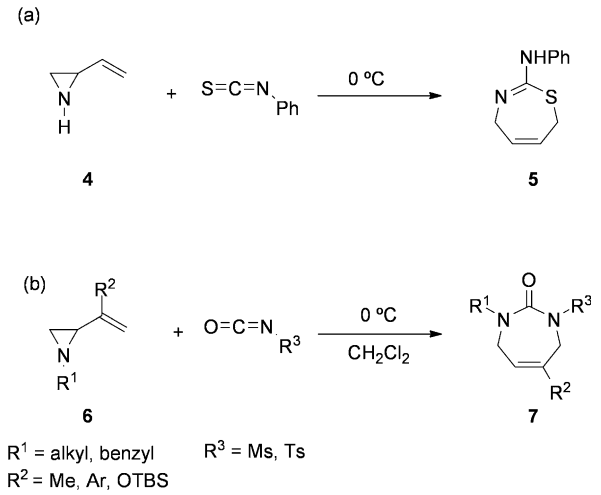
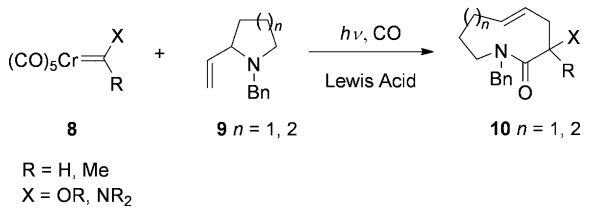
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302029. It contains experimental procedures, compound characterization data, Cartesian coordinates, and total energies of all computed stationary points and copies of the ^1H and ^{13}C NMR spectra of the new species prepared.



Scheme 2. Formal [5+2] cycloaddition reactions of 2-vinylaziridines.



Scheme 3. Photochemical reactions of 2-vinylpyrrolidines and -piperidines with Cr^0 carbene complexes.

of ketenes, that is, dimerization and the formation of undesired adducts.

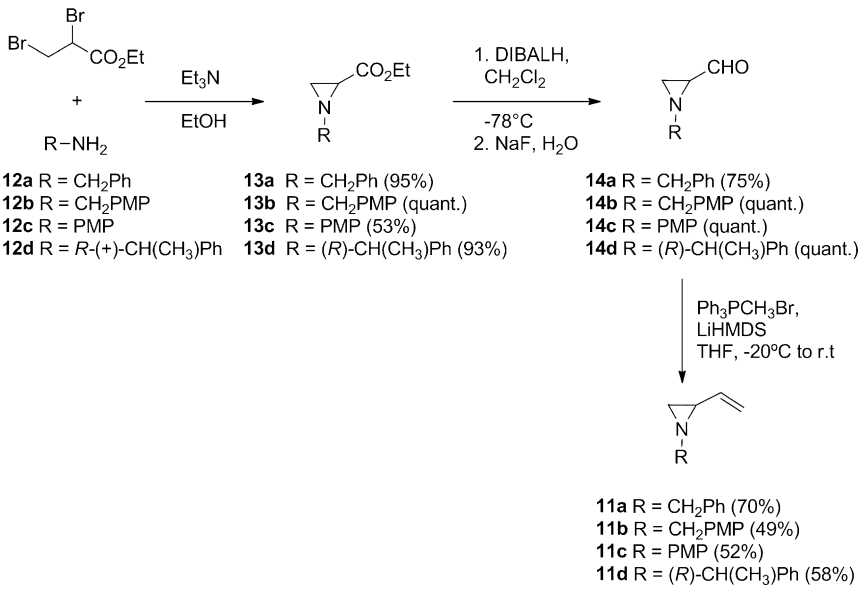
Interestingly, the reactions of photochemically generated ketenes from Cr^0 Fischer carbene complexes **8** and 2-vinylpyrrolidines or -piperidines **9** has been reported (Scheme 3).[11] The final products, ten- or eleven-membered-ring amides **10**, were obtained in acceptable to good yields in the presence of a Lewis acid. The formation of these cyclic compounds was thought to occur through a Malherbe–Bellus variant of the Claisen rearrangement.[12] Based on this report, we speculated that this type of electron-rich ketene may serve as a C2 unit in [5+2] or [6+2] cycloaddition reactions with vinylaziridines or vinylazetidines, respectively. Herein, the successful accomplishment of this hypothesis, which allows rapid access to azepanones and azocinones, shall be described. In addition, the extension of this reaction to bis(carbene) complexes, as well as the elucidation of the corresponding reaction mechanism by means of computational methods, will be reported.

Results and Discussion

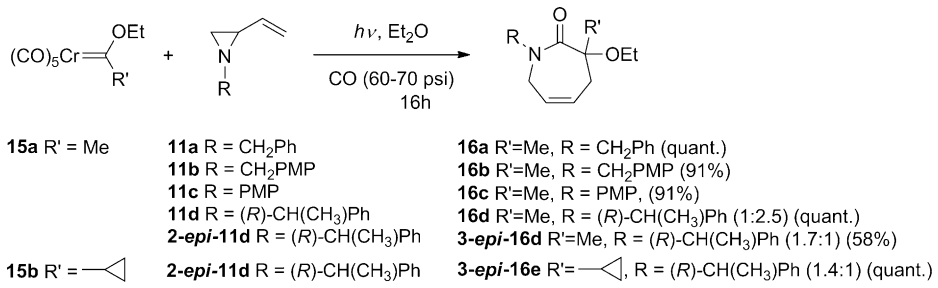
Aziridines **11** were prepared in moderate to quantitative yields by using a standard methodology, that is, reacting ethyl 2,3-dibromopropionate with amines **12** in EtOH as the solvent and in the presence of Et_3N (Scheme 4). Reduction of aziridine esters **13** to the corresponding aldehydes **14** occurred in the presence of DIBALH (diisobutylaluminium hydride) in CH_2Cl_2 at $-78\,^{\circ}C$, followed by quenching with an aqueous solution of NaF. Finally, a Wittig reaction with the $Ph_3P{=}CH_2$ ylide results in the desired vinylaziridines **11**.

Irradiation (450 W medium pressure Hg lamp, pyrex filter and pyrex well) of a mixture of pentacarbonyl[(ethoxy)-(methyl)carbene]chromium(0) (**15a**) and aziridine **11a** (1.2:1 molar ratio) in Et_2O under 60–70 psi of CO yielded *N*-benzyl-3,4-dihydroazepin-2-one (**16a**) in quantitative yield (Scheme 5).[13] Thus, it became clear that the envisioned formal [5+2] cycloaddition reaction is indeed possible, allowing for the introduction of electron-donor substituents in the azepinone skeleton. Moreover, this transformation proceeds smoothly at room temperature in the absence of Lewis acid additives, which contrasts with the related process involving 2-vinylpyrrolidines.[11]

The reaction was then extended to 2-vinylaziridines **11b** and **11c**, which yielded 3-ethoxyazepinones **16b** and **16c** in excellent yields. The introduction of chiral, enantiomerically pure diastereomeric aziridines **11d** and 2-*epi*-**11d**[14] formed the corresponding ethoxyazepinones **16d** and 3-*epi*-**16d** with excellent yields and as an inseparable mixture of diastereomers. As expected, the diastereoselectivity of the reaction was poor (1:2.5) and was inverted for **11d** with respect to 2-*epi*-**11d**, with the major product of the reaction of **11d** being the minor product in the reaction of 2-*epi*-**11d** (ratio 1.7:1). Clearly, the stereochemical outcome of the reaction is controlled by the



Scheme 4. Synthesis of 2-vinylaziridines **11**.



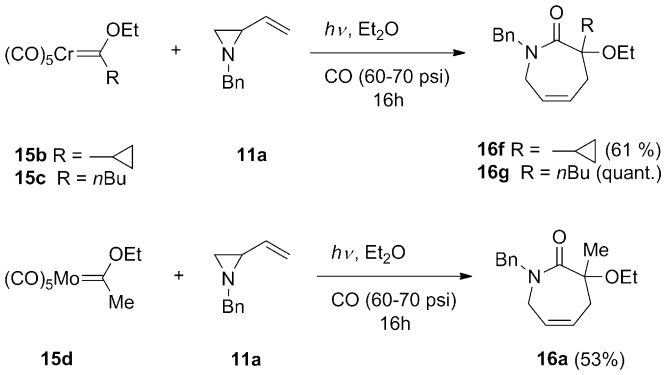
Scheme 5. Photochemical reactions of 2-vinylaziridines and Cr^0 Fischer carbenes.

stereochemistry of the vinylaziridine chiral center, with the exocyclic chiral center as a spectator. Unfortunately, the spectroscopic data are inconclusive with regard to the stereochemistry of the adduct **16d**. Furthermore, we were not able to grow crystals of any of the diastereomers of **16d** and, therefore, the stereochemistry of cycloadducts **16d** remains unknown. A similar result was obtained in the reaction of **15b** and 2-*epi*-**11d**, which yielded 3-*epi*-**16e** as a mixture of diastereomers also with low selectivity (1.4:1; Scheme 5).

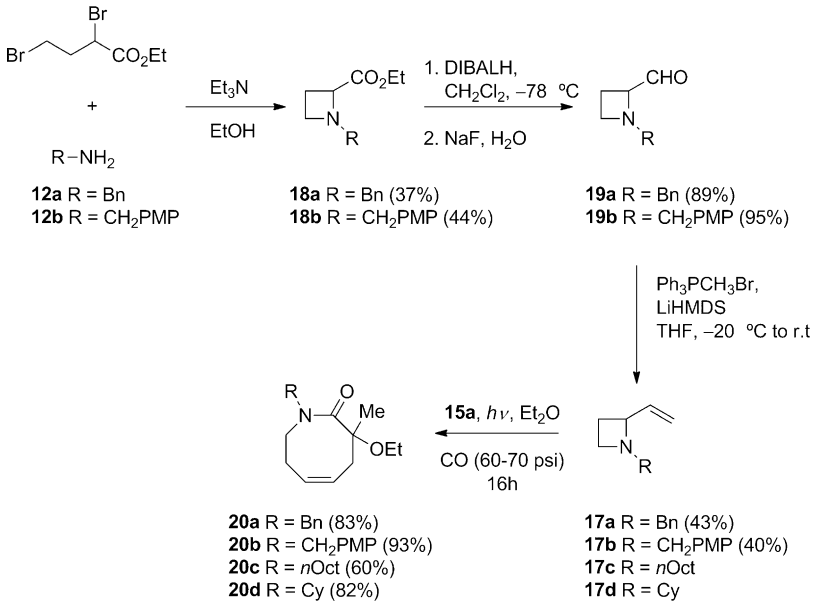
Complexes **15b** and **15c** also reacted smoothly with vinylaziridine **11a** (1.2:1 molar ratio), yielding the expected ethoxyazepinones **16f** and **16g** in 61% and quantitative yields, respectively (Scheme 6). It is noteworthy that the diastereoselectivity of the reactions between complexes **15a** and **15b** and 2-*epi*-**11d** were nearly identical, independent of the introduction of a bulky cyclopropyl group in complex **15b** compared to a methyl group in **15a**. In addition, the reaction was also extended to molybdenum(0) carbene complex **15d**, which formed the azepinone **16a** in 53% yield. This result is not surprising because of the known lower reactivity of Mo^0 carbene complexes compared to their Cr^0 counterparts in the photocarbonylation reaction.[15]

Vinylazetidines **17** were tested next. These species were prepared following a similar procedure to that described above for the synthesis of vinylaziridines **11**. Thus, ethyl 2,4-dibromobutanoate was converted into the corresponding azetidine esters **18** by reaction with amines **12**. Compounds **18** were transformed into aldehydes **19** (DIBALH) and finally, into vinylazetidines **17** through Wittig methylenation with the $Ph_3P{=}CH_2$ ylide (Scheme 7). The photochemical reactions of azetidines **17** and chromium(0) carbene complex **15a** formed the corresponding eight-membered-ring tetrahydroazocin-2-ones **20a–d** in good to excellent yields through a formal [6+2] cycloaddition reaction. These results clearly indicate that the reactivity of Fischer carbene complexes in these cycloaddition reactions is compatible with three- and four-membered rings supporting the vinyl group (Scheme 7).

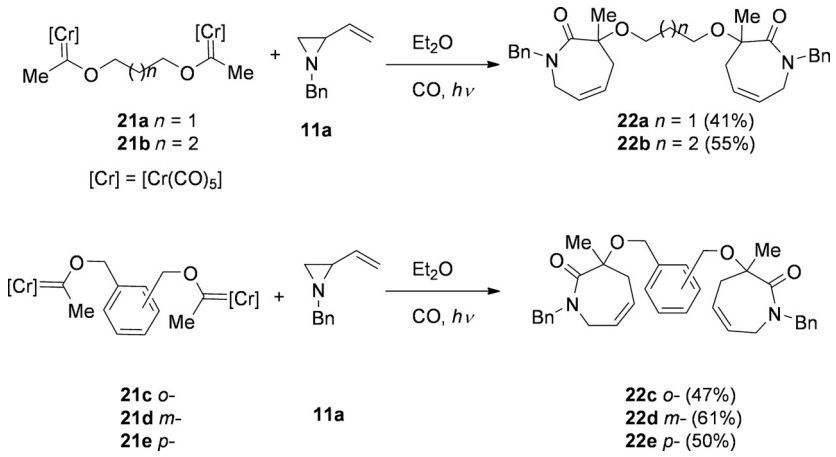
The reaction of thermally generated electron-rich, nonmetalated ketenes and vinylaziridine **11a** was also tested to assess the need to use ketenes derived from Fischer carbene complexes. To this end, the alkoxyketene derived from the reaction of phenyloxyacetyl chloride and Et_3N and the phenylketene derived from phenylacetyl chloride and Et_3N were prepared. In both cases, conditions to ensure the generation of the ketenes[16] ($-78\,^{\circ}C/CH_2Cl_2$, addition of Et_3N to a solution of the acid chloride) were used. Both nonmetalated ketenes afford complex reaction mixtures in their reactions with vinylaziridine **8a** instead of the clean, crude products observed when using Fischer car-



Scheme 6. Reactions of Cr^0 and Mo^0 carbene complexes and N-benzyl-2-vinyl aziridines.



Scheme 7. The synthesis of 2-vinylazetidines.



Scheme 8. The reactions of Cr^0 bis-carbene complexes with 2-vinylaziridines to yield bis(azepinones).

bene complex derived ketenes. This marked difference with respect to the reactions involving Fischer carbene complexes clearly illustrates the difficulties associated with the introduction of electron-donor substituents in the ketene, which can be easily overcome when using metalated ketenes generated by photocarbonylation of Fischer carbene complexes.

The efficiency of the aforementioned cyclization reactions led us to assess the reaction of chromium(0) bis(carbene) complexes **21a–e** and vinylaziridine **11a** to produce bis(azepinone)s. Thus, irradiation of bis(carbene) complexes **21** with **11a** in the same reaction conditions used for the mononuclear Fischer carbene complexes (1:2 molar ratio) afforded alkoxy-tethered bis(azepinone)s **22a–e** in moderate to good (41–61%) yields. Complexes having aliphatic (**21a** and **21b**) and aromatic (**21c–e**) tethers were compatible with the transformation (Scheme 8). Bis(azepinone)s **22** resulted from a double formal [5+2] cycloaddition reaction and were always obtained as inseparable diastereomeric mixtures. Both the ^1H and ^{13}C NMR spectra of compounds **22** show splitting of significant signals, especially those corresponding to the Me groups, which confirm the formation of the racemic (*RR*/*SS*) and *meso* (*RS*) forms. No appreciable selectivity was observed. This process is a single reaction step route to bis(azepinone)s, which are difficult to obtain by conventional organic chemistry procedures.

Finally, the reaction mechanism of the above-discussed cycloaddition reactions was studied by using density functional theory (DFT) calculations at the PCM(Et_2O)-B3LYP/def2-SVP level.[17] The corresponding computed reaction profiles of the metalated ketene **23** (generated by photocarbonylation of a pentacarbonyl[(methoxy)(methyl)carbene]chromium(0) complex following the reaction pathway previously reported by us)[10d] with the model vinylaziridine **11M**, to produce the [5+2] cycloadduct **16M**, are shown in Figure 1 (which gathers the respective free energies, at 298 K, in Et_2O).

As can be readily seen in Figure 1, our calculations suggest that the process begins with nucleophilic attack of the nitrogen atom of aziridine at the highly electrophilic carbonyl carbon atom of metalaketene **23**. This reaction leads to the zwitterionic complex **INT1-a** through **TS1**, a saddle point associated with the formation of the C–N single bond (activation barrier of 13.3 kcal mol^{-1}). Complex **INT1-a** rapidly isomerizes into zwitterion **INT1-b**, which is then able to undergo a ring-closing reaction to form the seven-membered-ring species **INT2**. This step occurs via the highly asynchronous transition state **TS2**,[18] which is associated with the formation of the new C–C bond with concomitant aziridine ring opening (i.e., C–N bond breaking). This process proceeds with a very low activation barrier ($\Delta G_{a,298} = 3.9$ kcal mol^{-1}) in a highly exergonic transformation ($\Delta G_{298} = -61.6$ kcal mol^{-1}), which clearly reflects the ease of this reaction step. Subsequent decoordination of the {$Cr(CO)_5$} fragment by use of CO or a molecule of coordinating solvent (Et_2O)[19] releases the final cycloadduct **16M**. Alternatively, the decoordination reaction may occur prior to the final ring closure in the metalated zwitterion **INT1-b**, producing **INT1-c**. Indeed, zwitterion **INT1-c** can also undergo a similar, facile ring-closure step (with an activation barrier of 5.4 kcal mol^{-1} and reaction energy of -72.9 kcal mol^{-1}) to produce the seven-membered-ring compound **16M** through the highly asynchronous transition state **TS2-c**.

From this computational study, it can be concluded that the [5+2] cycloaddition reaction between aziridines and metalated ketenes occurs stepwise in a process that resembles the [2+2] cycloaddition of these metalated ketenes with imines,[10d] that is, a process which involves the initial nucleophilic attack of the nitrogen atom followed by ring closure of the zwitterionic intermediate formed.

Conclusion

From the joint experimental and computational study reported herein, the following conclusions can be drawn: 1) Metalated ketenes, photochemically generated from Fischer carbene complexes, react with vinylaziridines and vinylazetidenes to produce azepanones and azocinones, respectively, with high to excellent reaction yields. 2) The peculiar electronic properties of these metalated ketenes allow the introduction of electron-rich substituents in the final reaction products. This constitutes a marked difference from the reported procedures, which are restricted to the use of electron-poor cumulenes. 3) These transformations, which can be viewed as formal [5+2] or [6+2] cycloaddition reactions, are compatible with chromium(0) Fischer bis(carbene) complexes as metalated ketene precursors, producing tethered bis(azepanone)s in a single step under mild reaction conditions. 4) DFT calculations suggest that the transformation occurs stepwise through the initial nucleophilic attack of the nitrogen atom of the aziridine at the

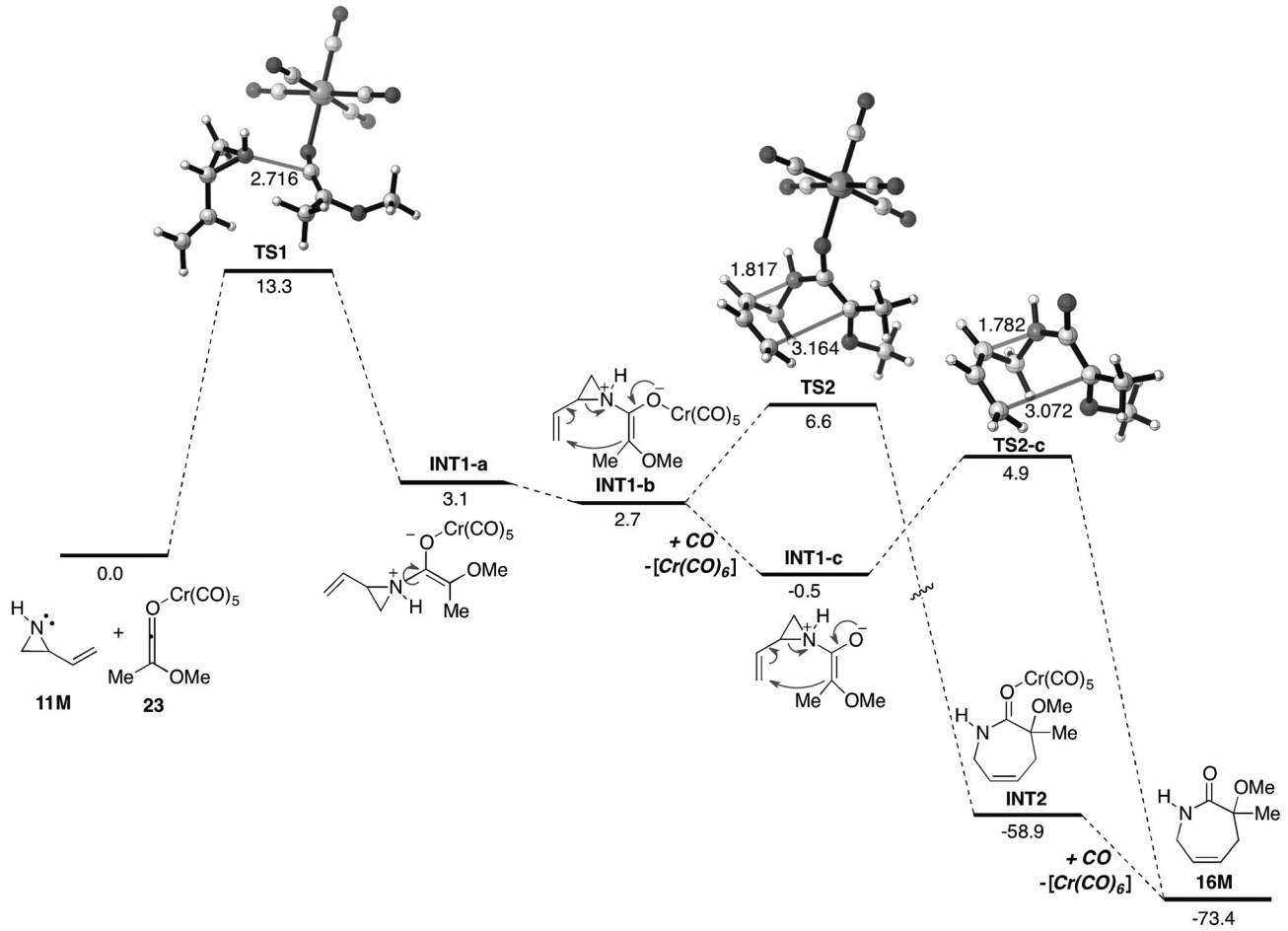


Figure 1. Computed reaction profile of metalated ketene **23** and vinylaziridine **11 M**. Relative free energy values (computed at 298 K) and bond lengths are given in kcal mol^{-1} and Å, respectively. All data have been computed at the PCM(Et_2O)-B3LYP/def2-SVP level.

metalated ketene, followed by ring closure of the zwitterionic intermediate thus formed. This reaction mechanism resembles that proposed for the [2+2] cycloaddition reaction of these metalated ketenes and imines.[10d]

Experimental Section

General: All reactions were carried out under an argon atmosphere. All solvents used in this work were purified by distillation and were freshly distilled immediately before use. Triethylamine (Et_3N) was distilled from calcium hydride, whereas diethyl ether (Et_2O) was purified by using a Pure Solv PS-MD-5 system. Flame-dried glassware was used for moisture-sensitive reactions. Silica gel (Merck: 230–400 mesh) was used as the stationary phase for purification of crude reaction mixtures by flash column chromatography under Ar pressure. Identification of products was made by thin-layer chromatography (Kieselgel 60F-254). UV light ($\nu = 254$ nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates. NMR spectra were recorded at 25 °C in $CDCl_3$, on a Bruker Avance 300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are given in ppm relative to $CDCl_3$ (^1H, $\delta = 7.27$ ppm and ^{13}C, $\delta = 77.0$ ppm). IR spectra were taken on an MIR (8000–400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent using the attenuated total reflectance (ATR) technique. MS spectra (HRMS) were acquired on a Fourier transform ion cyclone resonance mass spectrometer (4.7 T). Chromium carbene complexes **15** and **21**[20] were prepared by following previously reported procedures. Azetidines **17 c** and **17 d** were prepared according to reported procedures.[9b]

General procedure for the photochemical cycloaddition reactions: Photoreactions were carried out in oven-dried pressure tubes that were charged with the carbene complex **15** and the corresponding vinylaziridine **11** or vinylazetidine **18** (1.2:1 molar ratio) and dry, degassed Et_2O (3 freeze–pump–thaw cycles). The tube was fitted with a pressure head, purged three times with CO, and irradiated under CO (60–70 psi; medium pressure mercury lamp 450 W, pyrex filter and pyrex well) for 16 h. The solvent was removed under vacuum, the residue was taken up in hexane/EtOAc (1:1), and exposed to light to oxidize the remaining metal(0) compounds. The resulting mixture was filtered through Celite and the solvent was removed under vacuum to obtain the desired dihydroazepinones **16 a**–**f** (from vinylaziridines **11**) or the desired tetrahydroazocinones **20 a**–**b** (for vinylazetidines **18**).

1-Benzyl-3-ethoxy-3-methyl-3,4-dihydroazepinone (16 a): Following the general procedure, from carbene complex **15 a** (66 mg, 0.25 mmol) and vinylaziridine **11 a** (33 mg, 0.21 mmol), dihydroazepinone **16 a** was obtained as an orange oil (54 mg, quantitative yield, 53% when using carbene complex **15 d**). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.21 (m, 5H), 5.71–5.53 (m, 2H), 4.73–4.61 (m, 2H),

4.61–4.51 (m, 1H), 3.71–3.50 (m, 3H), 3.40–3.29 (m, 2H), 2.49–2.50 (m, 2H), 1.52 (s, 3H), 1.22 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.7$, 138.1, 128.9, 128.1, 127.9, 127.6, 125.2, 80.9, 59.9, 53.5, 47.0, 38.7, 23.6, 16.4 ppm; IR (ATR): $\tilde{\nu}=3027$, 2975, 2928, 1641, 1478, 1449, 1418, 1234 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}NO_2$: 259.1567 $[M]^+$; found: 259.1572.

3-Ethoxy-1-(4-methoxybenzyl)-3-methyl-3,4-dihydroazepinone (16b): Following the general procedure, from carbene complex **15a** (100 mg, 0.38 mmol) and vinylaziridine **11b** (60 mg, 0.32 mmol), dihydroazepinone **16b** was obtained as a yellow oil (83 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.17$ (d, $J=8.5$ Hz, 2H), 6.83 (d, $J=8.5$ Hz, 2H), 5.68–5.49 (m, 2H), 4.59 (s, 2H), 4.55–4.44 (m, 1H), 3.78 (s, 3H), 3.69–3.56 (m, 1H), 3.39–3.27 (m, 2H), 2.54–2.39 (m, 2H), 1.50 (s, 3H), 1.19 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.6$, 159.2, 130.2, 129.5, 127.8, 125.2, 114.2, 80.9, 59.9, 55.6, 52.8, 46.7, 38.7, 23.5, 16.3 ppm; IR (ATR): $\tilde{\nu}=2973$, 2928, 1638, 1511, 1476, 1444, 1394, 1349, 1301, 1242, 1172, 1104, 1060, 822, 639 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}NO_3$: 290.1751 $[M+H]^+$; found: 290.1747.

3-Ethoxy-1-(4-methoxyphenyl)-3-methyl-3,4-dihydroazepinone (16c): Following the general procedure, from carbene complex **15a** (100 mg, 0.38 mmol) and vinylaziridine **11c** (55 mg, 0.315 mmol), dihydroazepinone **16c** was obtained as a yellow oil (79 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.09$ (dd, $J=8.6$, 1.5 Hz, 2H), 6.88 (dd, $J=8.6$, 1.6 Hz, 2H), 5.90–5.66 (m, 2H), 5.07–4.95 (m, 1H), 3.80 (s, 3H), 3.77–3.69 (m, 2H), 3.59–3.47 (m, 1H), 2.65–2.47 (m, 2H), 1.51 (s, 3H), 1.33 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.6$, 158.3, 139.3, 128.4, 127.7, 125.3, 114.6, 81.0, 60.0, 55.8, 50.8, 38.8, 23.3, 16.4 ppm; IR (ATR): $\tilde{\nu}=2975$, 2932, 2839, 1653, 1508, 1455, 1400, 1370, 1327, 1294, 1243, 1059, 1032, 828, 636 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}NO_3$: 276.1594 $[M+H]^+$; found: 276.1600.

3-Ethoxy-3-methyl-1-[(*R*)-1-phenylethyl]-3,4-dihydroazepinone, from 11d (16d and 3-*epi*-16d): Following the general procedure, from carbene complex **15a** (43 mg, 0.16 mmol) and vinylaziridine **11d** (23 mg, 0.13 mmol), an inseparable mixture of dihydroazepinone **16d** and 3-*epi*-**16d** (1:2.5) was obtained as a yellow oil (35 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$; m/M, 1:2.5): $\delta=7.42$–7.20 (m, 10H), 6.25–5.98 (m, 2H), 5.85–5.62 (m, 1H; M), 5.65–5.50 (m, 1H; M), 5.56–5.42 (m, 1H; m), 5.40–5.30 (m, 1H; m), 4.37–4.25 (m, 1H; m), 4.21–4.04 (m, 1H; M), 3.79–3.59 (m, 2H), 3.48–3.26 (m, 2H), 3.16 (dd, $J=16.7$, 7.5 Hz, 1H; m), 3.07 (dd, $J=17.3$, 7.6 Hz, 1H; M), 2.59–2.41 (m, 4H), 1.55 (s, 3H; M), 1.54 (s, 3H; m), 1.50 (d, $J=7.0$ Hz, 3H; m), 1.46 (d, $J=7.0$ Hz, 3H; M), 1.25 (t, $J=7.0$ Hz, 3H; m), 1.17 ppm (t, $J=7.0$ Hz, 3H; M); ^{13}C NMR (75 MHz, $CDCl_3$; m/M, 1:2.5): $\delta=173.5$ (m), 173.3 (M), 141.3 (M), 141.1 (m), 128.8, 128.6, 128.2, 127.6, 127.5, 126.0 (M), 125.6 (m), 81.2 (M), 81.0 (m), 60.2 (M), 59.9 (m), 52.6 (M), 52.6 (m), 41.3 (m), 41.2 (M), 39.1 (M), 38.8 (m), 23.8 (m), 23.7 (M), 16.6 (m), 16.4 (M+m), 16.3 ppm (M); IR (ATR): $\tilde{\nu}=3025$, 2975, 2934, 2901, 1635, 1466, 1415, 1370, 1254, 1205, 1173, 1104, 1060, 920, 828, 778, 743, 700, 648 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NNaO_2$: 296.1621 $[M+Na]^+$; found: 296.1619.

3-Ethoxy-3-methyl-1-[(*R*)-1-phenylethyl]-3,4-dihydroazepinone, from 2-*epi*-11d (16d and 3-*epi*-16d): Following the general procedure, from carbene complex **15a** (57 mg, 0.22 mmol) and vinylaziridine 2-*epi*-**11d** (31 mg, 0.18 mmol), an inseparable mixture of dihydroazepinone **16d** and 3-*epi*-**16d** (1.7:1) was obtained as a yellow oil (29 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$; M/m, 1.7:1): $\delta=7.39$–7.23 (m, 10H), 6.21–6.05 (m, 2H), 5.80–5.67 (m, 1H; m), 5.66–5.54 (m, 1H; m), 5.54–5.45 (m, 1H; M), 5.41–5.31 (m, 1H; M), 4.38–4.26 (m, 1H; M), 4.19–4.06 (m, 1H; m), 3.77–3.60 (m, 2H), 3.44–3.28 (m, 2H), 3.17 (dd, $J=16.8$, 7.7 Hz, 1H; M), 3.12–3.02 (m, 1H; m), 2.55–2.44 (m, 4H), 1.55 (s, 3H; m), 1.54 (s, 3H; M), 1.51 (d, $J=7.0$ Hz, 3H; M), 1.47 (d, $J=7.0$ Hz, 3H; m), 1.26 (t, $J=7.0$ Hz, 3H; M), 1.18 ppm (t, $J=7.0$ Hz, 3H; m); ^{13}C NMR (75 MHz, $CDCl_3$; M/m, 1.7:1): $\delta=173.2$ (M), 173.1 (m), 141.0 (m), 140.8 (M), 128.6, 128.4, 127.9, 127.5,127.4, 127.3, 127.2, 125.7 (m), 125.3 (M), 81.0 (m), 80.8 (M), 59.9 (m), 59.6 (M), 52.4 (M+m), 41.0 (M), 40.9 (m), 38.8 (m), 38.6 (M), 23.5 (M), 23.5 (m), 16.4 (M), 16.1 (M), 16.1 (m), 16.0 ppm (m); IR (ATR): $\tilde{\nu}=3026$, 2975, 2934, 2901, 1634, 1464, 1415, 1369, 1318, 1205, 1103, 1056, 828, 779, 753, 699, 647 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NNaO_2$: 296.1621 $[M+Na]^+$; found: 296.1618.

3-Cyclopropyl-3-ethoxy-1-[(*R*)-1-phenylethyl]-3,4-dihydroazepinone, from 2-*epi*-11d (16e and 3-*epi*-16e): Following the general procedure, from carbene complex **15b** (80 mg, 0.28 mmol) and vinylaziridine 2-*epi*-**11d** (40 mg, 0.23 mmol), an inseparable mixture of dihydroazepinone **16d** and 3-*epi*-**16d** (1.4:1) was obtained as a green oil (69 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$; M/m, 1.4:1): $\delta=7.36$–7.25 (m, 5H), 6.23–6.07 (m, 1H), 5.74–5.33 (m, 2H), 4.35–4.04 (m, 1H), 3.97–3.40 (m, 2H), 3.27–3.06 (m, 1H), 2.25–1.86 (m, 2H), 1.78–1.68 (m, 1H), 1.55–1.43 (m, 3H), 1.29–1.17 (m, 3H), 0.78–0.46 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.7$, 173.5, 141.3, 141.1, 128.8, 128.6, 127.7, 127.6, 127.5, 127.3, 126.9, 126.0, 125.7, 82.1, 81.9, 77.9, 59.8, 59.6, 52.8, 52.7, 41.6, 32.2, 31.9, 17.0, 16.8, 16.6, 16.4, 16.2, 4.6, 4.5 ppm; IR (ATR): $\tilde{\nu}=3017$, 1639, 1496, 1061, 730 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{26}NO_2$: 300.1958 $[M+H]^+$; found: 300.1964.

1-Benzyl-3-cyclopropyl-3-ethoxy-3,4-dihydroazepinone (16f): Following the general procedure, from carbene complex **15b** (46 mg, 0.16 mmol) and vinylaziridine **11a** (21 mg, 0.13 mmol), dihydroazepinone **16e** was obtained as a colorless oil (22 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.22 (m, 5H), 5.70–5.52 (m, 2H), 4.76–4.63 (m, 2H), 4.57–4.46 (m, 1H), 3.93–3.83 (m, 1H), 3.47–3.36 (m, 2H), 2.24–1.96 (m, 2H), 1.74–1.63 (m, 1H), 1.23 (t, $J=7.0$ Hz, 3H), 0.77–0.67 (m, 1H), 0.65–0.48 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.9$, 138.2, 128.9, 128.2, 127.6, 127.0, 125.4, 81.8, 59.7, 53.7, 47.4, 31.9, 16.8, 16.3, 4.4, 1.0 ppm; IR (ATR): $\tilde{\nu}=3084$, 3032, 2974, 2920, 1643, 1476, 1450, 1350, 1230, 1167, 1089, 840, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{23}NNaO_2$: 308.1626 $[M+Na]^+$; found: 308.1626.

1-Benzyl-3-butyl-3-ethoxy-3,4-dihydroazepinone (16g): Following the general procedure, from carbene complex **15c** (100 mg, 0.32 mmol) and vinylaziridine **11a** (42 mg, 0.26 mmol), dihydroazepinone **16f** was obtained as a colorless oil (73 mg, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.34$–7.22 (m, 5H), 5.69–5.55 (m, 2H), 4.73 (d, $J=14.9$ Hz, 1H), 4.64–4.54 (m, 2H), 3.55–3.46 (m, 1H), 3.39–3.25 (m, 2H), 2.60 (dt, $J=18.6$, 3.6 Hz, 1H), 2.38–2.27 (m, 1H), 2.20–2.08 (m, 1H), 1.81–1.72 (m, 1H), 1.42–1.33 (m, 4H), 1.22 (t, $J=7.0$ Hz, 3H), 0.95 ppm (t, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.9$, 138.2, 128.9, 128.2, 127.7, 127.59, 125.33, 82.3, 59.2, 53.6, 47.1, 35.3, 34.1, 25.4, 23.6, 16.1, 14.6 ppm; IR (ATR): $\tilde{\nu}=3026$, 2957, 2827, 2869, 1642, 1475, 1450, 1417, 1232, 1166, 1106, 804, 730, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{27}NNaO_2$: 324.1939 $[M+Na]^+$; found: 324.1938.

1-Benzyl-3-ethoxy-3-methyl-3,4,7,8-tetrahydroazocinone (20a): Following the general procedure, from carbene complex **15a** (120 mg, 0.46 mmol) and vinylazetidine **17a** (66 mg, 0.38 mmol), tetrahydroazocinone **20a** was obtained as a colorless oil (67 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.36$–7.21 (m, 5H), 5.77–5.65 (m, 1H), 5.57–5.46 (m, 1H), 5.06 (d, $J=14.7$ Hz, 1H), 4.67–4.54 (m, 1H), 3.95 (d, $J=14.7$ Hz, 1H), 3.66–3.56 (m, 1H), 3.28 (dq, $J=9.0$, 7.0 Hz, 1H), 3.17–3.07 (m, 1H), 2.78 (dd, $J=13.6$, 9.7 Hz, 1H), 2.45–2.28 (m, 3H), 1.54 (s, 3H), 1.15 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=173.8$, 138.3, 129.2, 128.8, 128.5, 127.6, 127.2, 83.3, 60.4, 49.8, 44.4, 41.9, 26.6, 25.3, 16.1 ppm; IR (ATR): $\tilde{\nu}=3026$,

2974, 2928, 1639, 1421, 1365, 1252, 1197, 1158, 1108, 1067, 1034, 958, 702 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NNaO_2$: 296.1621 $[M+Na]^+$; found: 296.1625.

3-Ethoxy-1-(4-methoxybenzyl)-3-methyl-3,4,7,8-tetrahydroazocinone (20 b): Following the general procedure, from carbene complex **15 a** (70 mg, 0.26 mmol) and vinylazetidine **17 b** (45 mg, 0.22 mmol), tetrahydroazocinone **20 b** was obtained as a colorless oil (62 mg, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.74–5.62 (m, 1H), 5.46 (dt, J = 10.3, 5.1 Hz, 1H), 4.92 (d, J = 14.5 Hz, 1H), 4.55 (dt, J = 17.9, 9.5 Hz, 1H), 3.90 (d, J = 14.5 Hz, 1H), 3.77 (s, 3H), 3.62–3.52 (m, 1H), 3.28–3.17 (m, 1H), 3.09 (dt, J = 15.5, 3.8 Hz, 1H), 2.78–2.68 (m, 1H), 2.42–2.25 (m, 3H), 1.51 (s, 3H), 1.11 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 159.2, 130.4, 129.9, 129.3, 127.1, 114.2, 83.3, 60.4, 55.6, 49.2, 44.2, 41.9, 26.7, 25.3, 16.1 ppm; IR (ATR): $\tilde{\nu}$ = 2973, 2929, 2838, 1636, 1511, 1461, 1436, 1418, 1245, 1175, 1065, 1032, 983, 842, 812, 777, 755 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{25}NNaO_3$: 326.1727 $[M+Na]^+$; found: 326.1724.

3-Ethoxy-3-methyl-1-octyl-3,4,7,8-tetrahydroazocinone (20 c): Following the general procedure, from carbene complex **15 a** (80 mg, 0.31 mmol) and vinylazetidine **17 c** (50 mg, 0.25 mmol), tetrahydroazocinone **20 c** was obtained as a colorless oil (45 mg, 60 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.74–5.60 (m, 1H), 5.60–5.47 (m, 1H), 4.71–4.54 (m, 1H), 3.71–3.49 (m, 2H), 3.25–3.07 (m, 2H), 2.80–2.67 (m, 2H), 2.51–2.28 (m, 3H), 1.57–1.42 (m, 5H), 1.25 (s, 10H), 1.14 (t, J = 7.3 Hz, 3H), 0.86 ppm (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 129.1, 127.2, 83.3, 60.2, 47.4, 45.3, 41.9, 32.2, 29.8, 29.7, 28.1, 27.5, 27.1, 25.2, 23.0, 16.2, 14.5 ppm; IR (ATR): $\tilde{\nu}$ = 2927, 1641, 1466, 1369, 1066, 802, 711 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{34}NO_2$: 296.2584 $[M+H]^+$; found: 296.2579.

3-Ethoxy-3-methyl-1-cyclohexyl-3,4,7,8-tetrahydroazocinone (20 d): Following the general procedure, from carbene complex **15 a** (95 mg, 0.36 mmol) and vinylazetidine **17 d** (50 mg, 0.3 mmol), tetrahydroazocinone **20 d** was obtained as a colorless oil (65 mg, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.65 (m, 1H), 5.63–5.49 (m, 1H), 4.57–4.35 (m, 1H), 4.30–4.17 (m, 1H), 3.63–3.46 (m, 1H), 3.31–3.09 (m, 2H), 2.74–2.60 (m, 1H), 2.44–2.21 (m, 3H), 1.83–1.49 (m, 6H), 1.48 (s, 3H), 1.48–1.25 (m, 4H), 1.13 ppm (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 129.6, 127.5, 83.5, 60.2, 55.3, 42.1, 40.6, 31.4, 31.2, 29.4, 26.5, 26.3, 26.1, 25.5, 16.2 ppm; IR (ATR): $\tilde{\nu}$ = 2928, 1775, 1639, 1393, 1065, 1024, 712 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{28}NO_2$: 266.2115 $[M+H]^+$; found: 266.2121.

General procedure for the photochemical cycloaddition reactions involving biscarbene complexes 21: Photoreactions were carried out in oven-dried pressure tubes that were charged with the biscarbene complex **21** and vinylaziridine **11 a** (2:1 molar ratio) in dry, degassed Et_2O (3 freeze–pump–thaw cycles). The tube was fitted with a pressure head, purged three times with CO, and irradiated under CO (60–70 psi; medium pressure mercury lamp 400 W, pyrex filter, and pyrex well) for 20 h. The solvent from the crude reaction mixture was removed under vacuum, the residue was taken up in hexane/EtOAc (1:1), and exposed to light to oxidize the remaining chromium(0) compounds. This mixture was filtered through Celite and purified by silica gel chromatography (hexane/EtOAc, 4:1 to 2:1, TLC plates were developed in oleum) to produce the desired biscycloadducts **22**.

Bis(dihydroazepinone) 22 a: Following the general procedure, from biscarbene complex **21 a** (250 mg, 0.49 mmol) and vinylaziridine **11 a** (155 mg, 0.98 mmol), biscycloadduct **22 a** was obtained as a colorless oil (100 mg, 41 %). ^{1}H NMR (300 MHz $CDCl_3$): δ = 7.32–7.22 (m, 10H), 5.70–5.50 (m, 4H), 4.72–4.58 (m, 4H), 4.54–4.43 (m, 2H), 3.66–3.54 (m, 2H), 3.41–3.26 (m, 4H), 2.46 (s, 4H), 1.90–1.76 (m, 2H), 1.50 (s, 3H), 1.48 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 138.1, 128.9, 128.1, 127.9, 127.7, 125.1, 80.9, 61.2, 61.1, 53.6, 47.1, 47.0, 38.4, 31.8, 23.5, 23.4 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2987, 2932, 1639, 1495, 1480, 1453, 1345, 1171, 1114, 1077, 733, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}N_2O_4$: 502.2904 $[M+H]^+$; found: 502.2910.

Bis(dihydroazepinone) 22 b: Following the general procedure, from biscarbene complex **21 b** (279 mg, 0.53 mmol) and vinylaziridine **11 a** (170 mg, 1.06 mmol), biscycloadduct **22 b** was obtained as a colorless oil (150 mg, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 10H), 5.69–5.52 (m, 4H), 4.67 (s, 4H), 4.55–4.43 (m, 2H), 3.58–3.49 (m, 2H), 3.39–3.24 (m, 4H), 2.47 (s, 4H), 1.65–1.56 (m, 4H), 1.50 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 138.1, 128.9, 128.2, 127.9, 127.7, 125.2, 80.8, 64.1, 64.0, 53.6, 47.0, 38.4, 27.7, 27.6, 23.5 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2985, 2936, 1639, 1495, 1480, 1453, 1417, 1233, 1113, 1078, 853, 798, 733, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{40}N_2O_4$: 517.3061 $[M+H]^+$; found: 517.3068.

Bis(dihydroazepinone) 22 c: Following the general procedure, from biscarbene complex **21 c** (280 mg, 0.49 mmol) and vinylaziridine **11 a** (155 mg, 0.98 mmol), biscycloadduct **22 c** was obtained as a colorless oil (130 mg, 47 %). ^{1}H NMR (300 MHz $CDCl_3$): δ = 7.34–7.19 (m, 10H), 5.58 (d, J = 4.0 Hz, 4H), 4.76–4.61 (m, 6H), 4.46–4.36 (m, 2H), 4.34–4.25 (m, 2H), 3.36–3.18 (m, 2H), 2.67–2.43 (m, 4H), 1.62 (s, 3H), 1.60 (s, 3H), 1.65–1.59 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 173.3, 138.1, 136.6, 136.5, 129.0, 128.5, 128.28, 128.26, 128.17, 128.10, 127.8, 125.2, 81.39, 81.38, 64.1, 64.0, 53.71, 53.68, 47.3, 47.2, 38.6, 38.5, 23.61, 23.57 ppm; IR (ATR): $\tilde{\nu}$ = 3027, 2986, 2926, 2629, 1733, 1637, 1480, 1453, 1453, 1418, 1260, 1231, 1185, 1079, 733, 699, 644 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}N_2O_4$: 565.3061 $[M+H]^+$; found: 565.3073.

Bis(azepinone) 22 d: Following the general procedure, from biscarbene complex **21 d** (235 mg, 0.41 mmol) and vinylaziridine **11 a** (130 mg, 0.82 mmol), biscycloadduct **22 d** was obtained as a yellow oil (137 mg, 61 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 10H), 5.76–5.59 (m, 4H), 4.75 (s, 4H), 4.70 (d, J = 11.0 Hz, 2H), 4.60–4.46 (m, 2H), 4.36 (d, J = 11.0 Hz, 2H), 3.44–3.32 (m, 2H), 2.74–2.53 (m, 4H), 1.69 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 138.1, 137.9, 128.9, 128.2, 127.9, 127.77, 127.73, 125.1, 81.4, 66.4, 53.7, 47.2, 38.5, 23.7 ppm; IR (ATR): $\tilde{\nu}$ = 3026, 2987, 2932, 1639, 1495, 1480, 1453, 1345, 1173, 1078, 963, 875, 733, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}N_2O_4$: 565.3061 $[M+H]$; found: 565.3060.

Bis(azepinone) 22 e: Following the general procedure, from biscarbene complex **21 e** (230 mg, 0.4 mmol) and vinylaziridine **11 a** (128 mg, 0.8 mmol), biscycloadduct **22 e** was obtained as a colorless oil (114 mg, 59 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 10H), 5.60 (d, J = 4.3 Hz, 4H), 4.74–4.67 (m, 4H), 4.63 (d, J = 11.0 Hz, 2H), 4.52–4.42 (m, 2H), 4.31 (d, J = 11.0 Hz, 2H), 3.42–3.19 (m, 2H), 2.67–2.46 (m, 4H), 1.62 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 138.8, 138.1, 129.0, 128.2, 127.79, 127.76, 126.94, 126.90, 125.17, 125.15, 81.4, 66.5, 53.7, 47.2, 38.5, 23.7 ppm; IR (ATR): $\tilde{\nu}$ = 3028, 2920, 2851, 1719, 1636, 1519, 1495, 1375, 1263, 1189, 1110, 895, 786, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}N_2O_4$: 565.3061 $[M+H]^+$; found: 565.3079.

Computational details: Geometry optimizations without symmetry constraints were carried out by using the Gaussian 09 suite of programs[21] using the B3LYP[22] functional in combination with the double-ζ plus polarization def2-SVP basis sets[23] for all atoms in Et_2O as the solvent and using the polarizable continuum model (PCM) method.[24] This level is denoted PCM(Et_2O)-B3LYP/def2-SVP. Reactants and products were characterized by frequency calculations[25] and have positive definite Hessian matrices. Transition structures (TSs) 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 by using the intrinsic reaction coordinate (IRC) method.[26]

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