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Studies on the Himbert Intramolecular Arene/Allene Diels–Alder Cycloaddition. Mechanistic Studies and Expansion of Scope to All-Carbon Tethers

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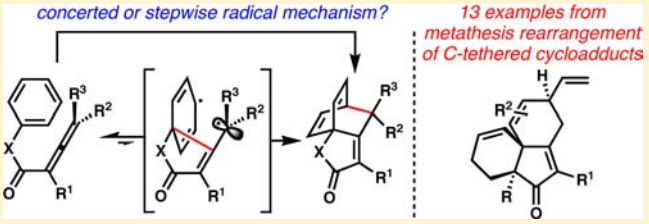
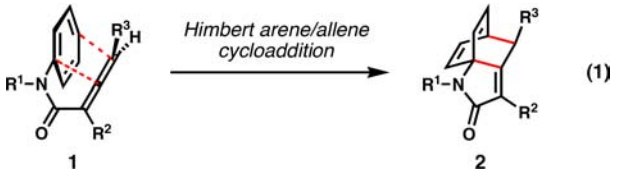
Supporting Information

ABSTRACT: The unusual intramolecular arene/allene cycloaddition described 30 years ago by Himbert permits rapid access to strained polycyclic compounds that offer great potential for the synthesis of complex scaffolds. To more fully understand the mechanism of this cycloaddition reaction, and to guide efforts to extend its scope to new substrates, quantum mechanical computational methods were employed in concert with laboratory experiments. These studies indicated that the cycloadditions likely proceed via concerted processes; a stepwise biradical mechanism was shown to be higher in energy in the cases studied. The original Himbert cycloaddition chemistry is also extended from heterocyclic to carbocyclic systems, with computational guidance used to predict thermodynamically favorable cases. Complex polycyclic scaffolds result from the combination of the cycloaddition and subsequent ring-rearrangement metathesis reactions.



INTRODUCTION

The unusual intramolecular arene/allene cycloaddition reaction reported over 30 years ago by Himbert and Henn[1,2] (eq 1)



converts relatively simple reactants into complex bridged polycyclic architectures that are themselves poised for further transformations. In what appears to be the first application of this chemistry, our UC Irvine laboratory used lactam-containing Himbert cycloadducts as the substrates for ring-rearrangement metathesis reactions, resulting in fused polycyclic lactams.[3] This chemistry is part of our broader program to take advantage of under-utilized processes to convert readily available aromatic systems into complex organic scaffolds.[4] In past cases when mechanistic details have been difficult to glean from experiment, our UC Irvine and UC Los Angeles laboratories have engaged in fruitful collaborations involving density functional theory (DFT) methods to provide useful insights into mechanism.[5] In this disclosure, we report our joint investigation of some mechanistic aspects of the fascinating dearomatizing cycloaddition first described by the Himbert group, and an expansion of scope to include carbocyclic products that required key computational insights for success.

BACKGROUND

Our recent work on the metathesis rearrangement of Himbert cycloadducts[3] (Scheme 1) points to the utility of this fascinating cycloaddition reaction in strategies to rapidly access complexity from simple substrates. That work represents the first of many applications of this reaction that we are interested in pursuing. As a result, a greater understanding of the mechanism of this dearomatizing intramolecular Diels–Alder (IMDA) cycloaddition, which will provide better predictability in reaction outcome, is critical to our ongoing studies.

Himbert and co-workers were the first to discover and study the scope of the intramolecular arene/allene cycloaddition reactions;[1,2] and on the basis of the relative insensitivity of cycloaddition rates to donor and acceptor groups on the arene in amide-tethered substrates, they were led to favor a concerted cycloaddition mechanism over a polar, stepwise alternative.[6] Trifonov and Orahovats studied closely related cycloadditions that were set up by the reaction of allenoic acids with *N*-arylcarbodiimides (eq 2).[7] After activated ester formation and *O*- to *N*-acyl transfer, a spontaneous cycloaddition of the in situ generated allene carboximide (**8**) ensued at ambient temper-

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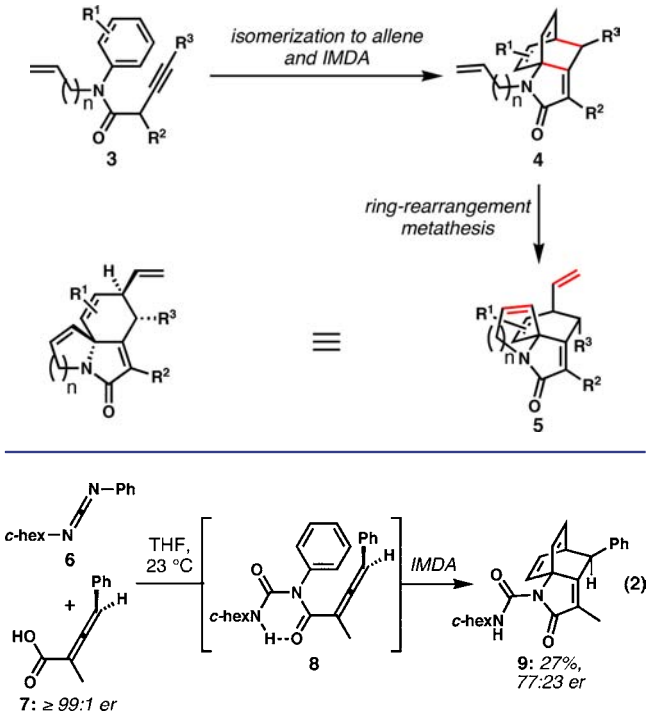
Scheme 1. Ring-Rearrangement Metathesis of Himbert Cycloadducts to Access Complex Polycyclic Lactams



ature. In contemplating a possible stepwise mechanism, they began with chiral, nonracemic allenoic acid **7**, and subjected it to reaction with a variety of carbodiimides (only one example shown). In all cases, a significant loss of enantiomeric purity was observed, and reasonable control experiments to ensure that the allenoic acid had not racemized prior to reaction were performed. Keeping in mind the results of Himbert that argued against a stepwise *polar* pathway, they suggested that a stepwise radical mechanism would account for all of the data that was available to them (see below).[7]

We posited that a greater comprehension of the reaction mechanism across various substrate types would inform on which, if any, cycloadditions would proceed with high levels of conservation of enantiomeric purity. The ability to transfer allenic axial chirality to point chirality would be critical to some applications of this chemistry in the synthesis of enantiopure complex molecules, including natural products and scaffolds for medicinal chemistry. Furthermore, such an improved mechanistic understanding might facilitate the expansion of scope to systems with different tethers. In the first portion of this disclosure, we present a computational investigation of both the Himbert cycloaddition of allene carboxamides and the Orahovats variant, as well as supporting experimental results. In the second part, we document the previously unknown cycloaddition reactions of benzyl allenyl ketones and show how computation provides a reliable predictive tool for these reactions.

RESULTS AND DISCUSSION

Cycloaddition Mechanism. The relatively narrow range of cycloaddition rates noted by Himbert among substrates with a broad range of electronically different arenes[6] (also observed in our studies) effectively militates against a polar stepwise mechanism. While there are no reported experimental observations that explicitly reject the notion of a concerted cycloaddition in the reactions studied by Himbert, the experiments of Orahovats do point to the possibility of a stepwise radical pathway. However, it should be noted that this specific system differed from most of the reactions studied by Himbert by the presence of the *N*-acylurea and, more importantly, the γ-phenyl substituent on the allene.

As noted by Orahovats and Trifonov,[7] molecular models indicate that close proximity and excellent alignment of the sp-hybridized allene carbon with the ipso carbon of the arene ring is easy to attain in these cycloaddition substrates; on the other hand, the distal carbons of each reacting π-system are not subject to such a perfect arrangement. This situation lends itself to the idea that five-membered ring formation—leading to a diradical intermediate of type **11** (eq 3)—might be a

mechanistically relevant first step. Recombination of the pentadienyl radical and the alkyl radical on the γ-carbon of the former allene would complete the formal cycloaddition process. The intermediacy of spiro-fused biradical **11** provides a means for loss of enantioenrichment via rotation about the former allene Cβ–Cγ σ bond. Certainly, a key consideration for the stepwise radical mechanism is the stability of the partially cyclized biradical intermediate. Appropriate substituents present on the allene γ-carbon can offer significant stabilization to the resulting radical, which does not benefit immediately from allylic stabilization owing to orbital orthogonality.

To learn more about the underlying cycloaddition mechanism in both of the Himbert and Orahovats systems, we studied the energetics of the two likely mechanisms using DFT. Furthermore, we investigated the Himbert case experimentally using both stereochemical probes and substrates designed to detect radical behavior.

Cycloaddition of Allene Carboxanilides. Beginning with the Himbert reaction of the type shown in eqs 1 and 3, both the concerted and the stepwise radical mechanisms were investigated. All stationary point structures were optimized using the B3LYP[8] functional and 6-31G(d) basis set in Gaussian09.[9] Single-point calculations on closed-shell species were conducted with M06-2X/6-311+G(d,p) on the B3LYP optimized geometries. In general, B3LYP and M06-2X produce similar optimized geometries.[10] However, activation energies and reaction energies as predicted by the two methods are different; as we have extensively benchmarked for cycloadditions such as those studied here,[10a] B3LYP is known to overestimate barriers by ~5 kcal/mol for concerted processes but provide sufficiently accurate values for reactions leading to diradicals. Additionally, the energies of cycloaddition reactions are predicted by B3LYP to be ~10 kcal/mol less exothermic than experiment.[11] We have found that M06-2X single-point calculations with reasonably large basis sets give much better values.

The M06-2X functional has been shown to provide accurate reaction energies and enthalpies for C–C bond formation, but has proven problematic for open-shell species.[12] We consider the M06-2X results to be most reliable for the concerted process; the relative energies of B3LYP open-shell (diradical)

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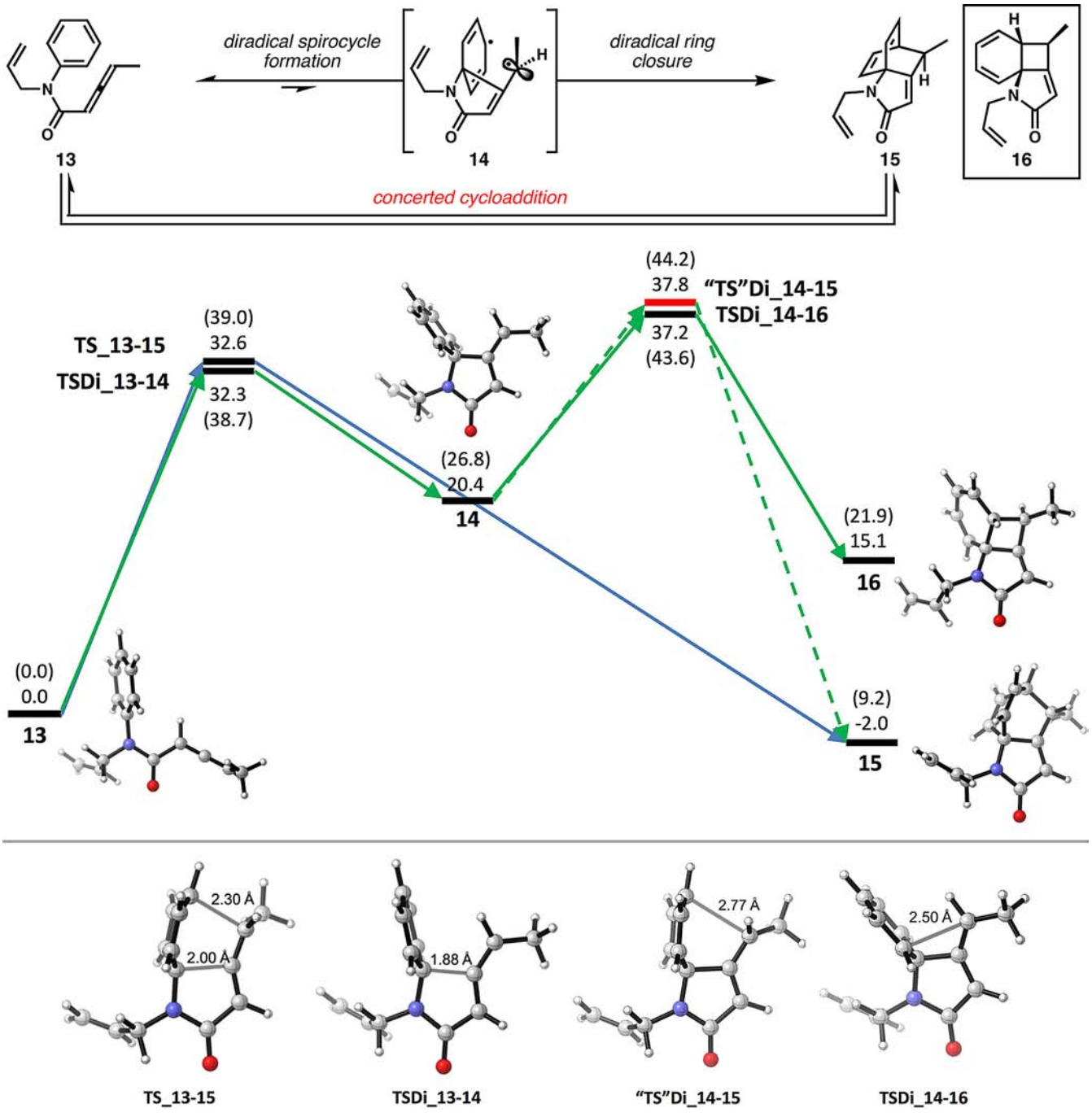

Figure 1. Calculated energies for the stepwise and direct cycloaddition of arene/allene **13**, with transition structure geometries shown below. All energies shown are in kcal/mol from M06-2X/6-311+G(d,p)/CPCM(xylenes) single-point calculations on geometries optimized with B3LYP/6-31G(d). "**TS"Di_14−15** (in red) was estimated by constraining the lactam C−C σ bond to 1.58 Å. (B3LYP energies are shown in parentheses).

and closed-shell species are more reliable. Thus, the difference is used to phase the energetics of diradical species. We refer to the latter as corrected M06-2X energies. All energies by both methods are given in the Supporting Information. Vibrational frequencies were computed to determine the nature of each stationary point; local minima and transition structures showed 0 and 1 imaginary frequency, respectively. The conductorlike polarizable continuum model (CPCM)[13] was used to compute solvation energies.

The reaction coordinate diagrams for both the concerted and stepwise mechanisms are shown in Figure 1. For the reaction **13** → **15**, the transition structures for the concerted reaction, **TS_13−15**, and the formation of the diradical, **TSDi_13−14**, are essentially isoenergetic, suggesting competition of both pathways. The formation of **15** is exergonic by 2.0 kcal/mol (M06-2X). B3LYP calculations suggest that this reaction is endergonic by 9.2 kcal/mol but, as alluded to earlier, this method is known to underestimate the exergonicity of cycloadditions.[11] The stepwise pathway initially leads to diradical intermediate **14**, which is 20.4 kcal/mol higher than the starting material. In this intermediate, the pentadienyl radical is extensively stabilized, but the other secondary radical does not initially benefit from allylic stabilization owing to the orthogonality of orbitals. From **14**, radical recombination with

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the para carbon of the phenyl ring again yields **15**. The transition structure for the second step, **TSDi_14−15**, could not be located on the potential energy surface; all efforts resulted in the concerted transition structure or led directly to ring-closure. In order to estimate the free energy value for this process, the C−C bond formed in the previous step was constrained to a value of 1.58 Å, slightly longer than its value of 1.55 Å in intermediate **14**. This process yielded an energy value for "**TS**"**Di_14−15** of about 37.8 kcal/mol, making it the rate-determining step of the stepwise reaction. Reversion of the diradical to reactants and subsequent concerted cycloaddition will be faster than ring-closure to the cycloadduct.

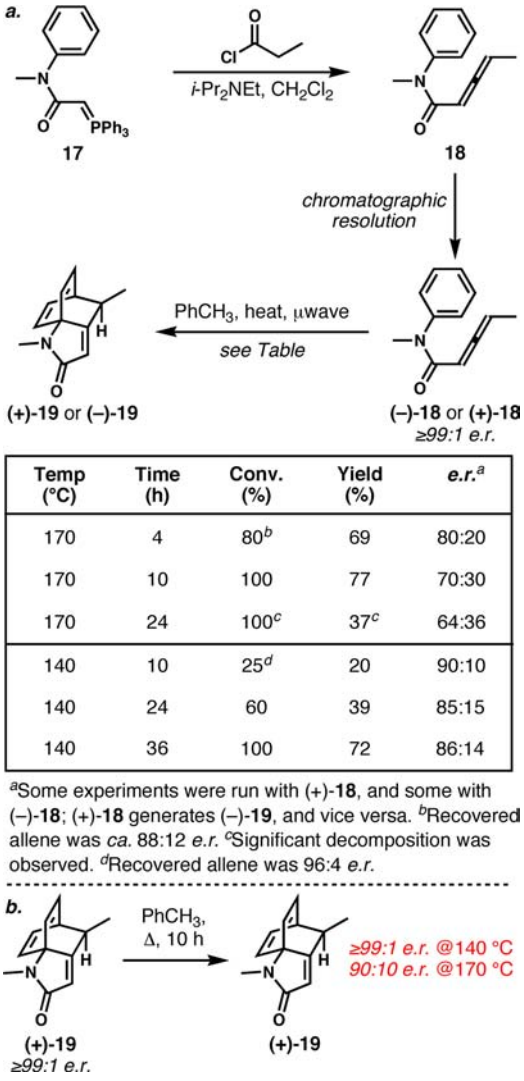
The transition state for the concerted and stepwise pathways have virtually identical energies; conceivably, a single transition state actually leads to both **15** and diradical **14**. This situation would require a bifurcation of the downhill pathway from **TS_13−15**, and related bifurcations have been found in ketene-diene cycloadditions.[14]

The energy barrier to cyclization to afford the formal [2 + 2] cycloaddition product **16** has a $\Delta G^{\ddagger}$ of 37.2 kcal/mol, similar to that for ring-closure to observed product **15**. However, **16** is substantially unfavorable thermodynamically and would, if formed at all, reform diradical **14** and proceed either toward initial allene **13** or the more stable product **15**. This conclusion is consistent with the failure to observe product **16** experimentally.

The optimized transition structures for the intramolecular cycloaddition of allenecarboxamide **13** are also shown in Figure 1. The concerted transition structure **TS_13−15** is slightly asynchronous, with forming-bond lengths of 2.0 Å and 2.3 Å. The diradical transition structure **TSDi_13−14** is relatively late, as indicated by the short C−C forming-bond length of 1.88 Å. By contrast, the two diradical-closing transition structures "**TS**"**Di_14−15** and **TSDi_14−16** are early, demonstrating longer bond lengths typical of radical recombinations.

The reaction is carried out at 170 °C and is nearly thermoneutral. Therefore, the reaction should be reversible and under thermodynamic control. An exergonicity of only 2.0 kcal/mol is consistent with the observed 74% yield of **15**. The computed equilibrium constant, [**15**]/[**13**] = 9.7. By examining the calculated thermodynamic energies of the reactants and products, the outcome of this reaction, as well as those of related analogs, can be predicted (see below).

These results predict that this particular Himbert cycloaddition proceeds via a concerted pathway, but that a single reversible cyclization to form diradical intermediate **14** is competitive with the direct Diels−Alder process. As a result, it might be possible to racemize chiral, enantioenriched allenes via diradicals of type **14**, even while the only productive pathway is via the concerted cycloaddition, a reaction that would be expected to be stereospecific. We have performed experiments, analogous to those of Orahovats and Trifonov, to test the idea that such a racemization pathway might occur (Figure 2a). Racemic *N*-methyl allenecarboxanilide **18** was prepared by Wittig reaction of the precursor phosphorane **17** with in situ generated methylketene as described by Himbert,[15] and it was resolved by semipreparative HPLC using chiral solid supports to obtain (−)-**18** and (+)-**18**, each of greater than 99:1 er.[16] At this stage, the absolute configuration of these enantiomeric allenes is unknown. Representative experiments shown in the table of Figure 2 revealed that our hypothesis—that racemization might be competitive with stereospecific cyclo-



Temp (°C)	Time (h)	Conv. (%)	Yield (%)	e.r.[a]
170	4	80[b]	69	80:20
170	10	100	77	70:30
170	24	100[c]	37[c]	64:36
140	10	25[d]	20	90:10
140	24	60	39	85:15
140	36	100	72	86:14

[a]Some experiments were run with (+)-**18**, and some with (−)-**18**; (+)-**18** generates (−)-**19**, and vice versa. [b]Recovered allene was *ca.* 88:12 *e.r.* [c]Significant decomposition was observed. [d]Recovered allene was 96:4 *e.r.*

Figure 2. (a) Cycloaddition studies on enantiomerically enriched allene **18**. (b) Racemization studies on enantiomerically enriched cycloadduct (+)-**19**.

addition—appears to be correct. When enantiomerically enriched **18** was heated to 170 °C, conversion was nearly complete after 4 h, affording cycloadduct **19** in 80:20 er. Further experiments revealed a time-dependent decrease in enantiopurity of the product, such that after 24 h the product was isolated with a 64:36 er and in low yield owing to thermal decomposition. However, running the reaction at 140 °C led to product formation with reasonable conservation of enantioselectivity. Therefore, the apparent competition between partial cyclization/allene racemization and direct stereospecific cycloaddition is worthy of concern, but the use of the minimal temperatures needed to promote cycloaddition can lead to products with useful levels of enantioenrichment.

We presumed that loss of enantioenrichment over time occurs in part via reversible cycloaddition with racemization of the allene via radical spirocyclization (also reversible). To test this idea, we investigated the thermal racemization of enantioenriched cycloadduct (Figure 2b), also obtained by semipreparative HPLC on chiral solid support. Heating of enantioenriched cycloadduct (+)-**19** to 170 °C for 10 h led to a slight erosion of enantiopurity (from ≥99:1 to 90:10 er), whereas heating to 140 °C for the same time led to recovery of

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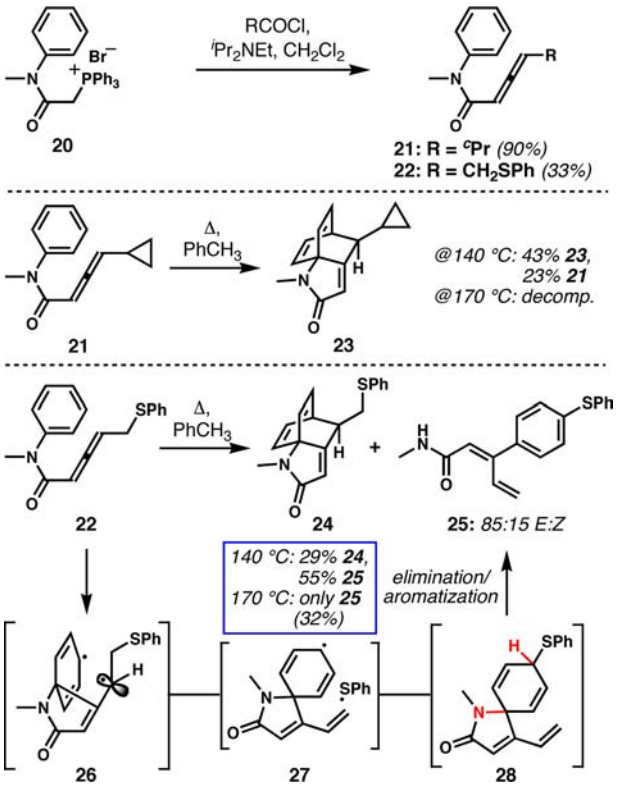
enantiopure material. All of this data points to a concerted cycloaddition that is readily reversible given enough thermal energy, and the idea that racemization occurs by reversible spirocyclization via a radical process appears reasonable. Of course, other means of allene racemization cannot be completely ruled out, but the neutral conditions in this case make racemization via acid−base chemistry or reversible nucleophilic attack to the allene unlikely. Furthermore, in reactions that did not proceed to complete conversion, recovered allene was still highly enantioenriched (96:4 er at 140 °C, 88:12 er at 170 °C).

Most importantly, we have shown that there is the possibility of these Himbert cycloadditions proceeding with a significant axial to central chirality transfer. The degree to which enantiopurity is conserved will likely be influenced by the radical stabilizing ability of the allene γ-substituent, and certainly by the reaction temperature.

For probes to detect the intermediacy of radical intermediates, we considered cyclopropane- and phenylthiomethyl-bearing allenes. Generation of γ-cyclopropyl-substituted allene **21** and γ-thiophenylmethyl allene **22** (Scheme 2)

Scheme 2. Experiments To Test for Radical Intermediates



was readily achieved using Wittig chemistry analogous to the method previously described by Himbert.[15,16] When cyclopropyl allene **21** was warmed to 140 °C for 8 h, a relatively clean mixture of unreacted allene and cycloadduct **23** was observed; however, at 170 °C, complete decomposition was observed. This result is consistent with the accessibility of the cycloreversion reaction, which might permit decomposition via radical intermediates related to **14**. In this case, cyclopropylcarbinyl radical ring-opening could lead to a host of different—and difficult to predict—reaction products. In search of a more compelling outcome, we examined thioether **22**. We assumed that the methylene spacer insulating the thioether from the allene in the presumed cycloaddition precursor would reduce any serious steric or electronic impact of this group. We hypothesized that, if the radical mechanism were operative, expulsion of phenylthiyl radical from an intermediate like **26** followed by radical recombination would lead to spirocyclic products related to **28**. When **22** was heated to 140 °C, we obtained a 1:1.7 ratio of cycloadduct **24** to diene **25** (*E*:*Z* mixture), whose origin is most easily explained by the radical cascade that we had predicted, followed by elimination of the amide to restore aromaticity. At 170 °C, rearranged diene **25** was the only identifiable product. We believe that the outcome of these experiments further supports the potential competition of radical-based reactions in these Himbert cycloadditions, and opens up possibilities to engineer intriguing new reactions based on the relatively facile formation of diradical intermediates of type **26**.

Cycloaddition of Allenic Imides. We have also computationally examined the substrate used by Orahovats.[7] Urea **8**, formed in situ as shown in eq 2, undergoes cycloaddition to form **9** at ambient temperatures. The key differences present in **9** and the Himbert substrate **13** are the *N*-acylurea group, which is able to engage in intramolecular hydrogen bonding, the methyl group on the allene α-carbon, and the phenyl substituent on the allene γ-carbon (in place of the methyl substituent in **13**). The concerted and stepwise cycloaddition pathways of **29**, a model for imide **8** wherein the cyclohexyl substituent has been replaced with a methyl group, were studied computationally and are presented in Figure 3.

The cycloaddition with the Orahovats *N*-acylurea compound shows a greater preference for the stepwise biradical pathway than the Himbert amide case, with **TSDi_29−30** located 1.5 kcal/mol lower than the concerted transition structure **TS_29−31**. Both pathways lead to the energetically favored cycloadduct **31**, with the radical pathway traversing through the diradical intermediate **30**. As expected, the phenyl group on the allene stabilizes the forming diradical; the intermediate is 16.2 kcal/mol higher than the starting material, compared with 20.4 kcal/mol for intermediate **14**. Radical recombination is still the rate-determining step at 24.3 kcal/mol. In short, the computed energetics for this reaction nicely explain the loss of enantioenrichment reported by Orahovats as shown in eq 2, and in close analogy to our observations with amide **18**.

The overall lowering of the energetics for the Orahovats imide may be attributed in part to the destabilization of reactant **29**; the methyl substituent on the allene prevents adoption of a conformation in which the p-orbitals of the allene are conjugated to the π-system of the amide, thereby preventing stabilization through conjugative effects. The hydrogen bonding arrangement (shown in eq 2 and Figure 3) likely also contributes to the facility of this reaction by biasing in favor of conformations conducive to cycloaddition.[17] As shown earlier, formation of the formal [2 + 2] cycloadduct is highly thermodynamically unfavorable and was not modeled in this reaction.

Our computational studies strongly suggest that the most favorable cycloaddition mechanism is a concerted pathway, because the second steps of the stepwise diradical mechanisms are highest in energy in both the Himbert and Orahovats systems. Previously described experimental results from Orahovats and new results from our group do corroborate the conclusion reached by computation that the first step of the stepwise diradical mechanism can be competitive with the

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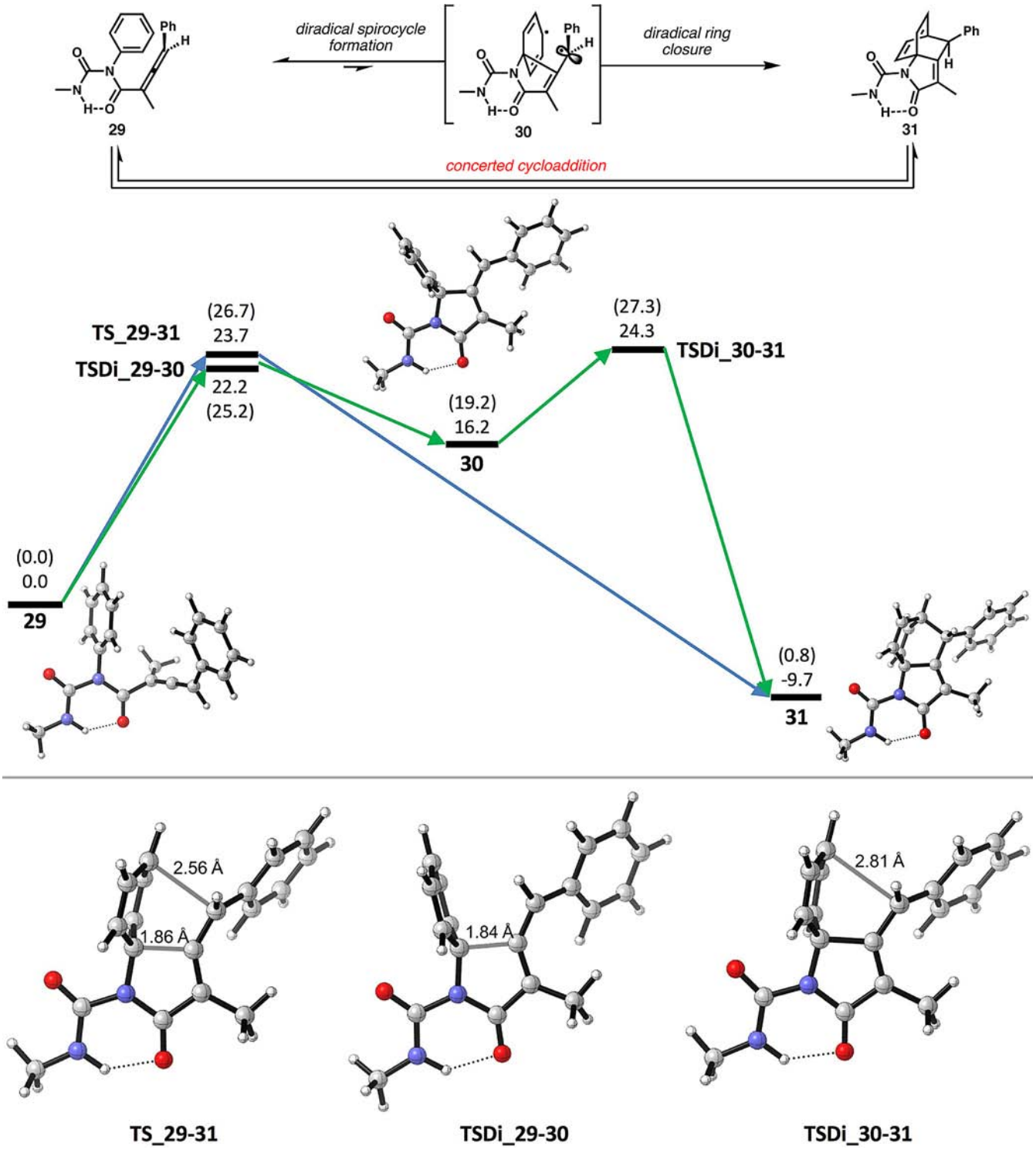

Figure 3. Calculated energies for the stepwise and direct cycloaddition of arene/allene **29**, with transition structure geometries shown below. All energies shown are in kcal/mol from M06-2X/6-311+G(d,p)/CPCM(THF) single-point calculations on geometries optimized with B3LYP/6-31G(d). (B3LYP energies are shown in parentheses.)

concerted cycloaddition in both systems; this phenomenon manifests itself in experiment by incomplete conservation of enantiopurity. The preference of one pathway over the other may be influenced by substituents on the benzene or allene components; substituents that stabilize the forming diradical should increase the likelihood of the diradical pathway. The fact that, at lower temperatures, we retained most of the enantioenrichment with substrate **18** (which bears only a methyl group in the γ-position of the allene) but the Orahovats example with the γ-phenyl group suffered greater degradation of enantioenrichment strongly supports this idea. Most importantly, a mechanism for racemization of chiral, enantioenriched allenes is presented by the relatively low barrier to spirocyclization via a radical manifold, and this potential issue needs to be considered in planning for the use of these types of cycloadditions to access enantioenriched

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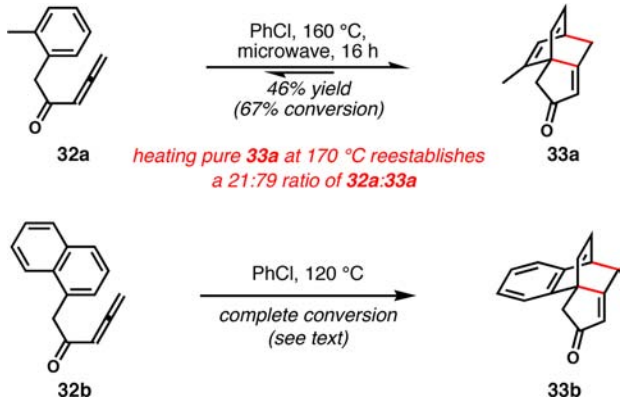
materials. Fortunately, it appears that computation can provide guidance in this regard.

Expansion of Substrate Scope to Carbocyclic Systems. In all of the experiments described by the Himbert and Orahovats groups, either carboxylic acid derivatives (amides, esters, thioesters, imides) or phosphorus-based groups (phosphonate esters, phosphinate esters, phosphinic amides) were used as tethers.[18] No examples of benzyl allenyl ketones were ever reported; therefore, as a first extension to different polycyclic architectures, we sought to extend the two-step sequence to carbon-linked systems. The allenyl ketone substrates were, for the most part, made by propargyl-metal additions to arylacetaldehydes followed by oxidation.[16,19]

Our efforts to extend Himbert cycloaddition reactivity to these carbon-linked systems were initially met with mixed results (Scheme 3). Benzyl allenyl ketone **32a** was partially

Scheme 3. Representative Himbert Cycloadditions with All-Carbon Tethers

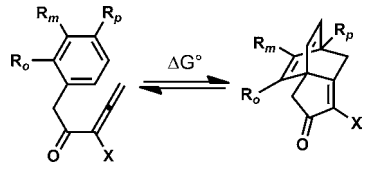


converted (~67%, with slight decomposition) to carbotricycle **33a** after heating to 160 °C for 12 h. Longer reaction times did not improve conversion. Heating isolated cycloadduct **33a** to 170 °C established an equilibrium mixture of allene/cycloadduct, clearly demonstrating that the limited conversion of benzyl allenyl ketone **32a** was a thermodynamic issue. On the other hand, naphthyl system **32b** proceeded with complete conversion—largely to tetracycle **33b**—under milder conditions, pointing to both a more kinetically facile and thermodynamically favorable dearomatization of the fused-arene system. Starting allene **32b** could not be purified to homogeneity; from material of only about 75% purity, a 54% yield of cycloadduct was obtained, indicating that the reaction is relatively efficient (~70% corrected).

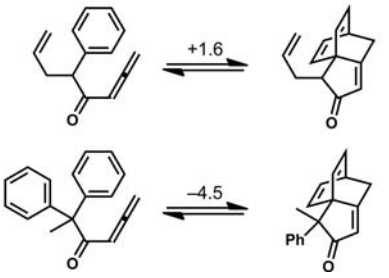
Thermodynamic Considerations and Computational Guidance. In combination with the calculated exergonicity of the cycloaddition of amide **13** of only 2 kcal/mol, the experiments with ketone **32a** suggested that many Himbert-type cycloadditions might be close to thermoneutral. This problem appears to be particularly prevalent for carbon-linked systems bearing monocyclic aromatic dienes. Because calculated energies of reaction for the amide-tethered cases using M06-2X were quite consistent with experimental results, we used computation as a predictive tool to see what substitution patterns on the benzyl allenyl ketone substrates should perturb the equilibrium toward products (Table 1).

The most important lesson learned from computational analysis of this reaction type was that substitution of most any

Table 1. Computed Thermodynamic Energies (M06-2X, in kcal/mol) of the Himbert Cycloadditions of Various Substituted Carbon-Linked Arene/Allenes



X	R	ΔG°	X	R	ΔG°
H	H	+0.4	H	R_o = OMe	–1.9
CO_2Me	H	–4.1	H	R_m = OMe	–1.8
CONHMe	H	–4.6	H	R_p = OMe	+2.0
SO_2Me	H	–3.0	H	R_o = Me	–2.1
Cl	H	–4.0	H	R_m = Me	+3.2
OMe	H	–2.1	H	R_p = Me	+0.8
Me	H	–2.3	H	R_o = F	+2.0
TMS	H	+2.4	H	R_o = Cl	–0.4
t-Bu	H	+0.1	H	R_o = CF_3	–0.8
Me	R_o = OMe	–5.0	H	R_o = $R_{o'}$ = Me	–2.5



group at the allene α-position would lead to a favorable reaction outcome. Most exciting was the observation that donor (methoxy) and acceptor (carbomethoxy, carboxamide) groups, alkyl groups (methyl), and a potentially removable substituent (chloride) all led to thermodynamically favored reactions according to computation; the fact that such different groups all led to predicted improvement in reaction outcome strongly suggests that the origin of the effect is steric in nature. Of the substrates evaluated by computation, the only outlier to this α-substituent effect is trimethylsilyl, which is most unusual. On its own, this result might be explained on the basis of allene stabilization; however, one would expect the α-methoxy group to have a significant stabilizing effect on the allene as well. Attribution to the extreme steric bulk of the group might be reasonable; however, placing a *tert*-butyl group at this position, while overall leading to a thermoneutral reaction, still has a net benefit on the thermodynamics of the cycloaddition relative to that of the unsubstituted case. At this stage, we do not have a clear hypothesis for the trimethylsilyl effect. Because this group is not beneficial to the cycloaddition chemistry, more detailed investigations did not seem warranted.

We had posited that placing a donor group on the aromatic ring to mimic the electronic effects of the nitrogen atom in the amide-linked cases might lead to equilibria that favored products. It is evident from the computational data that this hypothesis was too simplistic; methoxy groups ortho and meta to the tether lead to favored cycloadditions, whereas placement in the para position leads to less favorability. Methyl substitution at the meta position appears detrimental. Clearly, the thermodynamic profile of these reactions is affected by both electronic (possible perturbation of either starting material or

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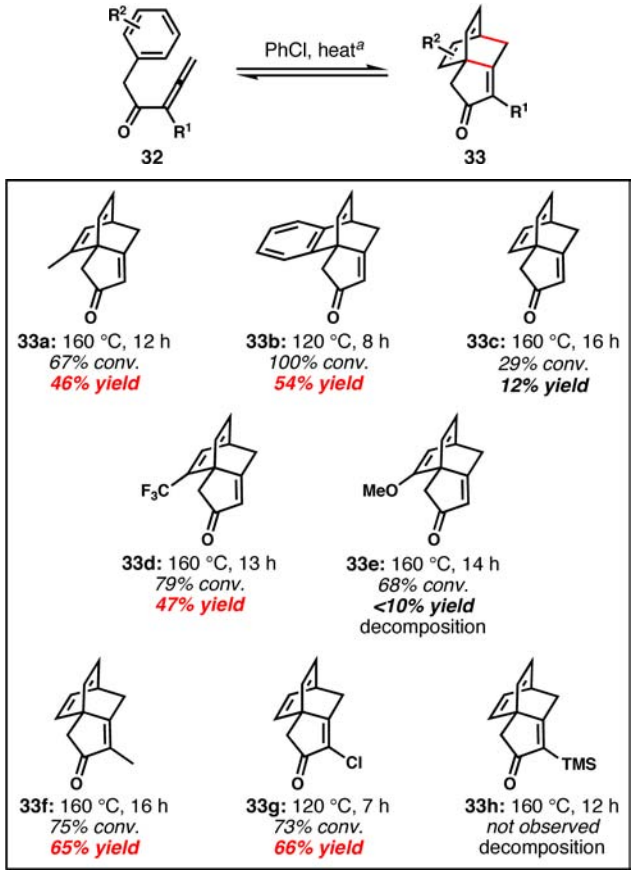
product ground state energies) and steric factors, and simple trends corresponding with, for example, Hammett parameters,[20] did not become obvious. The beneficial effects appear to be somewhat additive in some cases, with a highly favored reaction (5.0 kcal/mol) for the substrate with both allene α-methyl and arene o-methyl substituents.

Finally, we note that the presence of a tethered alkene at the ketone α-position (for prospective metathesis rearrangement) makes the cycloaddition less favorable, but a benzylic quaternary center leads to a reaction that is calculated to be highly favored.

Table 2 shows the outcome of many laboratory experiments that corroborate the computational results. We observed that

Table 2. Scope of the Himbert Arene/Allene Cycloaddition with All-Carbon Tethers



[a]Conversion values are NMR-based estimates of starting material disappearance, and undesired side products are often observed.

computational predictions were accurate in all reactions that cleanly proceeded to products; unfortunately, some of the cycloadditions with carbon tethers were more prone to decomposition than the amide-tethered cases, likely owing to facile enol formation and electrocyclic ring-closure, among other possibilities.[21,22] Certainly, the most important results are those that match the success predicted by computation with the α-methyl and α-chloro groups on the allene (**33f** and **33g**, respectively), simply because they indicate that either an alkyl group *or* a potentially removable/replaceable chloride will favor the formation of cycloadducts.

Although more detailed studies are required, if we assume additivity in the effects of substituents, the dramatic improvement afforded by the inclusion of certain substituents on the allene and the arene offers promise of a relatively general complexity-generating cycloaddition. Some noteworthy examples can be found in the next section.

At this stage, we are uncertain why the carbon-linked systems demonstrate different thermodynamic profiles compared with heteroatom-linked substrates; there is significant latitude with respect to linking heteroatoms (nitrogen, oxygen, sulfur)[18a,c,d] in the previous reports, suggesting that the detrimental effect of carbon cannot be readily explained by considerations of electronegativity or size of the linking atom. However, the synthetically useful yields obtained in many of the cases in Table 2 clearly demonstrate that an sp^2-hydridized heteroatom is not absolutely required for successful cycloadditions.

Rapid Generation of Complex Polycycles via Carbon-Tethered Himbert Cycloaddition and Ring-Rearrangement Metathesis. Because of our desire to access complex, all-carbon polycyclic scaffolds using this chemistry, we made several substrates bearing butenyl groups at the benzylic position. Himbert cycloadditions proceeded similarly to the unfunctionalized cases shown in Table 2. We are pleased to report that metathesis rearrangements of the products that we have generated in this way proceed smoothly to generate the complex carbopolycycles shown in Table 3. Second-generation Hoveyda–Grubbs-type catalyst **36**[23] performed well in these reactions, as they had in the lactam cases that we had previously reported.[3] In several cases, the cycloaddition efficiency is low, as expected on the basis of our computational results. On the other hand, most of the cases are quite efficient, and we note the excellent results when two substituents that predict favorability based on computation are combined (especially **37g** and **37h**). Finally, the metathesis rearrangement process is efficient in all cases, leading to tri- and tetracyclic compounds that bear natural-product-like scaffolds. Product **37l** is particularly noteworthy, because of its vicinal quaternary stereogenic centers.[24]

In all cases, the substrates were synthesized in racemic form, and the cycloadducts are therefore also obtained in racemic form. It is noteworthy that the cycloaddition reactions of substrates bearing groups at the ortho position of the aromatic ring (those leading to **37b–d**, **37g–k**, and **37m**) are highly diastereoselective, fortuitously providing as the major isomers those that can more easily undergo the subsequent metathesis rearrangement (see **38**) to afford polycyclic ketones **37**. Multiple side products were formed in the cycloadditions leading to **37b** and **37c**, preventing careful analysis of diastereoselectivity; however, the others were all formed in at least 9:1 dr. The high selectivity presumably arises from minimization of $A_{1,3}$-strain[25] in the reactive conformation/transition structure, as shown in Figure 4.

Perhaps not surprisingly, both the cycloaddition and metathesis rearrangement steps can be carried out in a single pot; after consumption of allene **34m**, addition of the ruthenium metathesis catalyst and an atmosphere of ethylene with warming directly provides **37m** in an improved yield as compared with the two-pot process, likely owing to the elimination of one purification step (eq 4).

■ CONCLUSIONS AND FUTURE DIRECTIONS

Through the combination of experiment and computation, we have learned that the dearomatizing arene/allene cycloaddition first reported by Himbert very likely proceeds by a concerted process rather than the stepwise radical process put forth by

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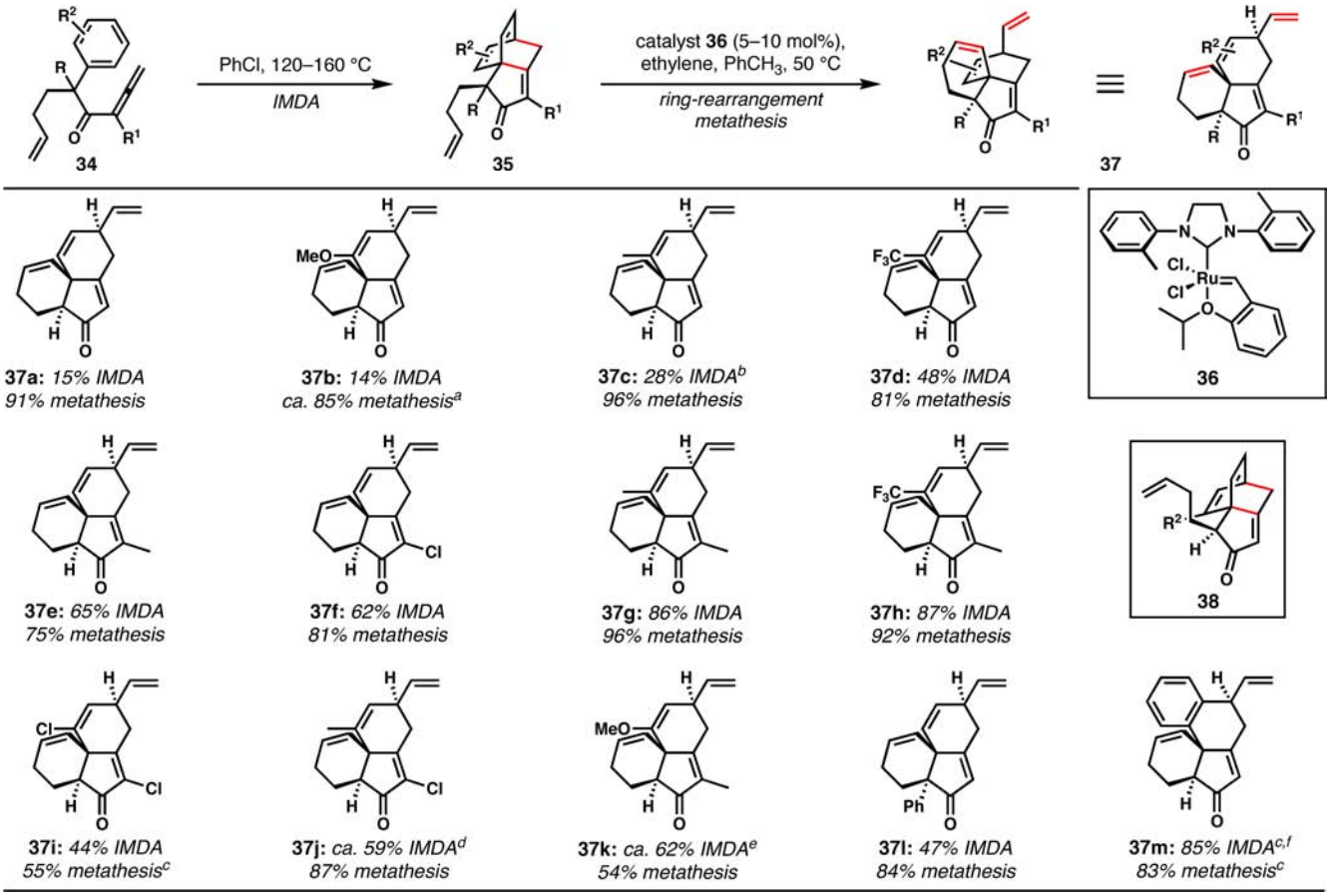
Table 3. Sequential Himbert Arene/Allene Cycloaddition and Ring-Rearrangement Metathesis to Access All-Carbon Polycycles



[a]While the metathesis reaction was very efficient as found on the basis of the NMR spectra of the crude reaction mixture, this product decomposed upon attempted purification. [b]17% of the allene starting material was recovered. [c]X-ray structure obtained. [d]The allene starting material was unstable and precluded accurate yield determination. [e]90:10 dr, 33% yield of the ketone derived from enol ether hydrolysis was also isolated. [f]94:6 dr.

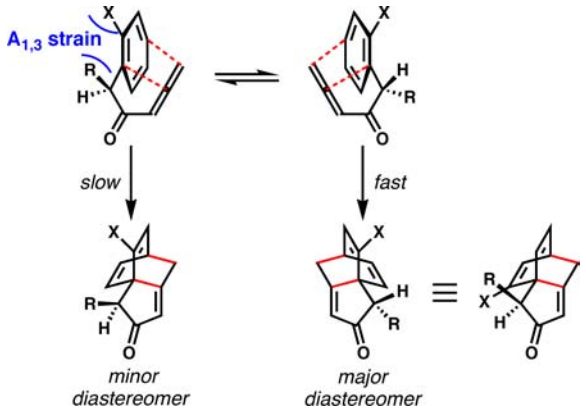
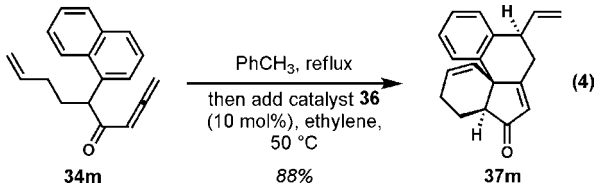


Figure 4. Plausible model for diastereocontrol based on minimization of allylic strain.



Orahovats. However, the first step of the two-step reaction proposed by Orahovats can be competitive and offers a mechanism for the racemization of chiral allenes. We have also determined that the carbon-tethered Himbert cycloaddition, which had not been reported previously, is feasible in many cases, but can suffer from thermodynamic unfavorability with some substrates. Furthermore, computation provides an excellent predictive tool for these reactions, which will permit the evaluation of specific cycloadditions prior to experiment.

Looking forward, we aim to further improve the scope and efficiency of the carbon-tethered variant, perhaps via catalysis. We will continue to use computation to evaluate new Himbert-type systems for feasibility, as we extend to other tether types, including temporary connections of arene diene and allene dienophile. Other, nonmetathesis rearrangements of the strained cycloadducts and applications in complex molecule synthesis are also under intense study in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental protocols, characterization data, and NMR spectra for new compounds; complete listing of references from the Himbert group and all computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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