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Radicals Masquerading as Electrophiles: Dual Orbital Effects in Nitrogen-Philic Acyl Radical Cyclization and Related Addition Reactions

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ABSTRACT

Free-radical chemistry has come a long way in a relatively short period of time. The synthetic practitioner takes for granted the wealth of mechanistic and rate constant data now available and can apply free-radical techniques to the synthesis of many different classes of target molecule with confidence. Despite this, there are still mechanistic anomalies that need to be addressed. This Account highlights recent work involving nucleophilic radicals with low-lying unoccupied orbitals, such as acyl, oxyacyl, silyl, stannyl, and germyl radicals. Through interesting singly occupied molecular orbital (SOMO)–π^* and highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) interactions during these reactions, the radicals involved are able to mask as electrophiles, providing high levels of regiocontrol and efficient methods for the synthesis of important heterocycles.

Introduction

Through important contributions from international researchers over the last two decades, radical chemistry has now gained the position it deserves among the key methodologies for organic synthesis.[1] As a result of this, special attention has been given to the potential that radical cyclization processes have for many useful tandem processes.[2] The propensity for 5-hexenyl radicals to undergo selective 5-*exo* cyclizations in preference to the corresponding 6-*endo* mode is a resource that many organic chemists have capitalized on, especially during the synthesis of carbocyclic and heterocyclic compounds

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Carl Schiesser received his Ph.D. in 1987 from the Australian National University working with Professor Athel Beckwith and was a postdoctoral fellow with Professor Alwyn Davies at University College London from 1988–1990. After joining the staff at the University of Melbourne in 1993, he was appointed as Professor of Chemistry in 2002. He is currently the Director of the Australian Research Council Centre of Excellence for Free Radical Chemistry and Biotechnology. In 2000, Carl was awarded a D.Sc. from his *alma mater*, and in 2006, he was awarded the prestigious A. J. Birch Medal of the Royal Australian Chemical Institute. Carl has extensive experience in free radical chemistry, ranging from molecular modeling, to mechanistic and kinetic studies, the development of new chemical methodology, and synthesis.

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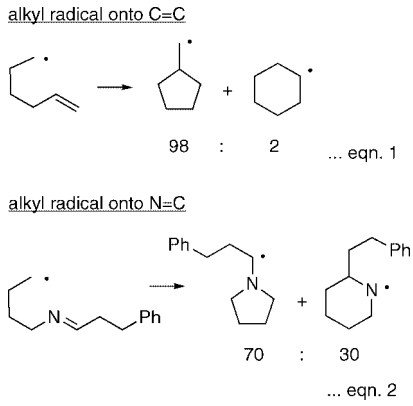


FIGURE 1. Preferred modes of 5-*exo*/6-*endo* alkyl radical cyclizations onto C=C and N=C double bonds.

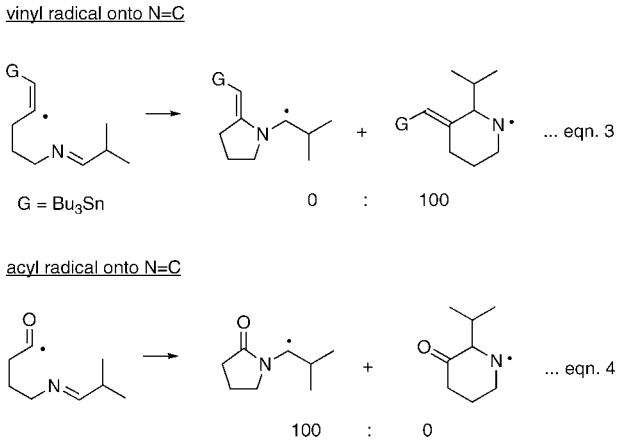


FIGURE 2. Preferred modes of 5-*exo*/6-*endo* vinyl and acyl radical cyclizations onto imines.

(Figure 1).[3] In search of a new strategy for the preparation of nitrogen heterocycles, radical cyclizations onto imine N=C double bonds were investigated by several researchers. Bowman and his coworkers are the pioneers in this area and the first to report that alkyl radicals also undergo 5-*exo*/6-*endo*-type cyclizations onto imine N=C bonds, but these reactions give rise to a mixture of pyrolidines and piperidines (eq 2, Figure 1).[4] The result is in stark contrast with the selective 5-*exo* cyclization mode of the 5-hexenyl radical, for which a Beckwith–Houk model involving a cyclohexane-chair-like transition state operates.[2,5] The lack of 5-*exo* selectivity in cyclizations onto imine π-systems has been rationalized by a *mismatch* between the nucleophilic alkyl radicals and the electron-rich nitrogen of the imine.

With a few exceptions involving double substitution at the imine carbon that effectively promote exclusive 5-*exo* cyclization onto the imine nitrogen,[6] aryl, and vinyl radicals cyclize onto the imine N=C bond in 5-azahexenyl-type systems in highly selective 6-*endo* reactions onto the carbon atom of this π-system (eq 3, Figure 2).[7,8] This is again in contrast with vinyl radical cyclizations onto C=C double bonds, in which 5-*exo* cyclization is kinetically favored.[9]

Recently, some of us have been interested in the development of useful carbonylation methods based on radical chemistry[10] and asked ourselves the following question: How would acyl radicals behave towards internal N=C double bonds? Acyl radicals have been recognized as nucleophilic radicals together with alkyl, vinyl, and aryl radicals.[11] As for cyclization, the kinetically preferred 5-*exo* mode in 5-*exo*/6-*endo* cyclizations onto C=C double bonds is a common feature for both acyl and vinyl radicals, and the cyclized five-membered ring radicals exhibit similar isomerization behavior to the thermodynamically more stable six-membered ring radicals.[12]

Intriguingly, however, this was not the case for cyclization onto imine N=C double bonds. We found that the cyclization of acyl radicals towards imine N=C double bonds in 5-azahexenoyl systems preferred five-membered ring formation with attack at the more electronegative nitrogen atom (eq 4, Figure 2).

Why do "nucleophilic" acyl radicals act in an "electrophilic" manner in their cyclizations onto N=C double bonds? Do these reactions involve ionic chemistry of the imine nitrogen onto the acyl carbon of the radical? With interest in the chemistry of acyl and related radicals, these were questions that inspired further investigation by our research groups in Osaka and Melbourne. This collaboration was initially launched to provide further insight into the mechanistic details of the seemingly perplexing reaction modes observed for acyl radicals. During this work, we discovered new radical chemistry that involves multicomponent orbital interactions that seems to be universally applicable to radicals that have low-lying unoccupied orbitals. In this Account, we begin by demonstrating the wide scope of N-philic acyl radical cyclizations and show that this chemistry provides a powerful method for the synthesis of lactams. Following from this, we discuss how *ab initio* and density functional molecular orbital techniques have helped in our understanding of the unusual selectivity of acyl radicals, discussed above, and go on to show that similar to the dimerization chemistry of singlet carbenes,[13] this selectivity is largely controlled by simultaneous singly occupied molecular orbital (SOMO)–(imine)π^* and highest occupied molecular orbital (HOMO)–(acyl)π^* interactions. Lastly, we will show that the concept of "dual orbital interactions" is common among radicals that are able to masquerade as electrophiles, such as those involving group 14 heteroatoms, and conclude that the radical center in a molecule may not necessarily be the most reactive component of that molecule.

Nitrogen-Philic Cyclizations of Acyl Radicals onto N=C π-Systems

As mentioned briefly above, acyl radical cyclizations onto N=C double bonds proceed with strong 5-*exo* selectivity. Figure 3 summarizes some results of carbonylation/annulation chemistry involving iminoalkyl radicals, in which the starting imines are obtained either from bromo- or phenylseleno-substituted alkylamines by condensation with aldehydes and ketones.[14] For example, the reaction of 3-bromopropylimine **1** with 80 atm of CO was carried

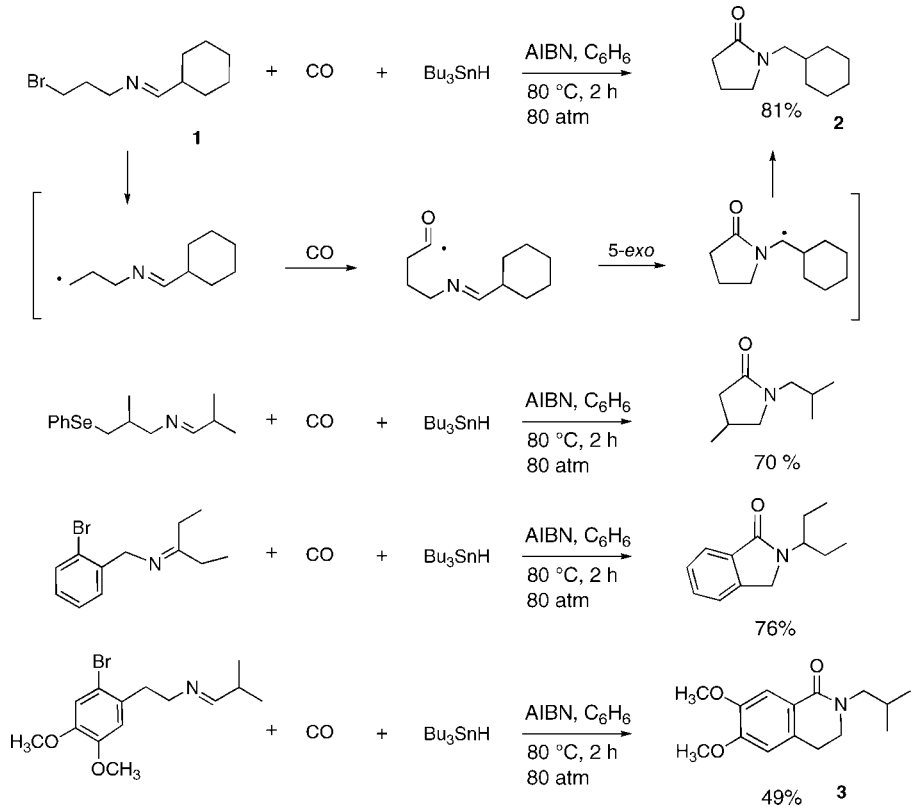


FIGURE 3. N-philic acyl radical cyclization onto imine N=C double bonds.

out in the presence of tributyltin hydride and a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) using an autoclave. The 5-*exo* product, 2-pyrrolidinone, **2** was obtained in 81% yield. No 3-piperidinone was detected in the reaction mixture. Both aldimines and ketimines are useful. This carbonylation/cyclization protocol can be successfully applied to the synthesis of 2-piperidinone, in which 6-*exo* cyclization onto nitrogen occurs. It should be noted that nitrogen-containing acyl radical precursors appear to be difficult to prepare, since there is a real possibility that the nucleophilic nitrogen will react with the carbonyl carbon. In contrast, the present carbonylation reaction system has the advantage that it allows for the *in situ* generation of the key acyl radicals.

How about the alternative regiochemistry; can we effect cyclization onto the carbon end of N=C π-systems? For the imines, we found that acyl radical ring closures proceed selectively in the 6-*endo* manner onto the nitrogen end of the imine π-system, irrespective of the orientation of the double bond, to give the corresponding δ-lactam radical, despite an alternative 5-*exo* cyclization pathway being available (Figure 4).[16] However, for hydrazones, Fallis and Brinza demonstrated that acyl radical cyclization proceeds in the 5-*exo* manner onto the carbon atom of the N=C π-system to give α-hydrazide-substituted cyclopentanones in good yield.[15]

When the imine **4**, prepared from 4-phenylselenobutanal and 3-aminopentane, was reacted with carbon monoxide in the presence of tributyltin hydride and AIBN, the 2-piperidinone **5** was obtained in 81% yield (Figure 5). This carbonylation–6-*endo* cyclization sequence was also successfully applied to the cyclization onto the C=N

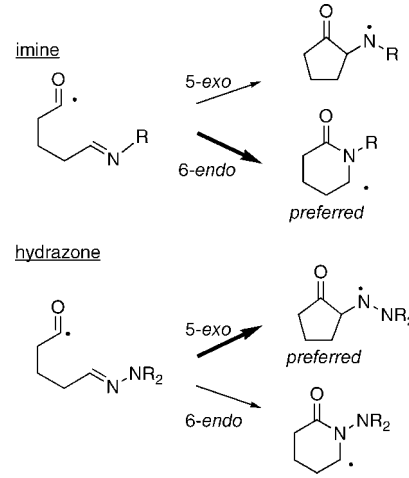


FIGURE 4. Possible cyclization modes and preferred modes for acyl radical cyclizations onto some N=C π-systems.

double bond in oxazoline **6**. The product **7** (Figure 5), serves as key intermediate for the synthesis of (–)-coniine.[17]

These nitrogen-philic cyclization reactions have been extended by us to include α,β-unsaturated acyl radicals. Carbonylation of vinyl radicals gives α,β-unsaturated acyl radicals, which exist in equilibrium with α-ketenyl radicals as predicted by computational studies.[18,19] These same MO calculations also predict the rapid interconversion of geometrical isomers. With this in mind, we examined the radical carbonylation of alkynyl imines, using radical mediators such as tributyltin hydride, tris(trimethylsilyl)-silane (TTMSS), and hexanethiol, in which heteroatom

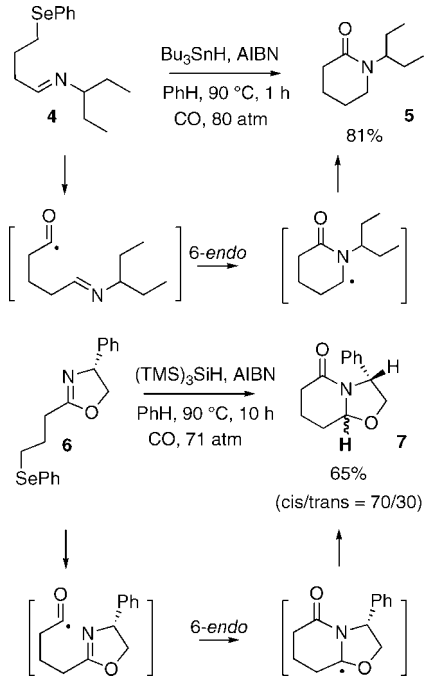


FIGURE 5. N-philic acyl radical cyclization onto imine and oxazoline N=C double bonds.

radicals add to carbon–carbon triple bonds to generate the precursor vinyl radicals in a convenient manner. For example, the reaction of 4-aza-2-methyl-3,8-nonenyne **8** with tributyltin hydride in the presence of AIBN resulted in the formation of the 3-(tributylstannyl)methylenepiperidine via a 6-*endo* process as a sole cyclization product. In contrast, when the reaction is repeated in the presence of carbon monoxide, the corresponding piperidinone **9** was obtained in 75% yield. This suggests that the 5 + 1 annulation sequence comprising carbonylation plus 6-*exo* cyclization is much faster than 6-*endo* cyclization of the vinyl radical onto the carbon end of the N=C double bond. (Figure 6).[20]

The stannylcarbonylation/N-philic acyl radical cyclization sequence of azaenynes has a remarkably large scope that covers 4-*exo*, 5-*exo*, 6-*exo*, 7-*exo*, and even 8-*exo* cyclizations.[20] Accordingly, a variety of lactams of varying ring size was prepared by the protocol (Figure 7). Tris(trimethylsilyl)silane (TTMSS) and hexanethiol can mediate similar annulation sequences involving azaenynes.[21] Generally, the tributyltin group tends to be disposed *syn* to the carbonyl group in the product lactam, whereas $(TMS)_3Si$ and alkylthio group are disposed *anti*. MO calculations suggest that favorable coordinative interactions between the tin atom and the carbonyl oxygen in the cyclization transition state may be responsible for this observation, as depicted in Figure 8.[21] A similar interaction between silicon and the carbonyl group is also possible; however, the bulky $(TMS)_3Si$ group almost certainly prefers to adopt an *anti* disposition for steric reasons.

We next examined the carbonylation of alkynyl imines derived from alkynyl ketones and aldehydes using tributyltin hydride and AIBN. The outcomes, after the reaction mixture was treated with TMSCl and MeOH to remove the tributyltin group, are displayed in Figure 9.[16] As in the case of the simple acyl radical (Figure 4), the cyclization of α,β-unsaturated acyl radicals proceeded with 6-*endo* selectivity. As a result, a series of α-methylene δ-lactams could be prepared. When the alkenyl iodide **10** was used as a vinyl radical precursor, a δ-lactam containing a C=C double bond in the ring was obtained. The 5 + 1 annulation reaction also works well for aldimines, ketimines, and oxazolines.

The Orbital Origin of Cyclization Selectivity

As discussed above, the ring-closure chemistry of acyl radicals with imines demonstrates remarkable N-selectivity. A simple model to rationalize this outcome is shown in the upper portion of Figure 10 which uses the 5-azahexenoyl radical as an example. It would seem reasonable to suggest that favorable matching of polarities between the carbonyl (acyl) carbon and the nitrogen of the imine in the cyclization transition state is responsible for the preferential formation of the pyrrolidinone product in the example given.

However, molecular orbital calculations reveal that the geometry of the transition state involved in the N-philic ring closure is not optimum for efficient SOMO–LUMO overlap (Figure 11, top), and we became suspicious that the reacting units were perhaps not interacting in a free-radical manner at all.[22] Accordingly, we initially proposed that this chemistry involves nucleophilic attack of the imine nitrogen at the acyl carbon as shown in the lower portion of Figure 10.[22] This explanation turned out to only be partially correct.

Since this initial proposal, it became clear to us that not only was the geometry of the transition state unusual but so also was the motion associated with the transition state imaginary frequency (transition state vector). When animated, the acyl carbon appears to swing above the imine nitrogen during bond formation, as indicated by the motion arrows in Figure 11 (bottom).[23] These unusual observations prompted us to investigate further the homolytic addition chemistry of acyl radicals in general.

The transition states for attack of acetyl radical at the nitrogen (**11**) and carbon (**12**) ends of methanimine are displayed in Figure 12, along with motion arrows for the transition state vector.[23] The "rocking and rolling motion" (see supporting information associated with ref 23 for AVI animations of the transition state motion vectors for **11** and **12**) observed during the cyclization of the 5-azahexenoyl radical is clearly evident in the analogous intermolecular transition state (**11**). On the other hand, attack at the carbon end of the imine (**12**) appears to involve a more "traditional" transition state for homolytic addition to a π-system. It is also interesting to note that in the absence of steric and ring-strain constraints, acyl radicals have a slight preference for attack at the carbon end of the imine π-system, with CCSD(T)/aug-cc-pVDZ calculated energies of 19.2 and 23.0 kJ mol^{-1} for attack at the C and N ends, respectively.

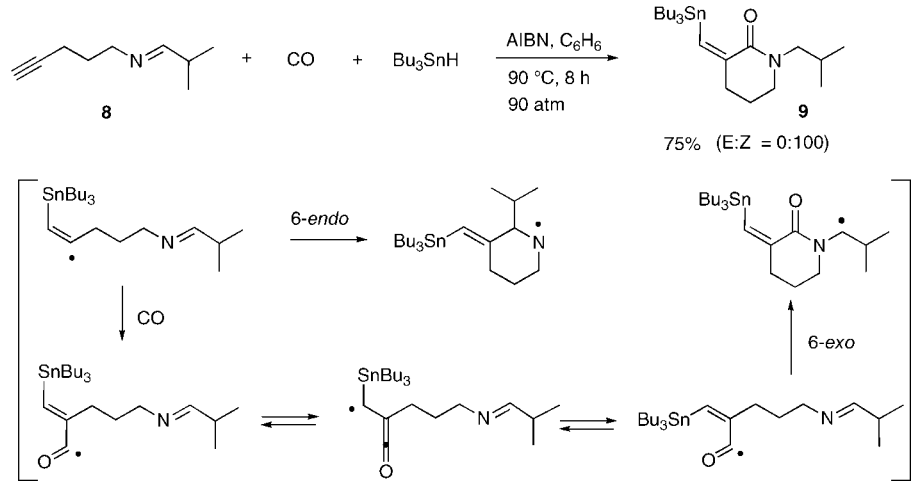


FIGURE 6. N-philic cyclization of α,β-unsaturated acyl radicals onto imine N=C double bonds.

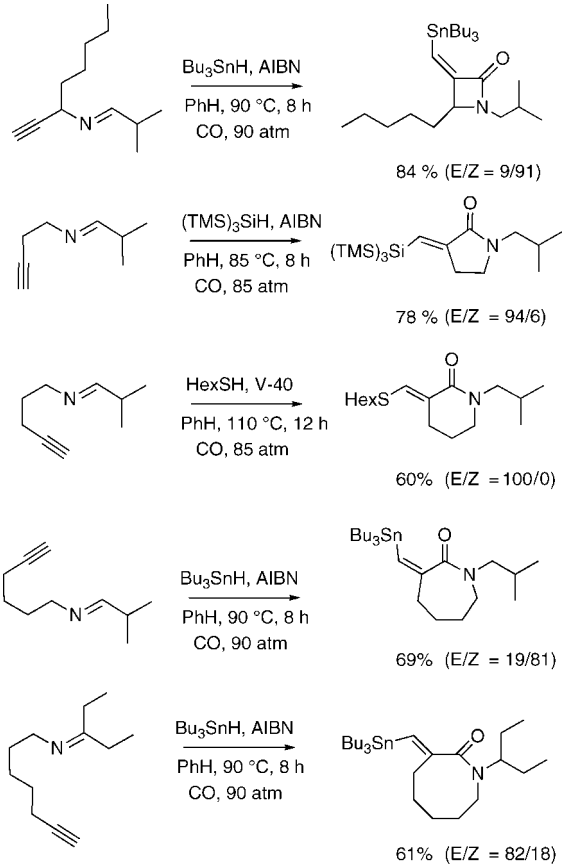


FIGURE 7. 4-*Exo*, 5-*exo*, 6-*exo*, 7-*exo*, and 8-*exo* cyclization of α,β-unsaturated acyl radicals onto imine N=C double bonds.

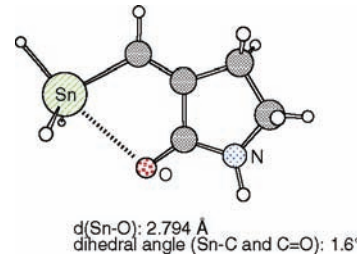


FIGURE 8. Optimized structure of a model stannylated lactam (B3LYP/DZP).

Visualization of the Kohn–Sham orbitals generated at the BHandHLYP/6-311G** level of theory reveals the origin of this unusual transition state motion. Not unexpectedly, the transition state "SOMO" (Figure 13, top) comprises interaction of the unpaired electron in the acetyl radical with the imine π^* orbital. Somewhat surprisingly however, of similar energy is a second orbital interaction comprising interaction of the nitrogen lone pair with the acetyl radical π^* orbital (Figure 13, center).

Natural bond orbital (NBO) analysis at the BHandHLYP/6-311G** level of theory reveals that the SOMO–π^* overlap depicted in this system is worth about 67 kJ mol^{-1}, with the LP–π^* interaction worth some 125 kJ mol^{-1}. Clearly then, these calculations suggest that the nucleophilic character of the imine dominates over the radical interaction in this example.

When these same computational techniques are applied to the detailed analysis of ring-closure transition states, a more satisfying rationale for N-philic cyclizations involving acyl radicals is arrived at: the "dual-orbital mechanism" appears to allow for excellent alignment of orbitals as depicted in Figure 14. At the highest level of theory used in this study (CCSD(T)/cc-pVDZ//BHandHLYP/cc-pVDZ), energy barriers of 36.1 and 47.0 kJ mol^{-1} are calculated for the N- and C-philic reactions respectively.[24] It is interesting to note that the LP–π^* interaction, once again, dominates in the ring-closure transition state.

Interestingly, selectivity during ring closure of the isomeric 6-azahexenoyl radicals depends on the geometry of the imine double bond, with the (*Z*)-isomer (**13**) predicted to have a profound preference for attack at the carbon end of the imine.[24] As can be seen in Figure 15, the transition state for intramolecular attack at the imine nitrogen in **13** derives no stabilization from LP–π^* interactions due to unfavorable steric interactions.

Having arrived at a satisfactory explanation for acyl radical ring-closure chemistry, an explanation in which the acyl radical masquerades as an electrophile in order to derive maximum stabilization in the transition state involved in this chemistry, we next sought to discover other systems in which the radical involved might also

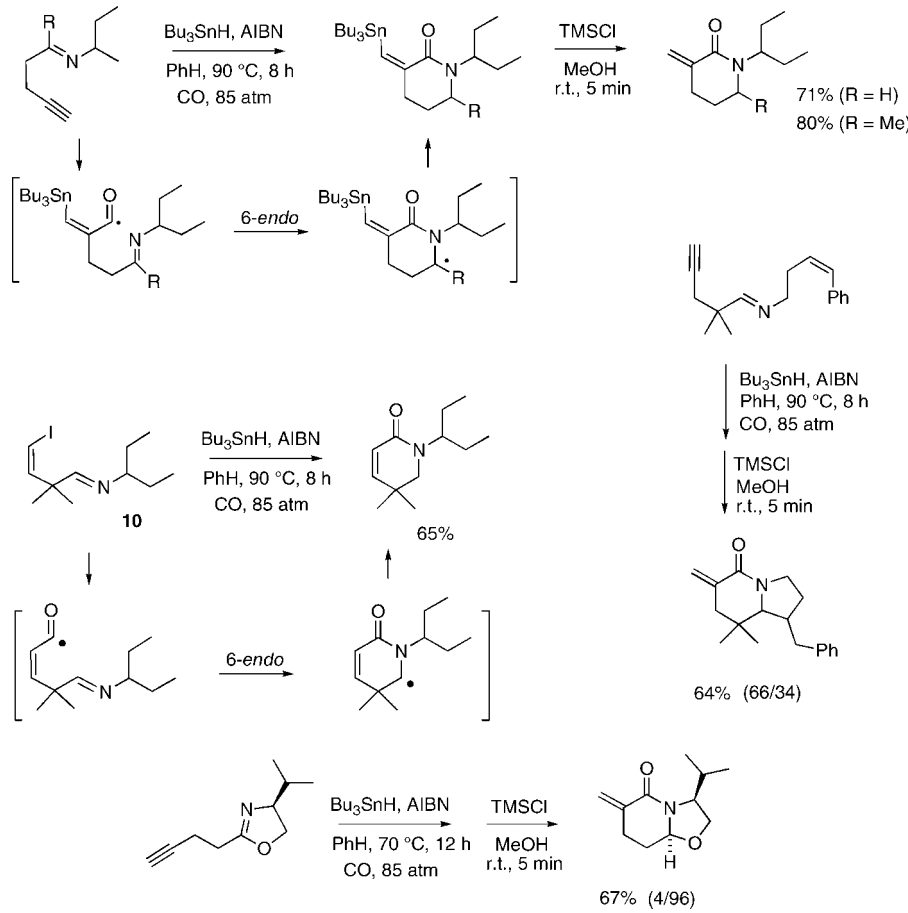


FIGURE 9. 6-*Endo* cyclization of α,β-unsaturated acyl radicals onto imine and oxazoline N=C double bonds.

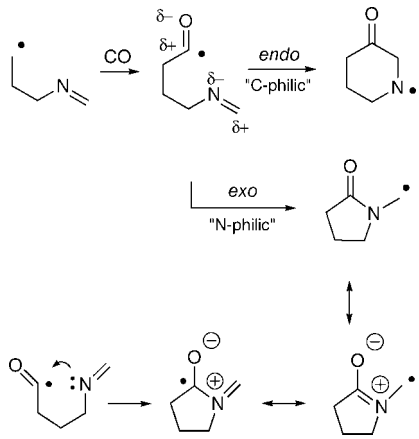


FIGURE 10. Rationalizing the N-selectivity during the ring closure of the 5-azahexenoyl radical.

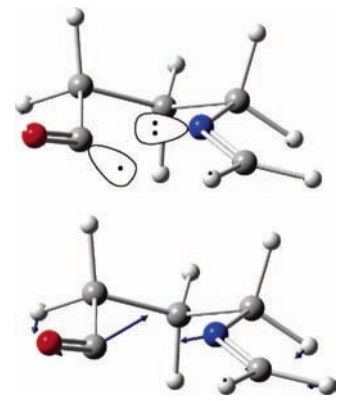


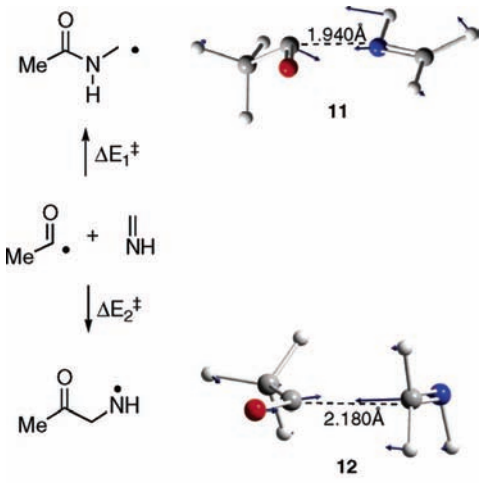
FIGURE 11. Calculated transition state for the ring closure of the 5-azahexenoyl radical: primary orbital alignment (top) and transition state motion vectors (bottom).

act in this manner. Recent work has discovered similar "dual-orbital" interactions in reactions involving acyl and oxyacyl radicals with hydrazones and electron-rich olefins such as enamines.[25] Some examples are provided in Figure 16.

Dual Orbital Effects in Group 14 Radical Addition Chemistry

In seemingly unrelated work, we became interested in the reaction of silyl radical with formaldehyde as part of a project aimed at further exploring the self-terminating radical chemistry developed by one of us.[26] As expected (Figure 17), radical addition to the oxygen atom in this system is calculated to be significantly exothermic, with an activation energy ($\Delta E_3^{\ddagger}$) of some 31 kJ mol^{-1} and reaction energy (ΔE) in excess of 120 kJ mol^{-1}.[23]

We became very curious about this reaction because of the unexpected geometry of the transition state and the associated transition state vector.[23] In particular, the silyl radical component appears to be "leaning back" with one of the O–Si–H angles (the attack angle θ) at about



Method	$\Delta E_1^{\ddagger}$	$\Delta E_2^{\ddagger}$
QCISD/aug-cc-pVDZ// MP2/aug-cc-pVDZ	28.8	23.9
CCSD(T)/aug-cc-pVDZ// MP2/aug-cc-pVDZ	23.0	19.2
BHandHLYP/6-311G**	22.6	19.5

kJ mol^{-1}

FIGURE 12. Reaction of acetyl radical with methanimine.

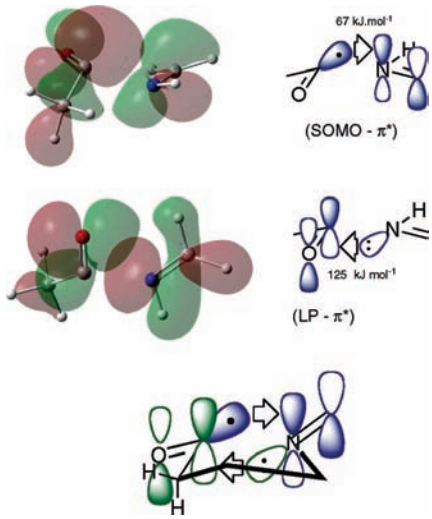


FIGURE 13. Kohn–Sham SOMO–π^* (top) and LP–π^* (center) orbitals for the reaction of acetyl radical at the nitrogen atom in methanimine and NBO calculated interaction energies. Alignment of orbitals for N-philic cyclization of 5-azahexenoyl radical (bottom). BHandHLYP/6-311G** level of theory.

145°, with the remaining angles at about 90°. When animated, the transition state appears to "dance" in a similar fashion to that described previously for the reactions involving acyl radicals.[23]

NBO analysis of the transition state orbitals at the BHandHLYP/6-311G** level reveals a similar orbital origin for the motion experienced by this transition state to that for the other transition states in this study (Figure 17).[23] It is interesting to note that these calculations predict a SOMO–π^* interaction, as well as an interaction between

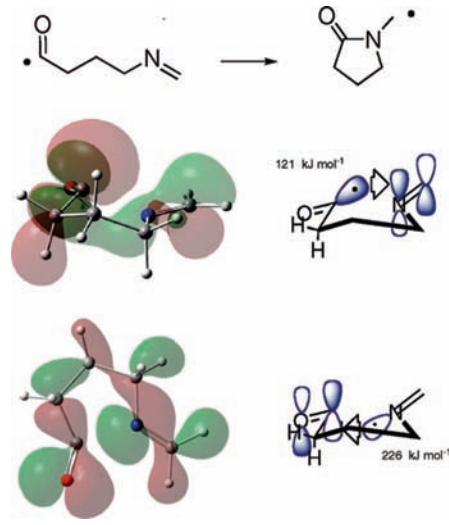


FIGURE 14. Kohn–Sham SOMO–π^* (top) and LP–π^* (bottom) orbitals for the reaction of for the N-philic ring closure of the 5-azahexenoyl radical and NBO calculated interaction energies; BHandHLYP/6-311G** level of theory.

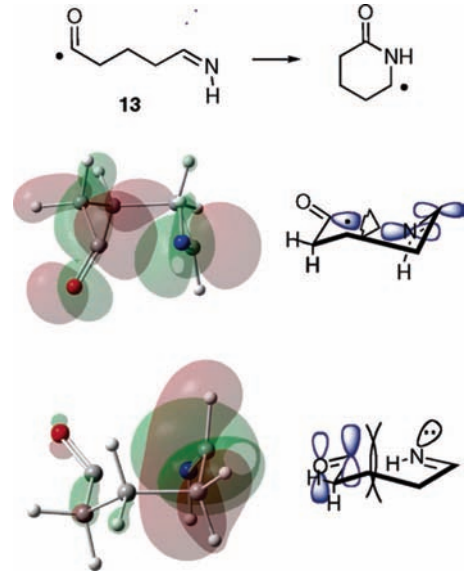


FIGURE 15. Kohn–Sham SOMO–π^* interactions (top) and nitrogen LP (bottom) in the *endo* cyclization transition state for the (*Z*)-6-azahexenoyl radical; BHandHLYP/6-311G** level of theory.

the lone pair on oxygen and the Si–H σ^* orbital; the former interaction is worth about 515 kJ mol^{-1}, while the LP–σ^* interaction is calculated to be worth some 163 kJ mol^{-1}.

The magnitude of the attack angle θ is a compromise between the two interactions described above and should be influenced by the nucleophilicity of the radicalophile, with θ increasing with stronger nucleophiles as the LP–σ^* interaction becomes more important. It was therefore gratifying to see that the transition state for the reaction of silyl radical with methanimine (CH_2=NH) does indeed have an increased attack angle (θ = 155.9°), as well as a reduced energy barrier for addition to the nitrogen ($\Delta E^{\ddagger}$ = 5.7 kJ mol^{-1} at BHandHLYP/6-311G**).[23] Similar observations have been made for analogous reactions involving germyl and stannyl radicals.[27]

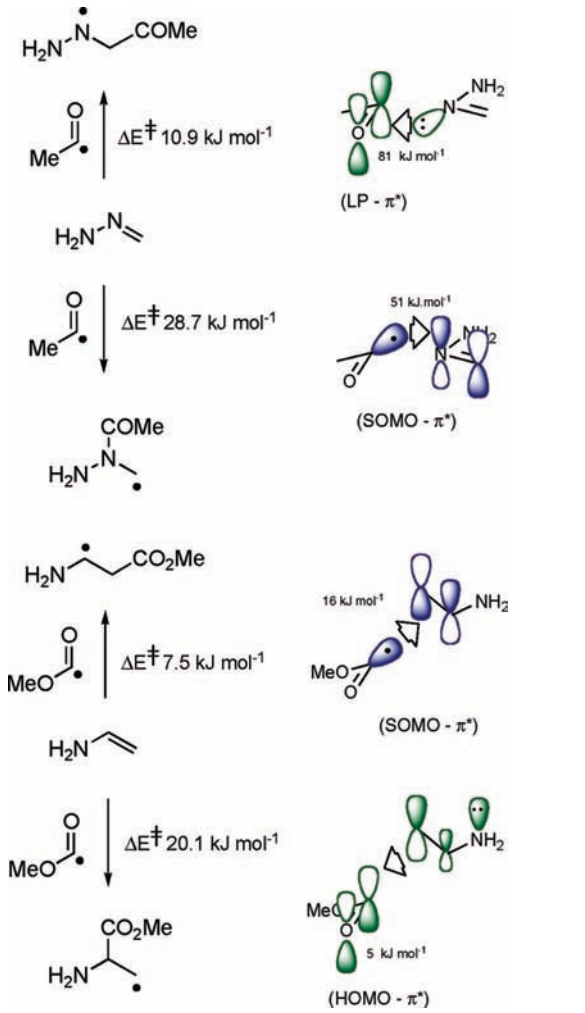


FIGURE 16. Examples of "dual orbital" interactions in reactions involving acyl and oxyacyl radicals. Energies calculated at the BHandHLYP/6-311G** level of theory.

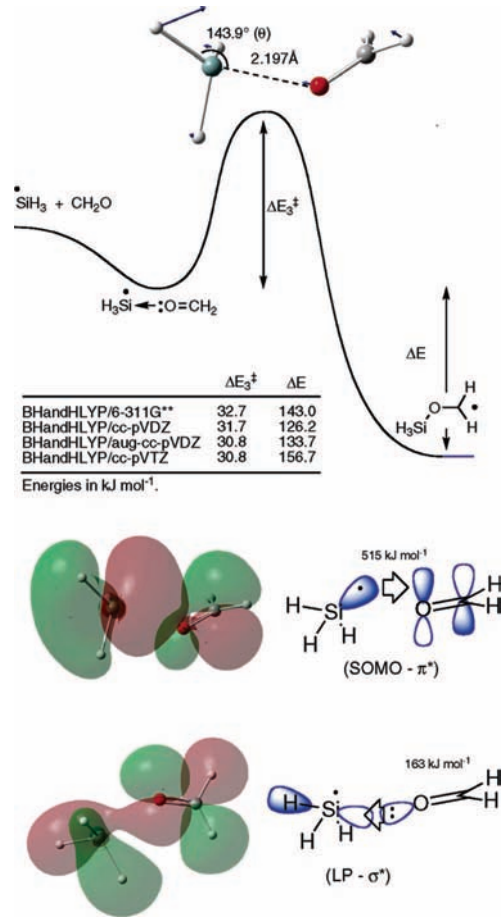


FIGURE 17. Reaction profile and transition state Kohn–Sham orbitals for the reaction of silyl radical with formaldehyde.

Interestingly, the calculations predict that the stereochemistry at the C=N double bond determines the preferred site of Si radical attack during the cyclization (Figure 18).[28] Thus, in the case of the *E* configurated Si-radical ***E*-14**, cyclization occurs with significant preference for the 6-*endo* mode ($\Delta E^{\ddagger}$ (6-*endo*) = 14.2 kJ mol^{-1} vs $\Delta E^{\ddagger}$ (5-*exo*) = 32.8 kJ mol^{-1} at BHandHLYP/6-311G**), to give the thermodynamically more favorable product **15**. NBO analysis at the BHandHLYP/6-311G** level of theory shows that the SOMO–π^* and LP–σ^* interactions are of equal importance (ca. 47 kJ mol^{-1}).

On the other hand, interactions of the LP at nitrogen with the σ^* orbital of a Si–H bond are dramatically reduced to ca. 5 kJ mol^{-1} in the *Z* configured imine ***Z*-14**. This results in a serious increase of the activation barrier for the 6-*endo* cyclization by ca. 24 kJ mol^{-1}, which becomes now kinetically slightly less favorable than the 5-*exo* cyclization mode. As expected, the activation barrier for the 5-*exo* cyclization onto the carbon of the imine C=N double bond is effectively unchanged by the stereochemistry of the C=N bond. As a consequence of the directing effects caused by dual-orbital interactions, cyclizations of Si radicals onto imine N=C double bonds, as for example in **16**, occur preferably in 5-*exo* fashion ($\Delta E^{\ddagger}$ (6-*endo*) = 19.7 kJ mol^{-1} vs. $\Delta E^{\ddagger}$ (5-*exo*) = 12.7 kJ mol^{-1} at BHandHLYP/6-311G**). In the transition state for the 5-*exo* cyclization, the contribution of the SOMO–π^* interaction is worth 70 kJ mol^{-1}, whereas the LP–σ^* interaction accounts for 58 kJ mol^{-1}.

The magnitude of the nucleophilic LP–σ^* interaction to the overall energy contribution is increased by electron-donating substituents at the carbon site of the C=N double bond, as is shown in the upper part of Figure 19. Thus, the presence of the phenyl substituent in the imine (*E* configuration) **17** leads to a dramatic reduction of the activation barrier of the 6-*endo* cyclization ($\Delta E^{\ddagger}$ = 8.3 kJ mol^{-1} at BHandHLYP/6-311G**). The increased nucleophilicity of the imine nitrogen is reflected by a strong LP–σ^* interaction of 36 kJ mol^{-1}, which outweighs the SOMO–σ^* interaction by nearly 50%. Compared with the unsubstituted imine ***E*-14** (see Figure 18), the activation barrier for the 5-*exo* cyclization of **17** is higher by some 9 kJ mol^{-1}. This difference may be attributed to an increase in steric hindrance at the imine carbon, which is also reflected by the significantly lower thermodynamic stability of the cyclization product **18**.

Similarly, the regioselectivity of the cyclization of Si-centred radicals onto carbonyl groups is also influenced by dual-orbital interactions.[29] Because of the lower nucleophilicity of oxygen compared with nitrogen, however, the effect

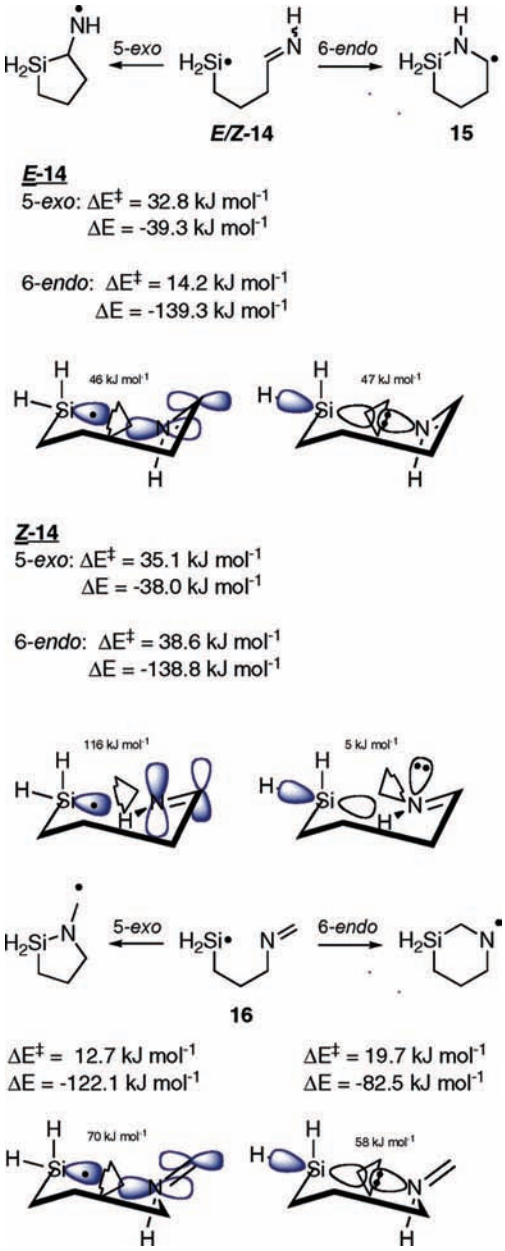


FIGURE 18. Examples for the role of "dual-orbital" interactions in determining the regioselectivity of cyclizations of Si-centred radicals onto imines (BHandHLYP/6-311G**).

is less dramatic. On the other hand, an increase of the electron density at the carbonyl oxygen by electron-donating substituents at the carbon site of the C=O double bond, leads to an increase of nucleophilic interaction in this radical addition. Cyclization of the Si-centred radical **19** occurs preferably in a 6-*endo* fashion, whereas the alternative 5-*exo* cyclization is not only kinetically disfavored but also significantly endothermic (lower part of Figure 19). Thus, in the transition state for the 6-*endo* pathway, the LP–σ^* interaction is worth 41 kJ mol^{-1}, which is 37% of the total interaction. On the other hand, when the phenyl group in **19** is replaced by hydrogen, the contribution of the LP–σ^* interaction in the 6-*endo* transition state reduces to only 18%. In this case, the 5-*exo* cyclization is becoming the kinetically favored pathway (data not shown).

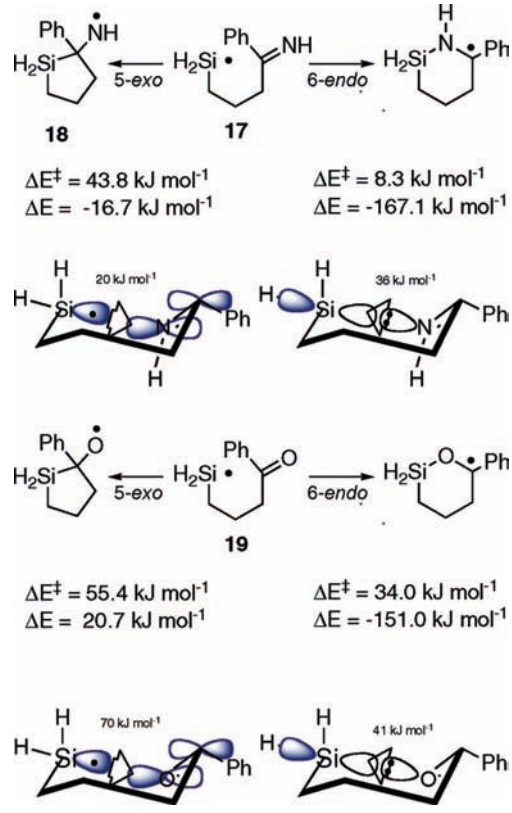


FIGURE 19. Examples for the role of electron-donating substituents on imine and carbonyl groups on the magnitude of "dual-orbital" interactions (BHandHLYP/6-311G**).

Conclusion

A novel class of selective radical cyclization reactions onto imine double bonds, which are useful for the preparation of nitrogen-containing heterocycles, have been developed. Nitrogen-containing acyl radicals are generated *in situ* from the corresponding nitrogen-containing alkyl radicals and carbon monoxide, which then undergo cyclization onto the nitrogen atom to give lactam rings. The profound N-selectivity observed in these reactions has been explained in terms dual SOMO–π^* and LP–π^* operating in the N-cyclization transition state and not available to the alternative regiochemistry. In many examples, the radical center has been shown not to be the most reactive part of the radicals undergoing reaction, and it has been shown that nucleophilic interactions often dominate in the transition states. This chemistry has been extended to include other radicals that can masquerade as electrophiles including silyl radicals that have been shown to benefit from favorable SOMO–π^* and HOMO–σ^* interactions. It is now possible to predict the regiochemistries of new radical addition reactions. Provided that the electrons involved are correctly orientated to take advantage of favorable orbital interactions, cyclization reactions involving radicals that are able to masquerade as electrophiles, such as those described in this Account, afford products arising from attack of the radical center at the most nucleophilic end of an electron-rich π-system.

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