# Theoretical Insights Regarding the Cycloaddition Behavior of Push−Pull Stabilized Carbonyl Ylides†

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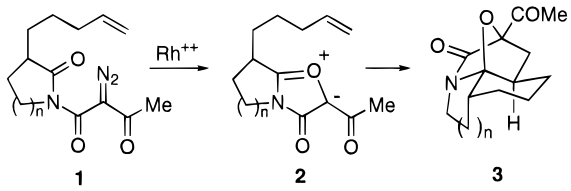
A series of diazoamido keto esters were prepared by the reaction of N-substituted 3-carbethoxy-2-piperidone with *n*-butylmagnesium chloride followed by the addition of ethyl 2-diazomalonyl chloride. Treatment of these diazo amides with rhodium(II) acetate afforded transient push−pull carbonyl ylide dipoles which could be readily trapped with electron deficient dipolarophiles. All attempts to induce the dipolar cycloaddition to occur across tethered alkenyl $\pi$-bonds failed to give internal cycloadducts. However, placing a $sp^2$ center on the tethered side chain was found to result in the formation of a tricyclic adduct in 95% yield. The stereochemistry of the cycloadduct was firmly established by an X-ray crystallographic study and occurred *endo* with respect to the amido carbonyl ylide dipole. A detailed computational study was undertaken to provide better insight into the factors that influence the intramolecular cycloaddition process. The calculations indicate that a severe cross-ring 1,3-diaxial interaction caused by the bridgehead methyl group promotes a boat or twist−boat conformation in the piperidine ring fused to the newly forming one. The presence of a carbonyl group in the dipolarophile tether helps to relieve the steric congestion by virtue of favoring a second boat in the latter ring. Without the C=O group, both nascent and piperidine rings are in the chair conformation at lowest energy, and the reaction barrier is disadvantaged by 5.6 kcal/mol, allowing other competing processes to intervene.

## Introduction

The generation of onium ylides by transition-metal-promoted cyclization has emerged as an important method for the assembly of ring systems that are difficult or impossible to prepare by other means.[1−5] Construction of azapolyheterocycles through metal intervention has been a particularly fruitful area of investigation, and the synthesis of various types of alkaloids by this approach has been carried out by several investigators.[6−16] Recent papers from these laboratories have described a route to azapolycyclic ring systems that involved the tandem *cyclization−cycloaddition* of a transient rhodium carbenoid (Scheme 1).[17] Isomünchnone (**2**) was easily prepared by the rhodium(II)-catalyzed cyclization of a suitable diazoimide precursor **1**.[18] The mesoionic oxazolium ylide **2** is the cyclic equivalent of a carbonyl ylide and readily undergoes 1,3-dipolar cycloaddition with suitable dipolarophiles.[19] This reaction is an integral part of our program aimed at developing new cascade reactions and achieving the total syntheses of various nitrogen-containing heterocycles. Our more recent achievements in this area involve the use of diazo ketoamides such as **4**.[20] Intramolecular attack of the amido carbonyl oxygen at the rhodium carbenoid center produces a carbonyl ylide (*i.e.*, **5**) that is isomeric with the isomünchnone class of dipoles. Several key questions emerged as a result of these investigations: (i) would bimolecular dipolar-cycloaddition of push−pull stabilized ylides such

**Scheme 1**




† Dedicated to my friend and former colleague Leon Mandell on the occasion of his 70th birthday.

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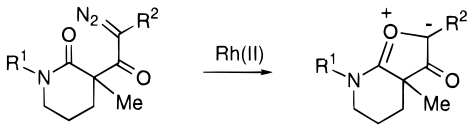



4 5

as **5** occur, (ii) would the related intramolecular cycloaddition reaction take place, and (iii) if so, what effect would the nature and length of the tether have on the course of the cycloaddition? We therefore initiated a study to probe the above issues and now wish to report results emanating from this investigation.

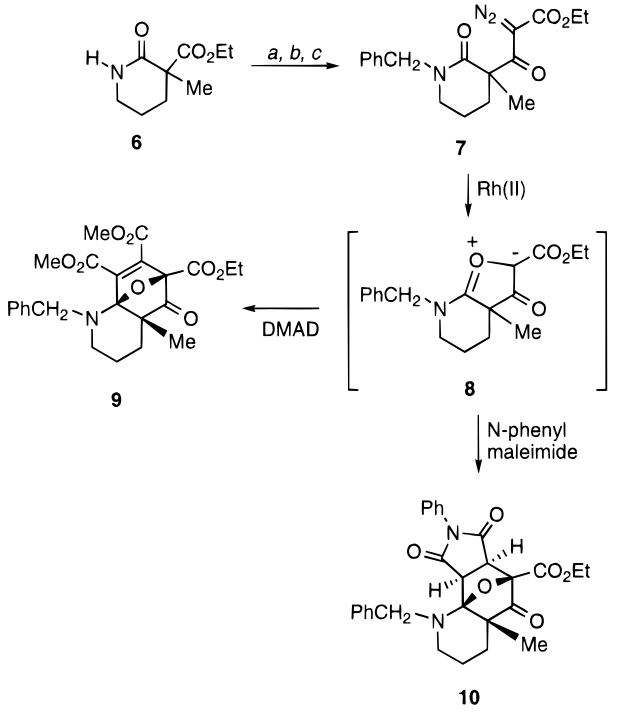
## Results and Discussion

To address the first question, the Rh(II)-catalyzed reaction of diazoamido ester **7** was examined. The prerequisite amide **7** necessary for dipole generation was obtained from the readily available 3-methyl-2-oxopiperidine-3-carboxylic acid ethyl ester (**6**)[21] (see Experimental Section). Formation of the push−pull carbonyl ylide dipole **8** proceeded smoothly upon heating a sample of diazoamido ester **7** in benzene in the presence of $Rh_2(OAc)_4$. The resultant dipole was trapped with either dimethyl acetylenedicarboxylate (DMAD) or *N*-phenylmaleimide to afford cycloadducts **9** (80%) and **10** (83%), respectively (Scheme 2). Structural assignments were made on the basis of their spectral properties. Cycloadduct **10** is produced with complete diastereoselectivity and is the result of *endo* cycloaddition with respect to the dipole and *anti* with respect to the methyl group at the ring juncture. The stereochemical assignment was unambiguously established by X-ray crystallography.[22]

Bolstered by this positive result, we next examined the Rh(II)-catalyzed behavior of several cyclic diazo amides containing tethered $\pi$-bonds, as these systems have great potential for the preparation of the basic ring skeleton found in a number of alkaloid families. Diazo amides **11** and **12** were prepared in good overall yield using a procedure similar to that described for diazoamido ester **7** (see Experimental Section).[23,24] Unfortunately, no products from an intramolecular dipolar cycloaddition across the tethered $\pi$-bond could be detected in the crude reaction mixture when rhodium(II) acetate was used as the catalyst. Similar results were obtained using more active rhodium(II) catalysts (*i.e.*, perfluorobutyrate or trifluoroacetate) or varying the nature of the solvent.[25] Although the conformational approach to the desired tricyclic ring systems seemed quite feasible based on Dreiding molecular models, only decomposition of the starting material and unspecific side reactions were observed. The push−pull dipole derived from diazo amide **12** did not undergo internal cycloaddition; however, it did cycloadd with DMAD to give the expected dipolar cycloadduct **13** in 78% isolated yield. This led us to consider the possibility that the failure of the internal cycloaddition might be a consequence of a large HOMO−LUMO energy gap in the transition state of the reaction.[26] Placement of a carbomethoxy substituent on the $\pi$-bond was carried out and the resultant diazo amide **14** was treated with Rh(II) acetate in refluxing benzene. All attempts to effect the intramolecular 1,3-dipolar cycloaddition across the activated $\pi$-bond were unsuccessful. No signs of the expected cycloadduct **15** could be detected in the crude reaction mixture.

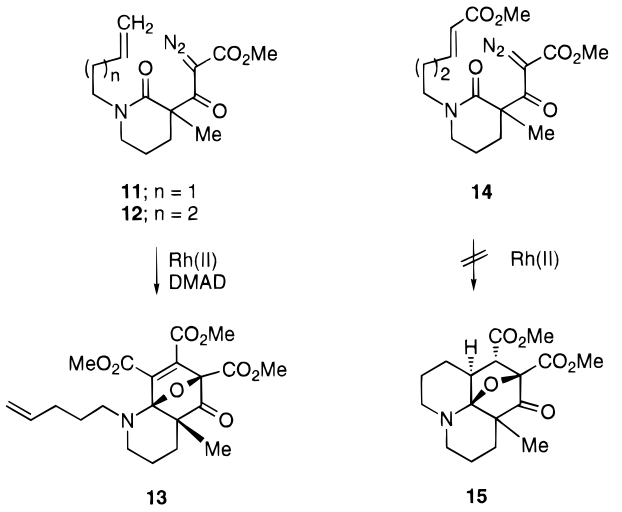
The interaction of two reactive groups within the same molecule has always been of paramount concern to organic chemists.[27] The geometric requirements for interaction are generally evaluated through systems that have the reacting centers connected together by a few intervening atoms. This linkage provides a cyclic transi-

**Scheme 2**[a]




6 7 8 9 10

[a] Reagents: (a) NaH, $PhCH_2Br$, KOH; Δ; (b) oxalyl chloride, n-BuMgCl, $EtO_2CCH_2CO_2H$; (c) $Et_3N$, $MsN_3$.




13 15

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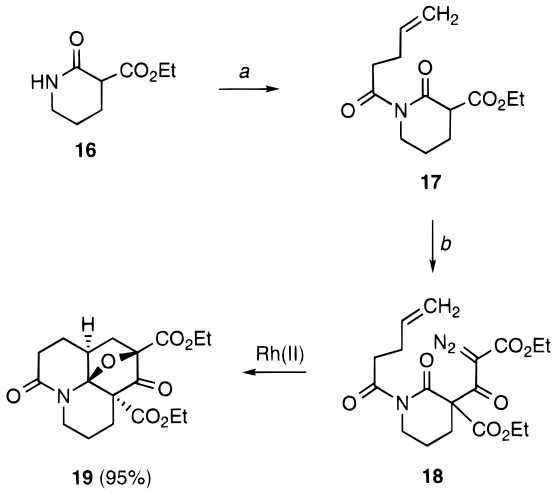
tion state, which imposes distinct restrictions upon the bond angles at the reacting centers.[28] With this in mind, we felt that it would be worthwhile to extend our studies by changing the nature of the tether so as to provide a more favorable pathway for the intramolecular cycloaddition. A strategy that was used to modify the relationship between the tethered alkene and dipole involved incorporating an amido group into the side chain. We hoped that by placing a $sp^2$ center on the tethered side chain, better overlap between the push−pull dipole and dipolarophile would occur and thereby facilitate the internal cycloaddition.

The synthesis of the requisite diazoimide to test this hypothesis was accomplished in two steps from the commercially available 3-carbethoxy-2-piperidone **16**.

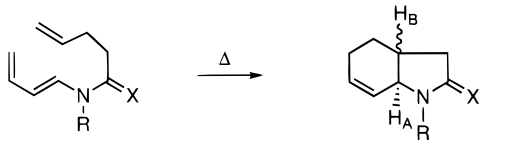



**16** **17** **19** (95%) **18**

Reagents: (a) n-BuLi, $CH_2{=}CH(CH_2)_2COCl$; (b) n-BuMgCl, $EtO_2CC(N_2)COCl$

Treatment of amido ester **16** with *n*-BuLi at −78 °C followed by the addition of 4-pentenoyl chloride afforded imide **17** in 60% yield. Earlier work in our laboratory showed that ethyl 2-diazomalonyl chloride is an effective diazoacylating reagent for a variety of amines, alcohols, thiols, and amides.[29] We envisioned that this reagent could also be coupled with the soft carbanion generated from the deprotonation of imide **17**. Indeed, the reaction of **17** in THF at 0 °C with *n*-butylmagnesium chloride, followed by the addition of ethyl 2-diazomalonyl chloride, afforded the desired diazoimide **18** in 55% yield. The formation of a magnesium chelate may render the oxygen atom of the enolate less susceptible to electrophilic attack by the acid chloride, and thus, C-alkylation becomes the dominant pathway. To the best of our knowledge, this reaction corresponds to the first known example of a diazo-acylating reagent being employed with a carbon nucleophile. Gratifyingly, treatment of **18** with a catalytic quantity of rhodium(II) acetate in benzene at 50 °C gave the tricyclic adduct **19** in 95% yield with complete diastereoselectivity. The stereochemistry of **19** was assigned initially on the basis of a detailed NMR analysis and was later established by an X-ray crystallographic study.[22] The cycloaddition occurs *endo* with respect to the amido carbonyl ylide dipole and is doubly diastereoselective in that the dipolarophile approaches exclusively from the same face as the carbethoxy group.

A related "*amido*" effect had previously been encountered by Oppolzer in a study of the intramolecular Diels−Alder reaction of azatrienes **20** and **21** which led to the




**20**; X=H, R=$CO_2Me$
**21**; X=O, R=$C_3H_7$
**22**; X=H, R=$C_3H_7$

**23**; X=H, R=$CO_2Me$
**24**; X=O, R=$C_3H_7$
No cycloadduct

fused bicyclic adducts **23** and **24**.[30] The steric course of the internal [4 + 2]-cycloaddition could be directed away from the *endo* adduct to the *exo* isomer depending on the location of the amido group. Most importantly, however, no product resulting from intramolecular Diels−Alder cycloaddition could be detected with the simple amino-substituted tether (*i.e.*, **22**). The above observations coupled with our own findings suggest that the efficiency of the internal cycloaddition of these aza-tethered systems may be related to an electronic effect at the nitrogen atom and/or conformational preferences in the transition state. In order to obtain a better insight into the factor(s) that influence these internal cycloadditions, we decided to evaluate the various contributing factors by a detailed computational study.

## Frontier Molecular Orbital (FMO) Analysis

Application of FMO theory to cycloaddition chemistry is well-established and has been used to predict the relative rate and regiochemical outcome of many cycloaddition reactions.[31−33] In short, perturbation theory examines a few occupied and virtual molecular orbitals of the appropriate symmetry surrounding the frontier MO gap in the reactants. Calculated energy differences and, in the case of a regioselective reaction, MO coefficients are employed to model the transition state. Such an approach is ideally suited to an understanding of the variable intramolecular reactivity of the carbonyl ylides arising from diazo amides **11**, **12**, and **14** with amine tethers and **18** with the amide tether. In this and subsequent computational analyses of reactivity, we assumed that reactivity differences lie in the differential structural and electronic properties of the bicyclic carbonyl ylides.

Depending on the calculated frontier MO energy gap, cycloaddition reactions have been classified by Sustmann as types I−III.[31c,33a] For type I cases, the major frontier orbital interaction is between the dipole HOMO and the dipolarophile LUMO. Type II cases are those in which the HOMO−LUMO separations are equivalent, and the dominant interaction is often governed by substituent effects. In type III cycloadditions, the interaction of the

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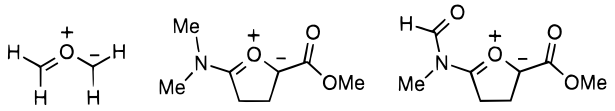
**Table 1. FMO Analysis of Ylides 25−27 and Energy Separation Relative to 1-Hexene**

| carbonyl ylide | HOMO (eV) | LUMO (eV) | energy separation, eV type I | energy separation, eV type III |
|---|---|---|---|---|
| **25** | −7.84472 | +0.12418 | 9.00 | 10.31 |
| **26** | −7.37024 | −0.82553 | 8.53 | 9.36 |
| **27** | −7.93454 | −1.01270 | 9.09 | 9.17 |

dipole LUMO and the dipolarophile HOMO determines reactivity.

For the purposes of the present work, one additional factor needs mention. In their successful predictions of regioselectivity for a number of dipolar cycloadditions, Houk and co-workers found that an electron-withdrawing group on the dipolarophile lowers both the HOMO and LUMO energies, while an electron-donating substituent tends to increase both the HOMO and LUMO energies.[31b] This observation is compatible with the experimental finding that 1,3-dipoles of type I are accelerated by electron-donating substituents in the dipole and by electron-withdrawing substituents in the dipolarophile. In both cases, the HO−LU energy separation is diminished.

PM3[34] geometry optimizations were performed on carbonyl ylides **25**, **26** and **27**. The latter two are simplified models for the dipoles (e.g. **5**) corresponding to diazoketones **12** and **18**, respectively.



**25** **26** **27**

The PM3 HO−LU energy separations for the optimized structures were computed and compared with respect to the model dipolarophile 1-hexene. The results are summarized in Table 1. Clearly the cycloaddition of the carbonyl ylide **25** is type I, the HOMO of the dipole contributing the dominating frontier electron density. The amino-substituted ylide **26** exhibits the smallest HO−LU energy gap and is predicted to react faster with 1-hexene than the amido-substituted ylide **27**. While this outcome does not explain why cycloadduct **15** is not formed in the reactions of diazo amide **14** with the rhodium(II) catalyst, it is consistent with Houk's observation that the HOMO energy level rises with an electron-donating substituent,[31b] thereby decreasing the HO−LU energy separation in a type I cycloaddition reaction.

## Transition State Strain as a Potential Source of Reactivity Variation

The lack of reactivity of amino-substituted ylides **5** is not predicted by the electronic factors associated with the FMO model of the dipolar transition state. Thus, an alternative explanation was sought in terms of relative strain in the transition state. Conversion of monocyclic diazo amides **11**, **12**, **14**, and **18** to cycloaddition products is thought to involve bicyclic intermediates that pass through transition structures to give highly condensed tetracyclic ring systems. The activation complexes most likely incorporate a high degree of internal strain. We assume that the cycloaddition reactions are exothermic, as is generally the case. If the products from the amido-substituted system (A) are stable relative to the amino products (B), the relative energy profiles are given qualitatively by Figure 1.

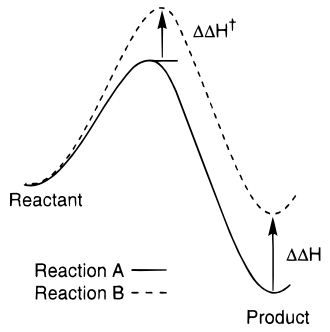



**Figure 1.** Possible reaction profiles.

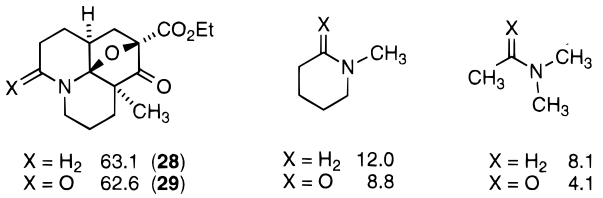



**Figure 2.** MM3* energies used in isodesmic reactions (kcal/mol).

Although Hammond's postulate argues that the transition structures in question are more reactant-like than product-like, relative strain energy differences in the products might nonetheless mirror a strain differential between the transition states. To explore this possibility, we have constructed isodesmic reactions[35] to compare the intramolecular cyclization products from the rhodium-catalyzed decomposition of **12** and **18** to give **28** and **29**, respectively. It should be recalled that isodesmic reactions are not "chemical" in nature; they do not occur in the laboratory. They are simply a numerical protocol for comparing diverse structures at a given level of computational theory. To minimize structural discontinuity in the comparison, tetracycle **19** is modeled as **29**; the bridgehead carbethoxy moiety is replaced by the slightly more sterically demanding methyl group. In this way, **28** and **29** differ only by the $CH_2$ to C═O replacement alpha to nitrogen. Molecular strain energy differences, if they exist, are thus traceable to substitution at a single carbon center.

The calculations were performed by optimizing the structures with the MM3* force field in MacroModel.[43] The energies of the expected products as well as the "strain free" fragments are summarized in Figure 2. The energies of the corresponding isodesmic reactions are given in Scheme 3.

Not only are the reaction energy differences ($\Delta E$) small, but they imply that the added carbonyl group increases the strain energy by about 3 kcal/mol (eqs 1 and 2). If significant differential strain energies for the cycloaddition transition states preceding **28** and **29** are responsible for the selective formation of **19**, they are clearly not reflected by the relative strain in product ground states.

## Open vs Closed Shell Carbonyl Ylides

Since the FMO-PM3 and -MM3 ground state models of the amine and amide tethered carbonyl ylide activation

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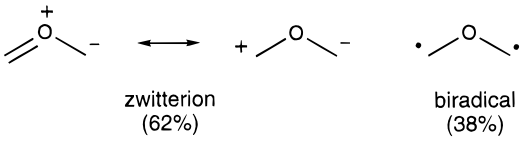
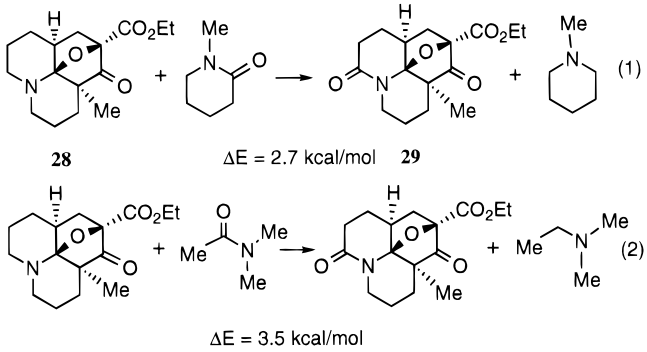



**Figure 3.** Zwitterionic and biradical character in ylide **25**.

**Scheme 3. Isodesmic Reactions Calculated by MM3***




complexes do not explain the variable reactivity of the corresponding diazo ketones, we decided to pursue a full-scale *ab initio* level transition state evaluation. As a preliminary step, the electronic characteristics of the dipoles were investigated. In the initial FMO analysis, we treated the carbonyl ylides as 1,3-zwitterions. The 1,3-dipoles are systems with potential for significant biradical character, however. Hayes and Siu have previously attempted to quantify the zwitterion vs biradical character of unsubstituted 1,3-dipoles by investigating the ring-opened acyclic forms of cyclopropane, ethylene oxide, and aziridine.[36] As illustrated for the parent carbonyl ylide (Figure 3), their results suggested that the zwitterionic representation of the 1,3-dipole is significantly contaminated by biradical character.

Subsequent evaluation by Houk suggested that, as donors and acceptors are placed on the opposite termini of a 1,3-dipole, the zwitterionic character of the molecule increases with a concomitant decrease in biradical attributes.[37] To test this supposition and to simultaneously determine the best method for calculating the transition states of the carbonyl ylide cycloadditions, we performed 3-21G//3-21G and 6-31G*//6-31G* *ab initio* calculations on both closed and open shell forms of several substituted carbonyl ylides (Table 2).

The open shell singlet calculations were carried out by employing the two configuration generalized valence bond (GVB) method.[38] GVB is a first-order configuration interaction method suitable for the treatment of open-shell singlet biradicals. For example, by allowing states of the same symmetry and similar energies to mix, the singlet biradical character of the carbonyl ylide is expressed. To allow comparison with the GVB and HF energies (Table 2), the optimized triplet states (pure diradicals) were generated as well. The resulting total energy differences are summarized in Figure 4. For the symmetrical parent **25** and monosubstituted cases **30** and **31**, the zwitterion is the least stable, while the biradical

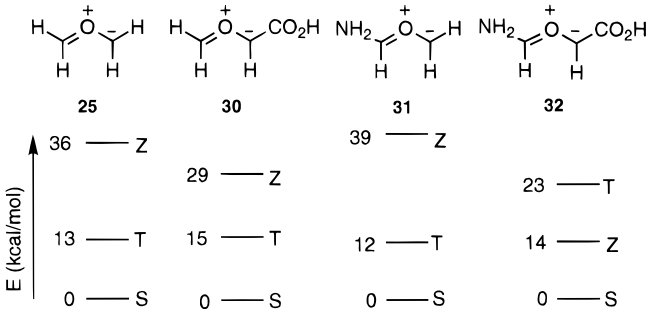



**Figure 4.** Relative energy differences between the Zwitterion, open shell singlet, and open shell triplet energies for substituted ylides.

**Table 2. *Ab Initio* Energies (HF) for Optimized Carbonyl Ylides (au)**

| | | zwitterion | triplet | singlet |
|---|---|---|---|---|
| **25** | 3-21G | -151.90847 | -151.94888 | -151.96906 |
| | 6-31G* | -152.75423 | -152.79174 | -152.81260 |
| **30** | 3-21G | -338.47666 | -338.49976 | -338.52446 |
| | 6-31G* | -340.38254 | -340.40487 | -340.42898 |
| **31** | 3-21G | -206.63404 | -206.67412 | -206.69285 |
| | 6-31G* | -207.77888 | -207.82217 | -207.84062 |
| **32** | 3-21G | -393.23447 | -393.22057 | -393.24666 |
| | 6-31G* | -395.43953 | -395.42564 | -395.46113 |

energy is lowest. The push−pull ylide **32,** however, exhibits its zwitterion energy between that of the triplet and the biradical in concert with the qualitative arguments of Houk.[37]

As a ground state biradical carbonyl ylide begins the bond-making process at the cycloaddition transition state, it can be expected that the biradical character will have diminished considerably. Consequently, for the push-pull carbonyl ylide dipoles considered in this paper, closed-shell zwitterionic transition states are quite reasonable models.

## DFT Transition States

Carbonyl ylide ground state and transition state structures for both amino and amido systems (X = $H_2$ and X = O) were optimized as closed shell entities to evaluate the relative activation energies for cyclization of ylides **5** derived from diazo ketones **12** and **18**. As above, the carbonyl ylide derived from **18** was modeled by replacing the ring-substituted $CO_2Et$ moiety by $CH_3$. Likewise, the terminal $CO_2Et$ groups in both **12** and **18** were replaced by $CO_2H$ groups to reduce the computational expenditure. The Becke3LYP nonlocal density functional method (DFT) in conjunction with a 3-21G basis set was applied to all optimizations (i.e. B3LYP/3-21G).[39] Each optimized structure was subsequently subjected to a single point B3LYP/3-21G//B3LYP/6-31G* energy evaluation. This protocol has been successfully applied to a number of pericyclic reactions.[40]

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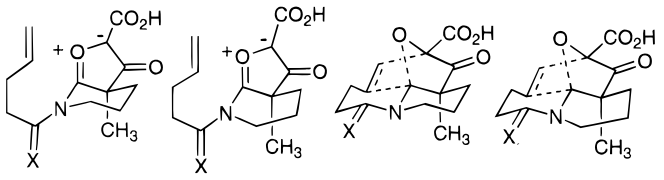
**Table 3. *Ab Initio* Energies (au)[a] for Both Chair and Boat Conformations 33−36 and $\Delta E$(ts − gs) (kcal/mol)**



**33** chair-gs **34** boat-gs **35** chair-ts **36** boat-ts

| X | basis set[a] | chair−gs | boat−gs | chair−ts[b] | boat−ts[c] | $\Delta E$[d] |
|---|---|---|---|---|---|---|
| $H_2$ | 3-21G | −895.587 55 | −895.585 67 | −895.567 06 | −895.569 19 | 11.5 |
| $H_2$ | 6-31G* | −900.515 99 | −900.514 49 | −900.484 32 | −900.483 93 | 19.8 |
| O | 3-21G | −969.200 46 | −969.195 96 | −969.175 77 | −969.181 13 | 12.1 |
| O | 6-31G* | −974.537 08 | −974.537 88 | −974.513 81 | −974.515 23 | 14.2 |

[a] 3-21G = B3LYP/3-21G// Becke3LYP/3-21G; 6-31G* = B3LYP/3-21G//B3LYP/6-31G*. [b] X = $H_2$, chair−chair; O, chair−twist boat. [c] X = H2, chair−twist boat; O, boat−twist boat. [d] Difference between the lowest ground state and transition state, respectively.

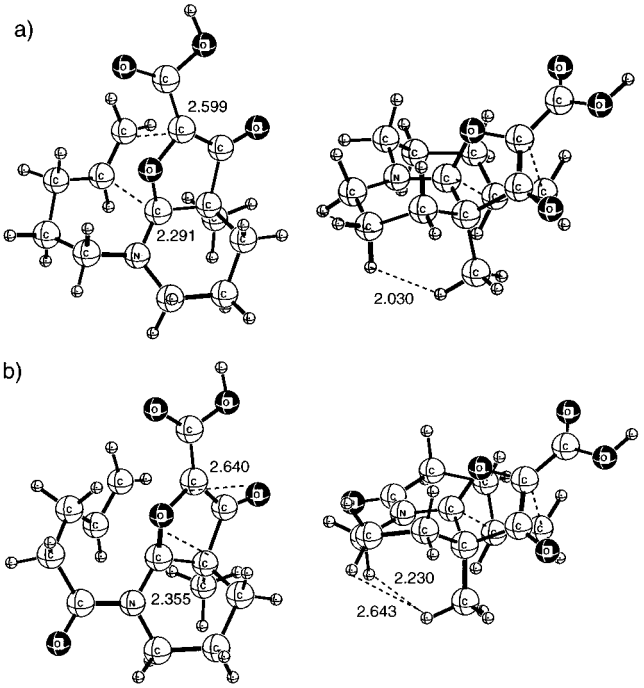



**Figure 5.** The Becke3LYP/3-21G optimized transition states for (a) amide (chair−chair) and (b) imide (boat−twist boat) transition states. H- - -H and C- - -C distances in Å. Two views each.

Although Table 3 presents the results for both the B3LYP/3-21G and B3LYP/6-31G* energies, the following discussion will refer only to the latter. Calculations were performed for chair and boat conformations within the nitrogen-containing six-membered ring for both X = $H_2$ and O. The calculated boat−chair energy differences are uncharacteristically small ($\Delta E$ < 1.0 kcal/mol). The amide (X = $H_2$) prefers a chair by 0.9 and 0.2 kcal/mol in the ground and transition states, respectively. The imide (X = O) favors a boat in both cases by 0.5 and 0.9 kcal/mol, respectively.

The diminished energy gaps can be traced to an increase in piperidine chair energies arising from unfavorable 1,3-diaxial interactions occasioned by the permanently axial bridgehead methyl group. Figure 5 illustrates the point for the lowest energy transition structures of both amide and imide. The amide chair−chair structure tolerates a very short H- - -H distance (2.03 Å) on the face of the molecule undergoing cycloaddition. This is considerably below the sum of the hydrogen van der Waals radii (2.4 Å).[41] Thus, the competing elements of a severe 1,3-diaxial interaction and the stability associated with a saturated six-membered ring balance to yield isoenergetic chair−chair and chair−twist boat structures. The imide system responds to the influence of both the 1,3-diaxial congestion and an amide group in the cycloaddition ring-forming tether by folding to boats in both the nascent and piperidine rings. The shortest H- - -H contact (2.23 Å) is just below the sum of van der Waals radii (Figure 5b).

The reason for having carried out the *ab initio* calculations concerns the facile intramolecular capture of the carbonyl ylide for imide tethers (**33**−**36**, X = O), but the complete lack of it for amide systems (X = $H_2$). Table 3 and Figure 5 suggest a basis for the cycloaddition selectivity. The last column of Table 3 predicts that the energy barrier for amide cycloaddition, $\Delta E$(ts − gs), is 5.6 kcal/mol higher in energy than the imide (X = O) structure. The considerable $\Delta\Delta E$(ts − gs) penalty for the amide system owes its source to the same influences that lead to isoenergetic boat and chair conformations described above. Namely, the amide transition state for intramolecular dipolar cycloaddtiion is severely hindered sterically (Figure 5a) as the new ring begins to form. Consequently, reaction channels that are uncompetitive in the imide case become so in the amide structure. For example, treatment of diazo ketones **11**, **12**, **14**, and **18** with rhodium catalysts most certainly generates a number of organometallic intermediates and possibly equilibria connecting them. Several of these are depicted below. Zwitterion **39**, of course, is the funnel to the observed cycloaddition products.

Thus for amino systems **11**, **12**, and **14**, the intermediates implied by **37**, **38**, and **40** most likely experience competing transformations that are lower in energy than intramolecular dipolar cycloaddition *via* **39**.

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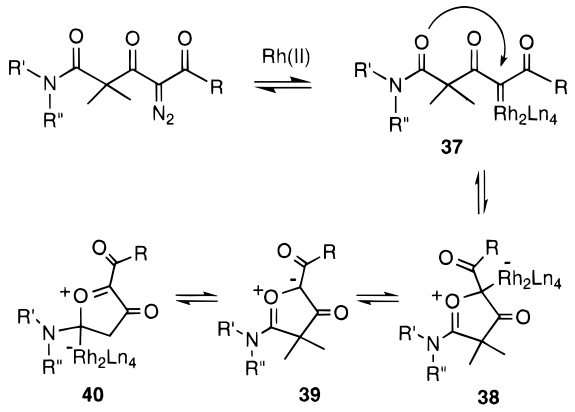


Finally, we have optimized the product ground states corresponding to **35** and **36** with MM3* in Macromodel. Both amide and imide systems (X = $H_2$ and O, respectively) reorganize to give chair−chair and half-chair (i.e. cyclohexene-like) conformations. The short nonbonded 1,3-diaxial interactions in the transition states are increased to a tolerable 2.41−2.42 Å as a consequence of full bond formation between dipole and dipolarophile. Thus, the steric congestion experienced by the bridgehead methyl in the activation complexes is unique to that stationary point and not translated to relaxed products.

## Conclusion

The rhodium-catalyzed formation of carbonyl intermediates from cyclic diazo amides provides tetracycles such as **19** in good yield provided that the tether engaged in ring formation carries a carbonyl group. Without the C═O, only decomposition is observed. By performing *ab initio* transition state geometry optimizations, we have learned that a severe cross-ring 1,3-diaxial interaction caused by the bridge-head methyl group promotes a boat or twist−boat conformation in the piperidine ring fused to the newly forming one.[45] Interestingly, the presence of a carbonyl group in the dipolarophile tether helps to relieve the steric congestion by virtue of favoring a second boat in the latter ring. Without the C═O group, though both nascent and piperidine rings are in the chair conformation at lowest energy, the reaction barrier is disadvantaged by 5.6 kcal/mol, thereby permitting competing processes to intervene. These results make it clear why the FMO and the ground state strain analyses of cycloaddition energy barriers failed. Neither treatment carries the factor that determines relative barrier heights for the amide and imide reactions. The principles outlined here would appear to have broader implications. Future work will address some of them.

## Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate−hexane mixture as the eluent unless specified otherwise.

(45) In the case of the carbonyl ylide corresponding to diazo amide **18**, the bridgehead $CO_2Et$ was replaced by $CH_3$ in the calculations. Though the energies in Table 3 are thereby altered slightly from the experimental system, we have no reason to suspect a change in the qualitatative or semiquantitative outcome.

**General Procedure for the Synthesis of Diazo Amides.** A variation of the procedure described by Taber and coworkers[24] was used to prepare the diazo amide system. To a solution containing 2 mmol of the appropriate amido ester and 2.2 mmol of mesyl azide in 5 mL of acetonitrile or $CH_2Cl_2$ was added 4.0 mmol of $NEt_3$ under $N_2$ at rt. After stirring the mixture for 3 h, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography.

**3-Methyl-2-oxopiperidine-3-carboxylic Acid Ethyl Ester (6).** To a stirred solution containing 5.00 g (29.2 mmol) of 2-oxopiperidine-3-carboxylic acid ethyl ester in 50 mL of THF at −78 °C was added 18.2 mL (29.2 mmol) of a 1.6 M *n*-butyllithium solution in hexane and the mixture was allowed to stir while warming to rt. The solution was cooled to −78 °C and 4.15 g (29.2 mmol) of iodomethane was added. The mixture was allowed to stir while warming to rt over a period of 12 h. The reaction was quenched with $H_2O$, the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give 4.70 (86%) of **6** as a yellow solid: mp 84−85 °C; IR ($CHCl_3$) 1730, 1664, 1260, and 1187 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.23 (t, 3H, $J$ = 7.1 Hz), 1.44 (s, 3H), 1.60−1.90 (m, 4H), 2.22 (m, 1H), 4.16 (q, 2H, $J$ = 7.1 Hz), and 6.61 (brs, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 19.4, 22.4, 33.1, 42.4, 50.2, 61.4, 172.1, and 173.5. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.48; N, 7.18.

**1-Benzyl-3-methyl-2-oxopiperidine-3-carboxylic Acid.** To a solution containing 1.00 g (5.4 mmol) of lactam **6** in 15 mL of THF was added 0.26 g (6.5 mmol) of 60% NaH in mineral oil. The solution was heated to reflux for 1 h and cooled to rt, and 1.85 g (10.8 mmol) of benzyl bromide and 1.62 g (10.8 mmol) of NaI were added. The solution was heated at reflux for 4 h, cooled to rt, and quenched with $H_2O$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were concentrated under reduced pressure. The residue was dissolved in 10 mL of methanol, 5 mL (15 mmol) of a 3 N KOH solution was added, and the mixture was allowed to stir at rt for 10 h. The solution was washed with ether, acidified to pH 2, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 1.10 g (82%) of 1-benzyl-3-methyl-2-oxopiperidine-3-carboxylic acid as a white solid: mp 122−123 °C; IR (KBr) 3436 (br), 2907, 1723, and 1604 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.58 (s, 3H), 1.70−2.30 (m, 4H), 3.24 (t, 2H, $J$ = 5.9 Hz), 4.54 (d, 1H, $J$ = 14.6 Hz), 4.61 (d, 1H, $J$ = 14.6 Hz), and 7.10−7.40 (m, 5H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.0, 25.7, 31.0, 47.8, 48.4, 51.0, 127.8, 127.9, 128.8, 136.0, 173.2, and 174.8. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.91; H, 6.75; N, 5.48.

**3-(1-Benzyl-3-methyl-2-oxopiperidin-3-yl)-3-oxopropionic Acid Ethyl Ester.** To a stirred solution of 0.40 g (1.8 mmol) of the above carboxylic acid in 10 mL of ether was added 0.5 mL (5.8 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and then concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in 1 mL of $CH_2Cl_2$ and this mixture was slowly added to 8 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen ethyl malonate at 0 °C. The solution was allowed to stir for 1 h and was then quenched with a 1 N HCl solution. The reaction mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.30 g (53%) of 3-(1-benzyl-3-methyl-2-oxopiperidin-3-yl)-3-oxopropionic acid ethyl ester as a colorless oil: IR (neat) 1746, 1710, 1699, 1252, and 1128 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.23 (t, 3H, $J$ = 7.2 Hz), 1.47 (s, 3H), 1.52−1.79 (m, 3H), 2.32−2.40 (m, 1H), 3.22 (td, 1H, $J$ = 6.1 and 1.7 Hz), 3.71 (s, 2H), 4.14 (q, 2H, $J$ = 7.2 Hz), 4.50 (d, 1H, $J$ = 14.5 Hz), 4.64 (d, 1H, $J$ = 14.5 Hz), and 7.20−7.35 (m, 5H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 19.6, 23.1, 31.0, 45.2, 47.6, 50.6, 56.4, 61.1, 127.5, 128.0, 128.6, 136.8,

167.4, 170.1, and 202.3. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.03; H, 7.22; N, 4.36.

**Rhodium(II)-Catalyzed Cycloaddition of 3-(1-Benzyl-3-methyl-2-oxopiperidin-3-yl)-2-diazo-3-oxopropionic Acid Ethyl Ester (7).** Diazo transfer of the above amido ester according to the general procedure gave **7** as a bright yellow oil (85%): IR (neat) 2136, 1716, 1638, and 1311 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.25 (t, 3H, $J$ = 7.1 Hz), 1.56 (s, 3H), 1.50−1.96 (m, 3H), 2.31 (td, 1H, $J$ = 13.1 and 4.2 Hz), 3.10−3.18 (m, 1H), 3.50 (td, 1H, $J$ = 12.1 and 4.2 Hz), 4.15 (q, 2H, $J$ = 7.1 Hz), 3.90 (d, 1H, $J$ = 14.7 Hz), 5.07 (d, 1H, $J$ = 14.7 Hz), and 7.19−7.29 (m, 5H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.3, 19.5, 23.3, 31.0, 46.9, 49.7, 54.5, 61.1, 127.2, 128.3, 128.4, 137.5, 160.9, 171.8, and 192.1.

Diazo amide **7** decomposed on standing and was immediately subjected to the rhodium(II)-catalyzed reaction. To a mixture of 20 $\mu$L (0.17 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) acetate in 1 mL of benzene at reflux was added 30 mg (0.09 mmol) of **7** in 0.5 mL of benzene over a period of 10 min. The reaction was heated at reflux for an additional 2 h, cooled to rt, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 33 mg (80%) of 2-benzyl-6-methyl-7-oxo-11-oxa-2-azatricyclo[6.2.1.0$^{1,6}$]undec-9-ene-8,9,-10-tricarboxylic acid 8-ethyl ester 9,10-dimethyl ester (**9**) as a bright yellow oil: IR (neat) 1731, 1527, 1435, and 1273 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.22 (s, 3H), 1.31 (t, 3H, $J$ = 7.1 Hz), 1.60−1.83 (m, 3H), 2.50−3.12 (m, 3H), 3.71 (s, 3H), 3.77 (s, 3H), 3.95 (d, 1H, $J$ = 13.9 Hz), 4.12 (d, 1H, $J$ = 13.9 Hz), 4.19-4.36 (m, 2H), and 7.00−7.40 (m, 5H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 18.8, 19.5, 33.9, 49.9, 52.1, 52.9, 54.3, 62.1, 62.3, 102.6, 125.9, 128.3, 128.4, 128.9, 136.0, 158.7, 161.7, 165.6, 166.6, 167.2. Anal. Calcd for $C_{24}H_{27}NO_8$ [+Li]: 464.1897. Found: 464.1899.

To a mixture of 30 mg (0.20 mmol) of *N*-phenylmaleimide and 2 mg of rhodium(II) acetate in 1 mL of benzene at reflux was added 30 mg (0.09 mmol) of **7** in 0.5 mL of benzene over a period of 10 min. The mixture was heated at reflux for an additional 2 h, cooled to rt, and concentrated under reduced pressure. The residue was crystallized from $CH_2Cl_2$/hexane to give 37 mg (83%) of 1-benzyl-6,9b-epoxy-4a-methyl-5,7,9-trioxo-8-phenyldodecahydropyrrolo[3,4]quinoline-6-carboxylic acid ethyl ester (**10**) as a white solid: mp 160−161 °C; IR (KBr) 1775, 1737, 1711, and 1374 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.38 (s, 3H), 1.39 (t, 3H, $J$ = 6.9 Hz), 1.60−2.00 (m, 4H), 2.90−3.55 (m, 2H), 3.55 (d, 1H, $J$ = 7.3 Hz), 3.63 (d, 1H, $J$ = 13.7 Hz), 3.88 (d, 1H, $J$ = 7.3 Hz), 4.28 (d, 1H, $J$ = 13.7 Hz), 4.30−4.50 (m, 2H), and 7.20−7.50 (m, 10H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.2, 17.2, 20.3, 26.2, 44.6, 53.4, 62.5, 87.8, 103.0, 126.2, 128.2, 128.3, 128.4, 128.5, 128.7, 129.4, 131.5, 139.3, 162.4, 171.9, 175.0, and 204.7. Anal. Calcd for $C_{28}H_{28}N_2O_6$: C, 68.84; H, 5.78; N, 5.73. Found: C, 68.63; H, 5.62; N, 5.71.

**3-Methyl-2-oxo-1-(3-butenyl)piperidine-3-carboxylic Acid.** To a stirred solution of 2.30 g (12.2 mmol) of 3-carbethoxy-3-methyl-2-piperidinone in 30 mL of THF was added 0.59 g (14.6 mmol) of 60% NaH in mineral oil. The solution was heated to reflux for 1 h and then cooled to rt, and 2.50 g (18.2 mmol) of 1-bromo-3-butene and 2.50 g (16.5 mmol) of NaI were added. The solution was heated at reflux for 2 h, cooled to rt, and quenched with $H_2O$. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were concentrated under reduced pressure, the residue was dissolved in $CH_3OH$, 15 mL (45 mmol) of 3 M KOH was added, and the solution was allowed to stir at rt for 10 h. The solution was washed with ether, acidified to pH 2, and extracted with $CH_2Cl_2$. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 2.01 g (78%) of 3-methyl-2-oxo-1-(3-butenyl)piperidine-3-carboxylic acid as a white solid: mp 120−121 °C; IR (KBr) 3439 (br), 2919, 1730, and 1621 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.48 (s, 3H), 1.72−1.90 (m, 3H), 2.10−2.22 (m, 1H), 2.27 (dd, 2H, $J$ = 14.0 and 7.0 Hz), 3.20−3.35 (m, 3H), 3.48 (ddd, 1H, $J$ = 13.5, 6.9, and 6.8 Hz), 4.90−5.10 (m, 2H), 5.60−5.80 (m, 1H), and 12.23 (brs, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 18.9, 26.5, 30.4, 31.4, 47.4, 47.6, 48.8, 117.3, 134.5, 173.5, and 174.4. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.43; H, 8.02; N, 6.60.

**3-[3-Methyl-2-oxo-1-(3-butenyl)piperidin-3-yl]-3-oxopropionic Acid Methyl Ester.** To a stirred solution of 0.30 g (1.3 mmol) of the above carboxylic acid in 20 mL of ether was added 0.40 mL (3.8 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in $CH_2Cl_2$ and was slowly added to 4 mL of a 0.5 M THF solution of the magnesium dianion of hydrogen methyl malonate at 0 °C. The solution was allowed to stir for 1 h and was then quenched with a 1 N HCl solution. The mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.30 g (75%) of 3-[3-methyl-2-oxo-1-(3-butenyl)piperidin-3-yl]-3-oxopropionic acid methyl ester as a colorless oil: IR (neat) 1742, 1707, 1627, and 1438 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.38 (s, 3H), 1.40−1.55 (m, 1H), 1.78 (ddd, 2H, $J$ = 12.1, 6.2, and 5.9 Hz), 2.20-2.39 (m, 3H), 3.20−3.59 (m, 4H), 3.66 (s, 3H), 3.67 (s, 1H), 3.68 (s, 1H), 4.97−5.06 (m, 2H), and 5.70−5.82 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.8, 23.2, 30.9, 31.6, 45.1, 47.1, 48.5, 52.1, 56.3, 116.9, 135.2, 168.0, 169.9, and 202.3. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.83; H, 7.77; N, 5.09.

**3-[3-Methyl-2-oxo-1-(3-butenyl)piperidin-3-yl]-2-diazo-3-oxopropionic Acid Methyl Ester (11).** Diazo transfer of the above amido ester according to the general procedure gave **11** as a yellow oil (62%): IR (neat) 2133, 1730, 1680, 1637, and 1319 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.47 (s, 3H), 1.50−1.58 (m, 1H), 1.75−1.89 (m, 1H), 1.90−2.08 (m, 1H), 2.20−2.34 (m, 3H), 3.15−3.27 (m, 2H), 3.60 (dt, 1H, $J$ = 10.5 and 5.6 Hz), 3.63 (dt, 1H, $J$ = 12.1 and 4.4 Hz), 3.70 (s, 3H), 4.94−5.06 (m, 2H), and 5.65−5.82 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.5, 23.3, 31.0, 31.2, 47.0, 48.0, 51.8, 54.4, 116.2, 135.9, 161.3, 171.3, and 192.0. Diazo amide **11** decomposed on standing and was immediately subjected to the rhodium-catalyzed reaction. All attempts to isolate an internal cycloadduct from the decomposition of **11** failed to give any characterizable product.

**3-Methyl-2-oxo-1-(4-pentenyl)piperidine-3-carboxylic Acid.** To a stirred solution of 2.80 g (15.0 mmol) of 3-carbethoxy-3-methyl-2-piperidone in 30 mL of THF was slowly added 0.66 g (16.5 mmol) of 60% NaH in mineral oil. The solution was heated to reflux for 1 h and cooled to rt, and 4.50 g (30.0 mmol) of 1-bromo-4-pentene and 2.50 g (16.5 mmol) of NaI were added. The solution was heated at reflux for 2 h, cooled to rt, and quenched with $H_2O$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were concentrated under reduced pressure, and the residue was dissolved in 30 mL of methanol. To this solution was added 15 mL (45 mmol) of a 3 M KOH solution and the mixture was allowed to stir at rt for 10 h. The solution was washed with ether, acidified to pH 2, and extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 3.2 g (82%) of 3-methyl-2-oxo-1-(4-pentenyl)piperidine-3-carboxylic acid as a white solid: mp 115−116 °C; IR (KBr) 3430 (br), 2917, 1729, and 1614 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.45 (s, 3H), 1.57 (ddd, 2H, $J$ = 14.9, 7.4, and 7.4 Hz), 1.72−1.90 (m, 3H), 1.96 (dd, 2H, $J$ = 14.1 and 7.0 Hz), 2.05−2.20 (m, 1H), 3.20−3.40 (m, 4H), 4.80−5.00 (m, 2H), 5.60−5.80 (m, 1H), and 11.90 (br s, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.0, 25.8, 26.0, 30.6, 30.8, 47.8, 48.5, 115.3, 137.3, 173.0, and 174.7. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.85; H, 8.37; N, 6.12.

**3-[3-Methyl-2-oxo-1-(4-pentenyl)piperidin-3-yl]-3-oxopropionic Acid Methyl Ester.** To a stirred solution of 0.40 g (1.8 mmol) of the above acid in 10 mL of ether was added 0.50 mL (5.8 mmol) of oxalyl chloride and one drop of DMF. The solution was allowed to stir at rt for 30 min and was then concentrated under reduced pressure to remove the excess oxalyl chloride. The residue was taken up in 1 mL of $CH_2Cl_2$ and this solution was added slowly to 8 mL of a 0.5 M THF

solution of the magnesium dianion of hydrogen methyl malonate at 0 °C. The solution was allowed to stir for 1 h and was then quenched with a 1 N HCl solution. The mixture was extracted with ether, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.35 g (67%) of 3-[3-methyl-2-oxo-1-(4-pentenyl)piperidin-3-yl]-3-oxopropionic acid methyl ester as a colorless oil: IR (neat) 1739, 1716, 1626, and 1432 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.38 (s, 3H), 1.46−1.65 (m, 3H), 1.79 (dt, 2H, $J$ = 12.0 and 6.0 Hz), 2.02 (dd, 2H, $J$ = 14.5 and 6.8 Hz), 2.30−2.40 (m, 1H), 3.09−3.43 (m, 4H), 3.64 (d, 1H, $J$ = 16.2 Hz), 3.67 (s, 3H), 3.73 (d, 1H, $J$ = 16.2 Hz), 4.92−5.02 (m, 2H), and 5.70−5.82 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.9, 23.2, 26.0, 30.9, 31.0, 45.1, 47.5, 48.3, 52.2, 56.3, 115.1, 137.6, 168.0, 169.7, and 202.4. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 63.86; H, 7.95; N, 4.88.

**Rhodium-Catalyzed Reaction of 3-[3-Methyl-2-oxo-1-(4-pentenyl)piperidin-3-yl]-2-diazo-3-oxopropionic Acid Methyl Ester (12).** Diazo transfer of the above amido ester according to the general procedure gave **12** as a yellow oil (70%): IR (neat) 2136, 1717, 1636, and 1312 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.46 (s, 3H), 1.30−2.10 (m, 7H), 2.26 (dt, 1H, $J$ = 13.0 and 4.2 Hz), 3.10−3.30 (m, 3H), 3.61 (dt, 1H, $J$ = 12.0 and 4.2 Hz), 3.68 (s, 3H), 4.86−4.98 (m, 2H), and 5.65−5.79 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 19.6, 23.3, 25.8, 30.9, 31.2, 47.1, 47.8, 51.9, 54.4, 114.7, 138.1, 161.2, 171.3, and 192.0. Diazo amide **12** decomposed on standing and was immediately subjected to the rhodium-catalyzed reaction. All attempts to isolate an internal cycloadduct from the decomposition of **12** failed to give any characterizable product. However, it was possible to isolate a bimolecular cycloadduct using DMAD as the trapping agent. To a mixture of 21 $\mu$L (0.17 mmol) of dimethyl acetylenedicarboxylate and 2 mg of rhodium(II) acetate in 2 mL of benzene at reflux was added 30 mg (0.1 mmol) of **12** in 0.5 mL benzene over a period of 10 min. The mixture was heated at reflux for an additional 2 h, cooled to rt, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 35 mg (78%) of 2-(4-pentenyl)-6-methyl-7-oxo-11-oxa-2-azatricyclo[6.2.1.0$^{1,6}$]undec-9-ene-8,9,10-tricarboxylic acid 8-methyl ester 9,10-dimethyl ester (**13**) as a bright yellow oil: IR (neat) 1730, 1650, 1520, and 1330 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.19 (s, 3H), 1.60−2.00 (m, 7H), 2.63 (t, 1H, $J$ = 13.1 Hz), 2.94−3.07, (m, 2H), 3.05−3.20 (m, 1H), 3.35 (dt, 1H, $J$ = 11.5 and 5.6 Hz), 3.67 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.87−4.96 (m, 2H), and 5.55−5.70 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 18.9, 19.8, 26.6, 30.1, 34.1, 50.7, 52.0, 52.7, 52.8, 54.5, 57.1, 77.3, 102.3, 115.8, 115.9, 136.8, 158.8, 162.1, 165.9, 166.5, and 198.6; HRMS calcd for $C_{21}H_{27}NO_8$: 421.1736. Found: 421.1732.

**3-[3-Methyl-2-oxo-1-(5-carbomethoxy-4-pentenyl)piperidin-3-yl]-3-oxopropionic Acid Ethyl Ester.** To a stirred solution containing 0.13 g (0.4 mmol) of 3-[3-methyl-2-oxo-1-(4-pentenyl)piperidin-3-yl]-3-oxopropionic acid ethyl ester in $CH_2Cl_2$ at −78 °C was added $O_3$ until the solution became light blue. Oxygen was then bubbled through the solution to remove the excess $O_3$. To this solution was added 0.12 g (2.0 mmol) of dimethyl sulfide and the solution was allowed to warm to rt while stirring over a period of 12 h. The solution was concentrated under reduced pressure to remove the excess dimethyl sulfide and the crude aldehyde was taken up in $CH_2Cl_2$. To this solution was added 0.21 g (0.6 mmol) of (carbomethoxymethylene)triphenylphosphorane and the solution was allowed to stir at rt for 2 h. The mixture was quenched by pouring into $H_2O$, the organic phase was separated, and the aqueous phase was extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.80 g (54%) of 3-[3-methyl-2-oxo-1-(5-carbomethoxy-4-pentenyl)piperidin-3-yl]-3-oxopropionic acid ethyl ester as a colorless oil: IR (neat) 1770, 1750, 1670, 1640, 1500, and 1475 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.23 (t, 3H, $J$ = 7.1 Hz), 1.35 (s, 3H), 1.45−1.78 (m, 5H), 2.15 (dd, 2H, $J$ = 13.9 and 7.1 Hz), 2.26−2.35 (m, 1H), 3.19−3.40 (m, 4H), 3.57 (d, 1H, $J$ = 16.2 Hz), 3.64 (s, 3H), 3.67 (d, 1H, $J$ = 16.2 Hz), 4.08 (q, 2H, $J$ = 7.1 Hz), 5.78 (d, 1H, $J$ = 15.7 Hz), and 6.88, (dt, 1H, $J$ = 11.3 and 5.1 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 19.8, 23.1, 25.3, 29.5, 30.9, 45.2, 47.4, 48.3, 51.4, 56.3, 61.1, 121.5, 148.0, 166.8, 167.6, 169.9, and 202.4. Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.04; H, 7.24; N, 4.16.

**Rhodium(II)-Catalyzed Decomposition of 3-[3-Methyl-2-oxo-1-(5-carbomethoxy-4-pentenyl)piperidin-3-yl]-2-diazo-3-oxopropionic Acid Ethyl Ester (14).** Diazo transfer of the above amido ester according to the general procedure gave **14** as a yellow oil (70%) which was used immediately used in the next step: IR (neat) 2140, 1717, 1644, and 1312 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.21 (t, 3H, $J$ = 7.1 Hz), 1.45 (s, 3H), 1.50−2.10 (m, 5H), 2.13 (dd, 2H, $J$ = 14.6 and 7.4 Hz), 2.26 (dt, 1H, $J$ = 13.0 and 4.1 Hz), 3.10−3.20 (m, 1H), 3.23 (t, 2H, $J$ = 7.4 Hz), 3.56−3.65 (m, 1H), 3.66 (s, 3H), 4.13 (q, 2H, $J$ = 7.1 Hz), 5.78 (d, 1H, $J$ = 15.6 Hz), and 6.91 (dt, 1H, $J$ = 15.6 and 6.9 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.2, 19.6, 23.2, 25.0, 29.8, 30.9, 47.1, 47.9, 51.3, 54.4, 61.0, 121.1, 148.7, 160.9, 166.9, 171.5, and 192.0. Diazo amide **14** decomposed on standing and was immediately subjected to the rhodium-catalyzed reaction. All attempts to isolate an internal cycloadduct from the decomposition of **14** failed to give any characterizable product.

**3-Carbethoxy-1-(1′-oxo-4′-pentenyl)-2-piperidone (17).** To a stirred solution of 0.50 g (2.9 mmol) of 2-oxopiperidine-3-carboxylic acid ethyl ester (**16**) in 20 mL of THF at −78 °C was added 4.0 mL (6.4 mmol) of a 1.6 M *n*-butyllithium solution in hexane and the mixture was allowed to stir while warming to 0 °C. The solution was cooled to −78 °C and 0.38 g (3.2 mmol) of 4-pentenoic acid chloride in 1 mL of $CH_2Cl_2$ was added. The mixture was allowed to stir while warming to rt over a period of 2 h. The reaction was quenched with $H_2O$, the organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.44 g (60%) of **17** as a colorless oil: IR (neat) 1734, 1692, 1299, and 1148 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.22 (t, 3H, $J$ = 7.1 Hz), 1.68−2.20 (m, 4H), 2.32 (dd, 2H, $J$ = 14.0 and 7.2 Hz), 2.94 (td, 2H, $J$ = 7.4 and 2.1 Hz), 3.45 (t, 1H, $J$ = 7.4 Hz), 3.55−3.75 (m, 2H), 4.16 (q, 2H, $J$ = 7.1 Hz), 4.80−5.05 (m, 2H), and 5.70−5.85 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 20.6, 24.1, 28.8, 38.5, 43.5, 51.4, 61.7, 115.2, 137.2, 169.8, 176.0. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.48; H, 7.39; N, 5.52.

**3-[3-Carbethoxy-2-oxo-1-(1′-oxo-4′-pentenyl)piperidin-3-yl]-2-diazo-3-oxopropionic Acid Ethyl Ester (18).** To a stirred solution of 0.13 g (0.5 mmol) of imide **22** in 20 mL of THF at 0 °C was added 0.30 mL (0.6 mmol) of a 2.0 M solution of *n*-butylmagnesium chloride in THF. The solution was allowed to stir at 0 °C for 1 h and then 0.20 g (1.1 mmol) of ethyl 2-diazomalonyl chloride was added. The solution was allowed to stir at 0 °C for 2 h and was then quenched with $H_2O$. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel to give 0.11 g (55%) of **18** as a yellow oil which was immediately used in the next step as a consequence of its lability: IR (neat) 2140, 1736, 1703, 1696, and 1637 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.26 (t, 3H, $J$ = 7.1 Hz), 1.27 (t, 3H, $J$ = 7.1 Hz), 1.60−2.00 (m, 2H), 2.30−2.45 (m, 3H), 2.63 (dt, 1H, $J$ = 9.2 and 4.2 Hz), 2.80−3.05 (m, 2H), 3.66−3.89 (m, 2H), 4.20 (q, 2H, $J$ = 7.1 Hz), 4.28 (q, 2H, $J$ = 7.1 Hz), 4.92−5.05 (m, 2H), and 5.72−5.85 (m, 1H);$^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 13.9, 14.2, 20.4, 28.2, 28.9, 37.9, 43.5, 61.9, 62.8, 69.9, 115.1, 137.3, 160.7, 166.6, 168.4, 176.3, and 186.9.

**9,10b-Epoxy-3,8-dioxodecahydropyrido[3,2,1-*ij*]quinoline-7a,9-dicarboxylic Acid Diethyl Ester (19).** To a 50 mg (0.12 mmol) sample of diazo amide **18** in 0.5 mL of benzene was added 2 mg of rhodium(II) acetate. The mixture was heated at 50 °C in an oil bath for 4 h. The mixture was

concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel to give 0.42 g (95%) of **19** as a white solid: mp 120−121 °C; IR (neat) 1735,-1656, and 1054 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.26 (t, 3H, $J$ = 7.2 Hz), 1.31 (t, 3H, $J$ = 7.2 Hz), 1.64−1.86 (m, 4H), 1.90 (dd, 1H, $J$ = 13.5 and 4.1 Hz), 2.02 (td, 1H, $J$ = 13.3 and 4.1 Hz), 2.12−2.32 (m, 2H), 2.37 (dd, 1H, $J$ = 13.3 and 8.2 Hz), 2.48−2.62 (m, 2H), 2.96 (td, 1H, $J$ = 12.8 and 3.4 Hz), 4.21 (qd, 2H, $J$ = 7.1 and 2.0 Hz), 4.30 (q, 2H, $J$ = 7.2 Hz), and 4.64−4.76 (m, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) d 14.0, 14.1, 19.8, 25.0, 27.4, 32.0, 34.9, 37.7, 37.8, 57.7, 62.0, 62.4, 86.8, 94.3, 164.7, 167.7, 169.6, and 198.6. Anal. Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.02; H, 6.31; N, 43.81.

**Computational Procedures**. PM3 calculations were carried out within Spartan.[42] MM3* results were obtained with Macromodel, version 4.5.[43] All other calculations were of the *ab initio* type and performed by application of Gaussian-94.[44] Geometry optimizations for zwitterions, triplets, and open-shell singlets **25**−**32** were carried out within the RHF, RHF, and GVB frameworks, respectively. The latter utilized two perfect-pairing electron pairs (GVB(2)). The DFT calculations (B3LYP = Becke3LYP) for **33**−**36** were limited to the 3-21G and 6-31G* basis sets. Geometry optimizations were carried out with the B3LYP/3-21G basis set followed by single point energies at the 6-31G* level (i.e. B3LYP/3-21G//B3LYP/6-31G*). Transition states were subjected to a frequency analysis to assure that they show a single negative force constant (Nimag = 1).

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**Supporting Information Available:** $^1$H-NMR and $^{13}$C-NMR spectra for all compounds with high-resolution mass spectra together with ORTEP drawings for structures **10** and **19** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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