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Carbonylative Approaches to α,β-Unsaturated Acyl Radicals and α-Ketenyl Radicals. Their Structure and Applications in Synthesis

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The carbonylation of vinyl radicals gives α,β-unsaturated acyl radicals. This transformation was successfully applied to tandem radical reactions, resulting in assembling three and four components. In these reactions, both halogen abstraction from vinyl halides and hetero atom radical additions to alkynes are used to generate the parent vinyl radicals. Ab initio calculations and density functional methods predict that α,β-unsaturated acyl radicals and the isomeric α-ketenyl radicals are not canonical forms, but are isomeric species that undergo interconversion. Calculations also indicate that α,β-unsaturated acyl radicals are more stable than α-ketenyl radicals, whereas α-ketenyl radicals containing a heteroatom, such as Si, Ge, and Sn, at α-position are more stable than the corresponding α,β-unsaturated acyl radicals. This represents a promising resource for developing new synthetic applications that involve the use of the α-ketenyl radicals. Indeed, following the prediction by calculation, we succeeded in trapping of a tin-attached α-ketenyl radical by imines and amines in an intramolecular fashion. We were also able to achieve the intermolecular trapping of α-ketenyl radicals, providing a new method for alkyne carbonylation by hybrid radical/ionic reactions.

1. Introduction

Radical carbonylation chemistry has experienced many new discoveries since the evolution of the first efficient reaction to give aldehydes, reported in 1990.[1,2] Since the carbonylation step involves the addition of carbon radicals to carbon monoxide, the chemistry inherently deals with acyl radicals.[3] A wide range of alkyl radicals are generally known to participate in radical carbonylation chemistry, whereas aryl and vinyl radicals are also potential radical species that could be carbonylated (Scheme 1). This Account specifically focuses on the carbonylation of vinyl radicals, in which α,β-unsaturated acyl radicals are formed as key radical species, since, until recently, the real figure for well-known radical species which exists in an equilibrium with α-ketenyl radicals have not been evaluated precisely, from either the synthetic and theoretical points of view.

The results of electron paramagnetic resonance (EPR) spectroscopic studies suggest that α,β-unsaturated acyl radicals exist as σ-type acyl radicals whose structures resemble the corresponding α,β-unsaturated aldehydes.[4] For example, the photolysis of bis[(*E*)-4,4-dimethylpent-2-enoyl] peroxide at low temperature, afforded both the *s-trans* and *s-cis* rotamers of the (*E*)-4,4-dimethylpent-2-enoyl radical (Scheme 2).[5] This study from the Ingold group also revealed that the *s-trans* structure is the more stable conformation.

In the meantime, rapid growth in the synthetic application of α,β-unsaturated acyl radicals,[6] has posed intriguing mechanistic questions concerning the roles of α-ketenyl radical isomers. Pattenden and co-workers have shown[7–9] that the radicals formed by the reaction of phenylseleno esters, react exclusively via the α-ketenyl form and that these radicals can be trapped efficiently by rapid intramolecular radical reactions such as 5-exo cyclization (Scheme 3)[7] and cyclopropylmethyl radical ring opening to form another radical.[8] Work in our laboratories has also found that α-ketenyl radicals are most likely generated during radical carbonylation processes that involve vinyl radicals.[10–13]

In this Account, we describe unique synthetic methods for carbonyl compounds based on the carbonylation of vinyl radicals, in which α,β-unsaturated acyl radicals and α-ketenyl radicals play a key role. We also describe some of our recent computational studies based on ab-initio and DFT calculations, which predict that α,β-unsaturated acyl and α-ketenyl radicals are distinct species, rather than canonical forms of a common radical.[14,15] The calculations indicate that the energy barriers between both types of radical species are small, suggesting that these species are readily interconverted. Furthermore, group 16 heteroatom (Si, Ge, and Sn) substituted α-ketenyl radicals are more stable than the corresponding α,β-unsaturated acyl radicals. We shall start with computational studies concerning the structure and relation of α,β-unsaturated acyl radicals and the corresponding α-ketenyl radicals and then discuss aspects of the synthetic chemistry of α,β-unsaturated acyl radicals.

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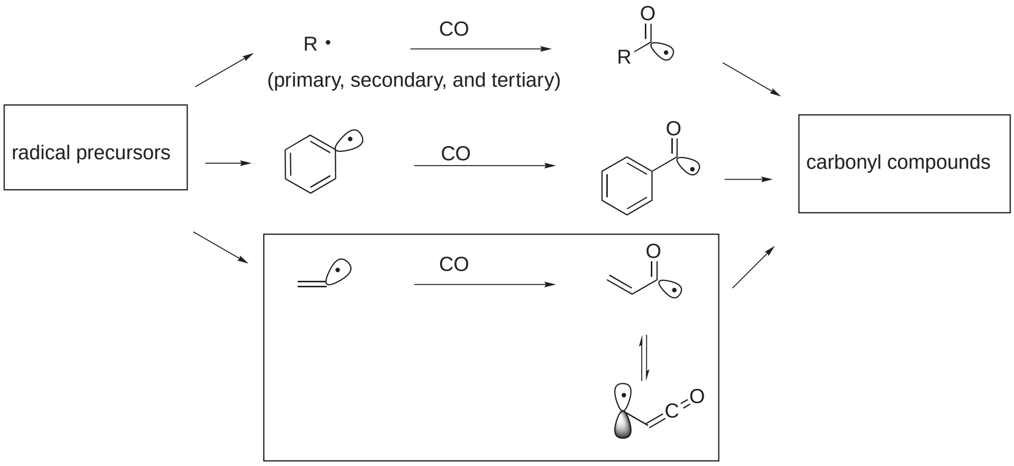
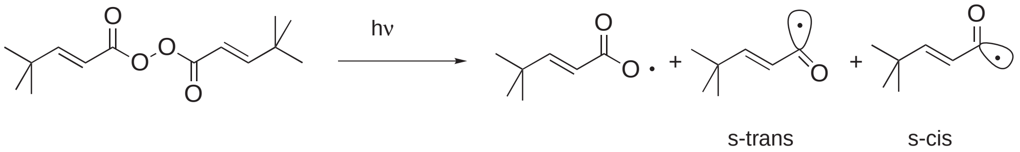
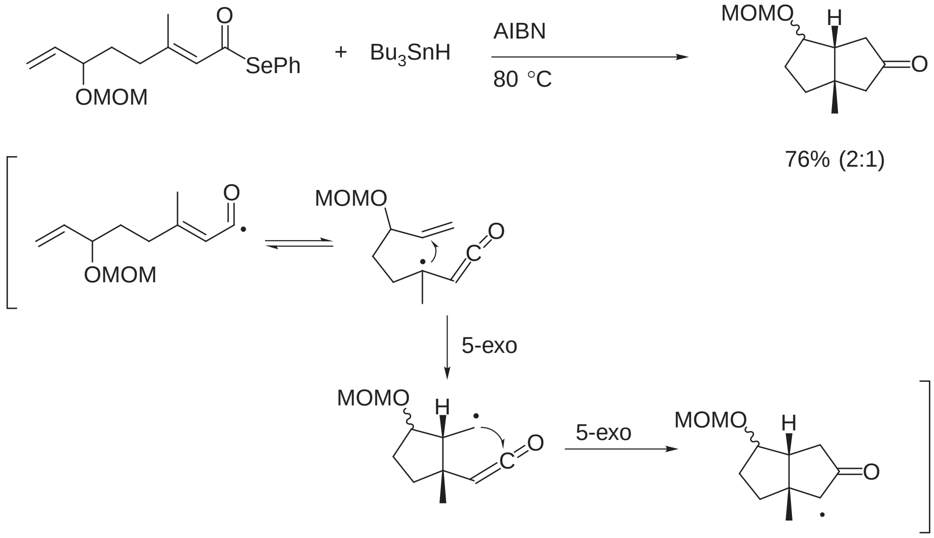


Scheme 1. Concept of radical carbonylations and starting radicals.



Scheme 2. Isomerization characteristics of α,β-unsaturated acyl radicals.



Scheme 3. Trapping of α-ketenyl radicals by a C–C double bond.[7]

2. Computational Studies

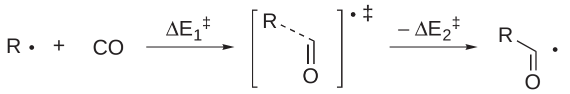
The calculated energy barriers for carbonylation ($\Delta E_1{}^{\ddagger}$ and $\Delta E_2{}^{\ddagger}$) of methyl,[16] ethyl, isopropyl, *t*-butyl, and vinyl radicals with carbon monoxide are summarized in Table 1. The reaction profiles of carbonylation of ethyl and vinyl radicals calculated on the BHandHLYP/6-311G** are highlighted in Scheme 4. An inspection of the Table 1 and the Scheme 4 reveals that the energy barrier for the forward process, involving a vinyl radical, is smaller than any types of alkyl radicals, and the reaction is predicted to be the most exothermic. Thus, computational chemistry predicts that a vinyl radical would easily react with carbon monoxide to give propenoyl radical and the product would not release carbon monoxide readily.

We calculated the energy barriers ($\Delta E_1{}^{\ddagger}$, $\Delta E_2{}^{\ddagger}$, $\Delta E_3{}^{\ddagger}$, and $\Delta E_4{}^{\ddagger}$, Scheme 5) for the isomerization of the propenoyl radical, which are listed in Table 2.[14] With the exception of calculations by the B3LYP method, in which neither the *s-cis* isomer nor the corresponding isomerization transition state could be found, we were able to calculate the energy barriers. B3LYP calculations involving radical reactions sometimes provide data that are inconsistent with other theoretical treatments.

The reaction profile of this isomerization calculated at the CCSD(T)/aug-cc-pVDZ//BHandHLYP/aug-cc-pVDZ level of theory is summarized in Scheme 6. The calculated energy barriers for isomerization processes involving the *s-trans* and *s-cis* radicals ($\Delta E_1{}^{\ddagger}$ and $\Delta E_4{}^{\ddagger}$) are 15.1 and 5.6 kJ mol^{-1}, respectively, indicating that these isomerizations are predicted to occur readily at ambient temperatures. Both of the acyl radicals (**1a** and **3a**) are calculated to be more stable than the ketenyl isomer **2a** and the *s-trans* radical is predicted to be more stable than the *s-cis* radical. Therefore, the reaction equilibrium for these isomerization reactions favor the formation of the *s-trans*-propenoyl radical (**1a**).

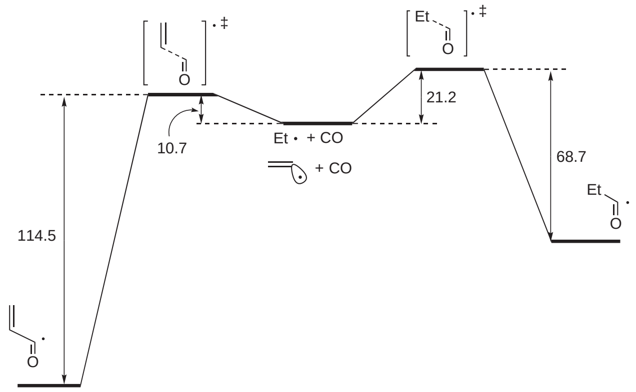
The isomerization of substituted propenoyl radicals, **1b**, **1c**, **1d**, and **1e**, in which the β hydrogen of the propenoyl carbonyl is replaced by methyl, silyl, germyl, or stannyl group to the corresponding ketenyl species were also investigated by computational techniques (Chart 1).[14] The propenoyl derivatives are predicted to have two geometric isomers (*E* and *Z*) at the carbon–carbon double bond as well as *s-trans* and *s-cis* isomers at the acyl group. Therefore, four isomers of each radical are possible, while the ketenyl radicals seem to have two stereoisomers. For example, as shown in Scheme 7, the *s-trans*-(*E*)-crotonoyl radical (R = CH_3) **E-1b** can isomerize to afford the (*E*)-2-carbonyl-1-methylethyl radical **E-2b**, while the *s-cis*-(*E*)-crotonoyl radical **E-3b** transforms to give **E-2b** as well. On the other hand, both the *s-trans*-(*Z*)-crotonoyl radical **Z-1b** and the *s-cis*-(*Z*)-crotonoyl radical **Z-3b** can isomerize in the same manner to the (*E*)-isomers giving the (*Z*)-2-carbonyl-1-methylethyl radical **Z-2b**. The ketenyl radicals can transform into each other via transition state **4b**. Interestingly, while the crotonoyl radical **1b** and the 3-stannylpropenoyl radical **1e** are predicted to exist as four isomers, the 3-silylpropenoyl radical **1c** is predicted to have no *cis* isomers. In the case of the germanium-containing system, while the acyl radical with an *s-cis* conformation is found at all levels of theory used (BHandHLYP/DZP and UHF/DZP), we were only able to locate a transition state with the *s-cis* conformation at the UHF/DZP level of theory.

Table 1. Calculated Energy Barriers[a)] for Carbonylation ($\Delta E_1{}^{\ddagger}$) and Decarbonylation ($\Delta E_2{}^{\ddagger}$) of Alkyl and Vinyl Radicals



R	Method	$\Delta E_1{}^{\ddagger}$	$\Delta E_2{}^{\ddagger}$
Me	MP2/aug-cc-pVDZ	31.9[b)]	89.4
	QCISD/aug-cc-pVDZ	29.7[b)]	74.2
	CCSD(T)/aug-cc-pVDZ	24.0[b)]	72.7
	BHandHLYP/6-311G**	22.4[c)]	81.0
Et	BHandHLYP/6-311G**	21.2[c)]	68.7
i-Pr	BHandHLYP/6-311G**	20.7[c)]	57.2
t-Bu	BHandHLYP/6-311G**	20.0[c)]	48.0
Vinyl	BHandHLYP/6-311G**	10.7[c)]	114.5

a) Energies in kJ mol^{-1}. b) Cited from Ref. 16. c) Unpublished.



Scheme 4. Reaction profile of carbonylation of ethyl and vinyl radicals. Energies (in kJ mol^{-1}) are calculated on the BHandHLYP/6-311G**.

Energy barriers calculated on the BHandHLYP level for isomerization reactions involving substituted propenoyl radicals

1a: R = H
1b: R = CH_3
1c: R = SiH_3
1d: R = GeH_3
1e: R = SnH_3

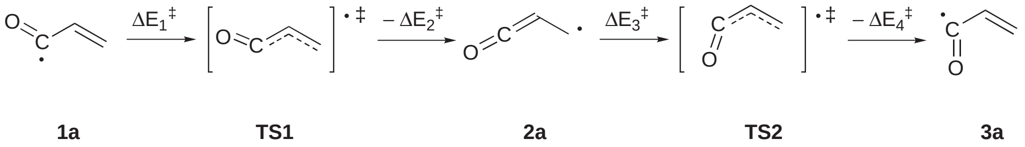
2a: R = H
2b: R = CH_3
2c: R = SiH_3
2d: R = GeH_3
2e: R = SnH_3

Chart 1.

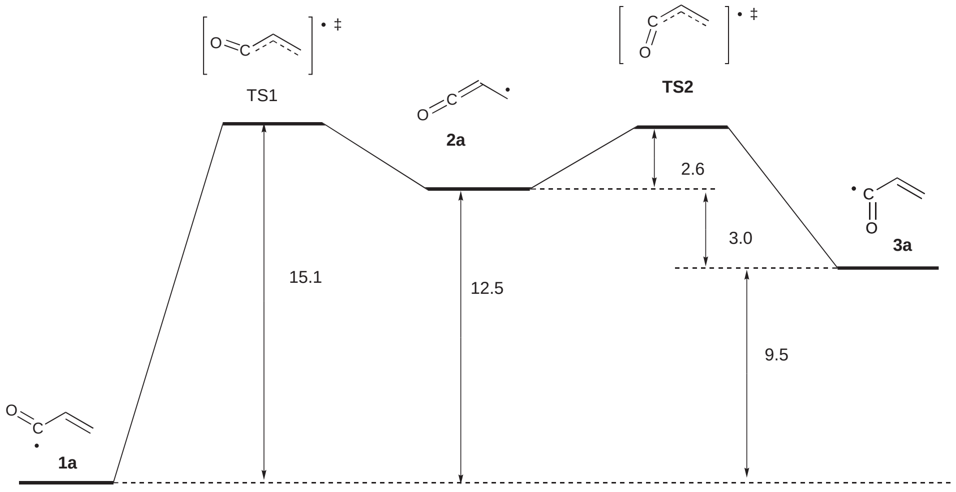
Table 2. Calculated Energy Barriers[a)] for the forward ($\Delta E_1{}^{\ddagger}$ and $\Delta E_4{}^{\ddagger}$) and Reverse ($\Delta E_2{}^{\ddagger}$ and $\Delta E_3{}^{\ddagger}$) Isomerization of *s-trans* and *s-cis* Propenoyl Radicals **1a** and **3a** to 2-Carbonylethyl Radical **2a**

	$\Delta E_1{}^{\ddagger}$	$\Delta E_2{}^{\ddagger}$	$\Delta E_3{}^{\ddagger}$	$\Delta E_4{}^{\ddagger}$
UHF/6-311G**	12.4	14.3	12.9	3.0
BHandHLYP/6-311G**	13.9	18.5	16.3	2.4
BHandHLYP/cc-pVDZ	14.3	17.7	15.5	3.0
BHandHLYP/aug-cc-pVDZ	13.1	12.9	11.0	0.3
QCISD/cc-pVDZ//BHandHLYP/cc-pVDZ	15.2	7.4	5.7	6.1
QCISD/aug-cc-pVDZ//BHandHLYP/aug-cc-pVDZ	14.2	2.8	2.8	4.6
CCSD(T)/cc-pVDZ//BHandHLYP/cc-pVDZ	16.2	7.0	5.3	7.0
CCSD(T)/aug-cc-pVDZ//BHandHLYP/aug-cc-pVDZ	15.1	2.6	2.6	5.6
B3LYP/6-311G**	10.6	18.8	—[b)]	—[b)]
B3LYP/cc-pVDZ	10.9	17.9	—[b)]	—[b)]

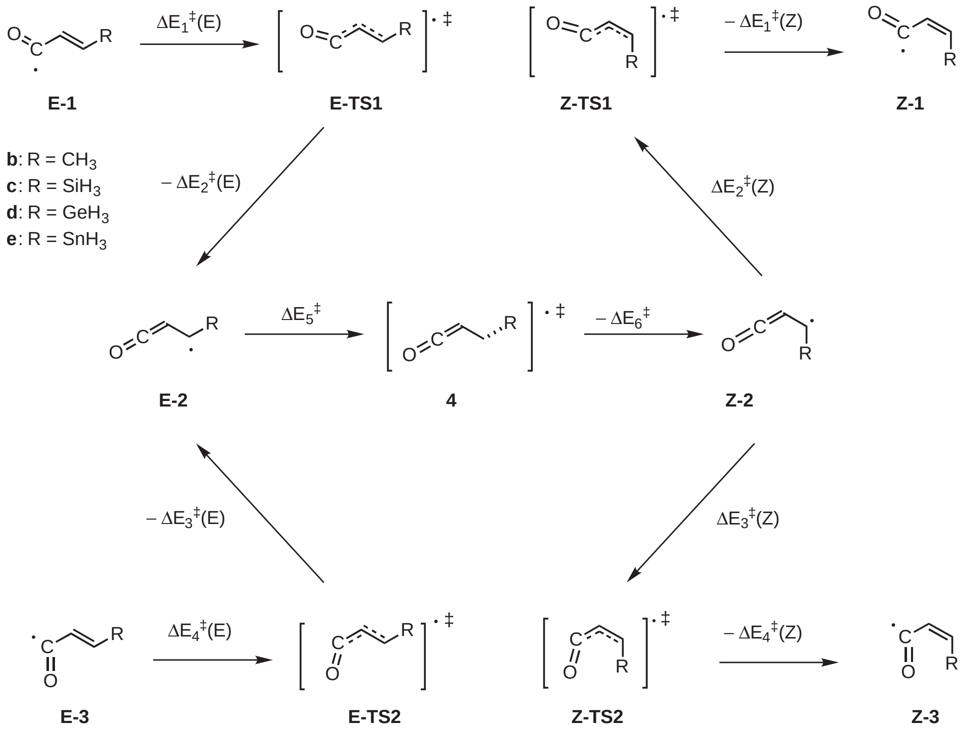
a) Energies in kJ mol^{-1}. b) No transition states were found.



Scheme 5. Isomerization of propenoyl radical.



Scheme 6. Reaction profile of isomerization of propenoyl radical. Energies (in kJ mol^{-1}) are calculated on the CCSD(T)/aug-cc-pVDZ//BHandHLYP/aug-cc-pVDZ.



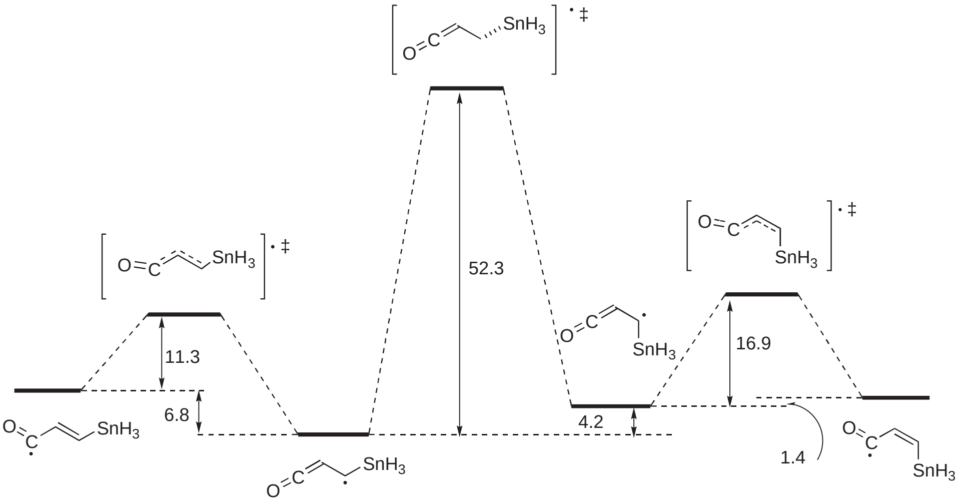
Scheme 7. Isomerization of 3-substituted propenoyl radicals.

Table 3. BHandHLYP-Calculated Energy Barriers[a] ($\Delta E^{\ddagger}$; Scheme 2) for the Isomerization of Crotonoyl Radical and Silicon-, Germanium-, and Tin-Substituted Propenoyl Radicals

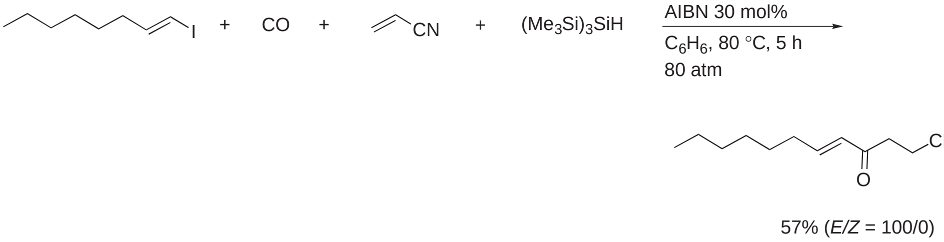
R	Method	$\Delta E_1{}^{\ddagger}(E)$	$\Delta E_2{}^{\ddagger}(E)$	$\Delta E_3{}^{\ddagger}(E)$	$\Delta E_4{}^{\ddagger}(E)$	$\Delta E_1{}^{\ddagger}(Z)$	$\Delta E_2{}^{\ddagger}(Z)$	$\Delta E_3{}^{\ddagger}(Z)$	$\Delta E_4{}^{\ddagger}(Z)$	$\Delta E_5{}^{\ddagger}$	$\Delta E_6{}^{\ddagger}$
CH_3	BHandHLYP/cc-pVDZ	21.6	11.9	10.3	11.2	17.0	12.5	10.7	6.8	43.6	45.0
SiH_3	BHandHLYP/DZP	10.4	20.4	—[b]	—[b]	9.0	20.5	—[b]	—[b]	53.3	49.8
GeH_3	BHandHLYP/DZP	11.3	18.4	—[b]	—[b]	11.3	18.2	—[b]	—[b]	51.9	48.7
SnH_3	BHandHLYP/DZP	11.3	18.1	17.4	3.1	15.5	16.9	15.1	9.9	52.3	48.1

a) Energies in kJ mol^{-1}. b) No transition states were found.

1b, **1c**, **1d**, and **1e** are listed in Table 3, while a reaction profile for the isomerization of **1e** at the BHandHLYP/DZP level is summarized in Scheme 8 where the profile of only the *s-trans* isomers is shown in order to avoid complicating the figure. In the case of crotonoyl radical **1b**, the ketenyl radicals **2b** are calculated to be less stable than the corresponding crotonoyl radicals. In addition, the (*E*)-crotonoyl radicals (**E-1b** and **E-3b**) are predicted to be more stable than the (*Z*)-crotonoyl



Scheme 8. Reaction profile of the isomerization of the 3-stannyl-substituted propenoyl radical. Energies (in kJ mol^{-1}) are calculated on the BHandHLYP/DZP.



Scheme 9. Three-component coupling reaction involving α,β-unsaturated acyl radicals.

radicals (**Z-1b** and **Z-3b**), while the (*E*)-2-carbonyl-1-methylethyl radical (**E-2b**) is calculated to be slightly less stable than (*Z*)-2-carbonyl-1-methylethyl radical (**Z-2b**).

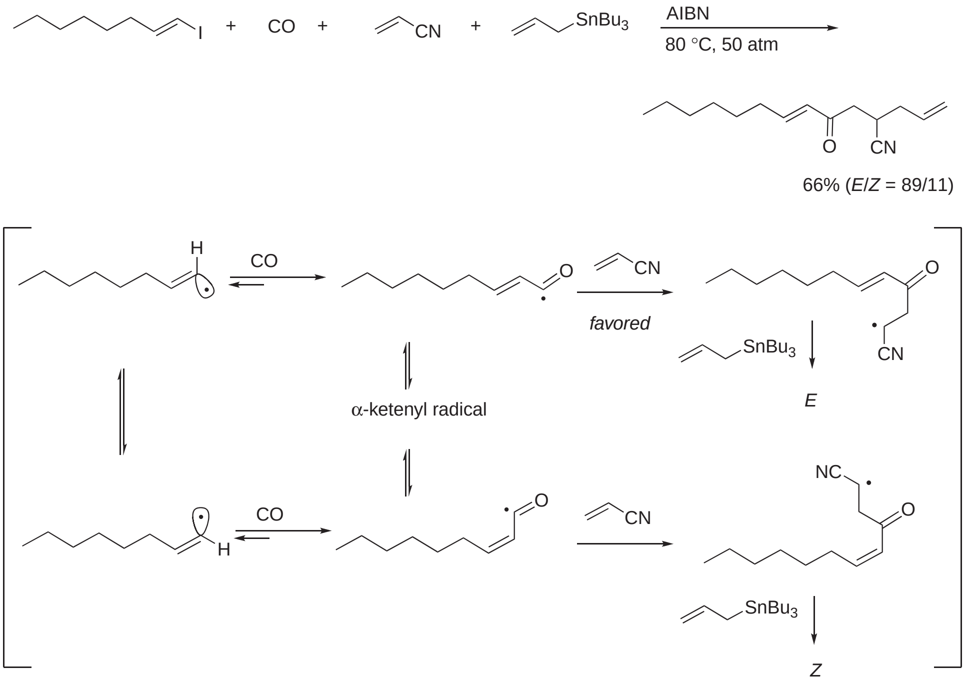
It is interesting to note that, as shown in Table 3, group (XIV) heteroatom (Si, Ge, and Sn) substituted α-ketenyl radicals **2c**, **2d**, and **2e** are more stable than the corresponding α,β-unsaturated acyl radicals **1c**, **1d**, and **1e**, providing that the heteroatom substituted at the β position stabilizes α-ketenyl radicals rather than α,β-unsaturated acyl radicals.

Importantly, these studies confirm that α-ketenyl and α,β-unsaturated acyl radicals are distinct species, rather than canonical forms of a common radical. The energy barriers between both types of radical species are calculated to be small (less than about 22 kJ mol^{-1}) suggesting that these species can interconvert readily and exist in equilibrium at temperatures typically used in radical reactions.

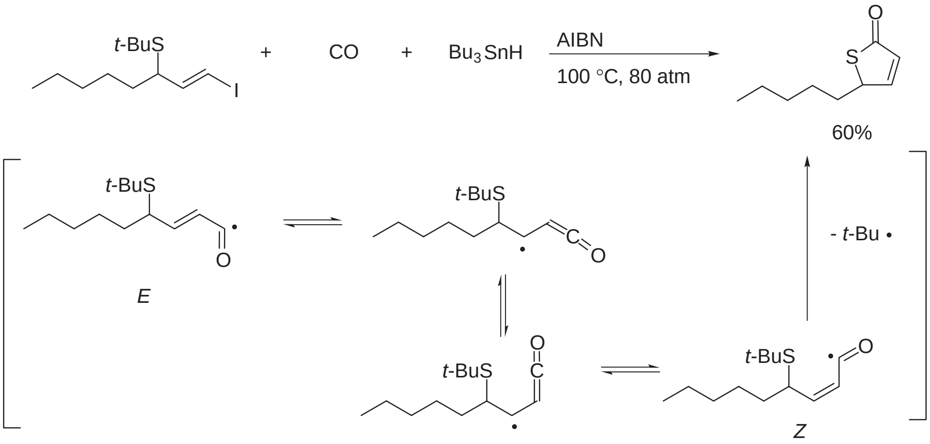
3. Trapping of α,β-Unsaturated Acyl Radicals

3.1 Intermolecular Trapping of α,β-Unsaturated Acyl Radicals. Radical cascade reactions which can combine multi-components by a single operation have great potentials in organic synthesis.[17,18] Vinyl bromides and iodides can be used for silicon and tin mediated carbonylative multi-component coupling reactions under radical reaction conditions.[17] We examined carbonylative multi-component coupling reactions under radical reaction conditions. For example, the azobis(isobutyronitrile) (AIBN) initiated reaction of (*E*)-1-iodo-1-octene with carbon monoxide in the presence of tris(trimethylsilyl)silane (TTMSS)[19] gave 4-oxo-5-dodecenenitrile in 57% yield (Scheme 9).[10] Only the *E*-form of the product was obtained in this case. A similar reaction using (*Z*)-1-iodo-1-octene also gave the same *E* product. This is consistent with the fact that the σ-vinyl radical is quickly inverted, even at low temperature.[20] On the other hand, the preferential formation of an *E* isomer may be attributed to the fact that addition reaction of the *E*-form of an acyl radical with acrylonitrile is sterically less demanding than that of *Z*-form. The resulting radical then abstracts hydrogen from TTMSS to give the product with liberation of a $(TMS)_3Si$ radical, which participates in subsequent chain propagation. An attempted similar three component coupling reaction using tributyltin hydride gave the same product but in lower yields due to the more rapid rate of hydrogen abstraction from tributyltin hydride by vinyl radical, which caused the premature quenching of the vinyl radical.

The AIBN-initiated reaction of 1-iodo-1-octene with carbon monoxide in the presence of allyltributyltin gave 6-oxo-1,7-tetradecadiene-4-carbonitrile, the four-component coupling product in good yield (Scheme 10).[11] The diastereomer ratio was 9:1 in favor of the *trans* isomer. The consequence of the four component coupling is a result of kinetics. (i) The vinyl radical adds to CO at a high concentration (50 atm) to give an α,β-unsaturated acyl radical. Acyl radicals have a nucleophilic characteristics and therefore the radical prefers the electron-deficient alkene to the electron-rich allyltributyltin. The resulting radical, containing an electron-withdrawing CN group prefers to add to the electron-rich C–C double bond of allyltin, which then liberates a tributyltin radical to provide the four-component coupling product. The preference of the



Scheme 10. Four-component coupling reaction involving α,β-unsaturated acyl radical.



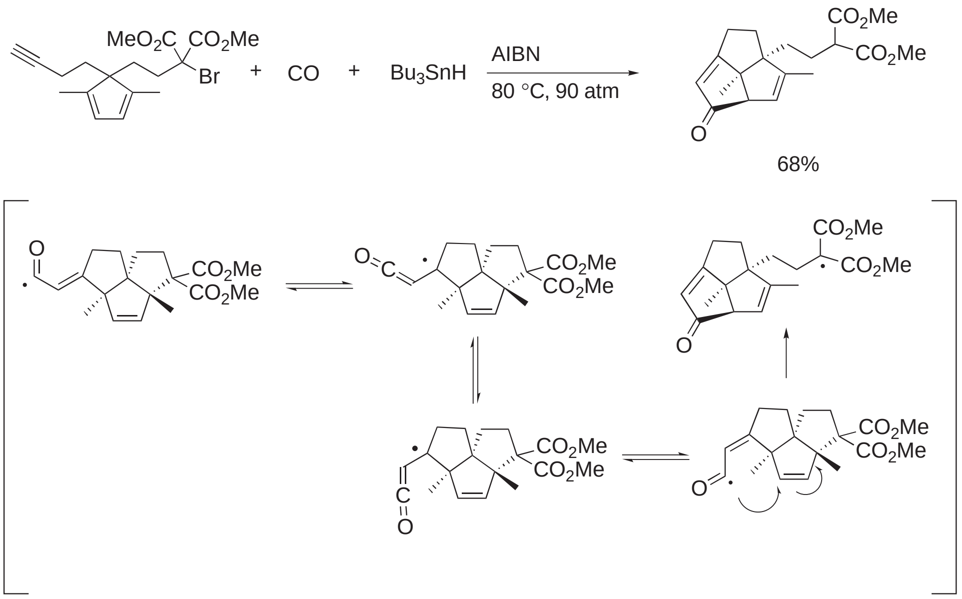
Scheme 11. Carbonylative S_Hi reaction involving α,β-unsaturated acyl radical.

E isomer can again be rationalized by the sterically less demanding transition state in the addition to acrylonitrile.

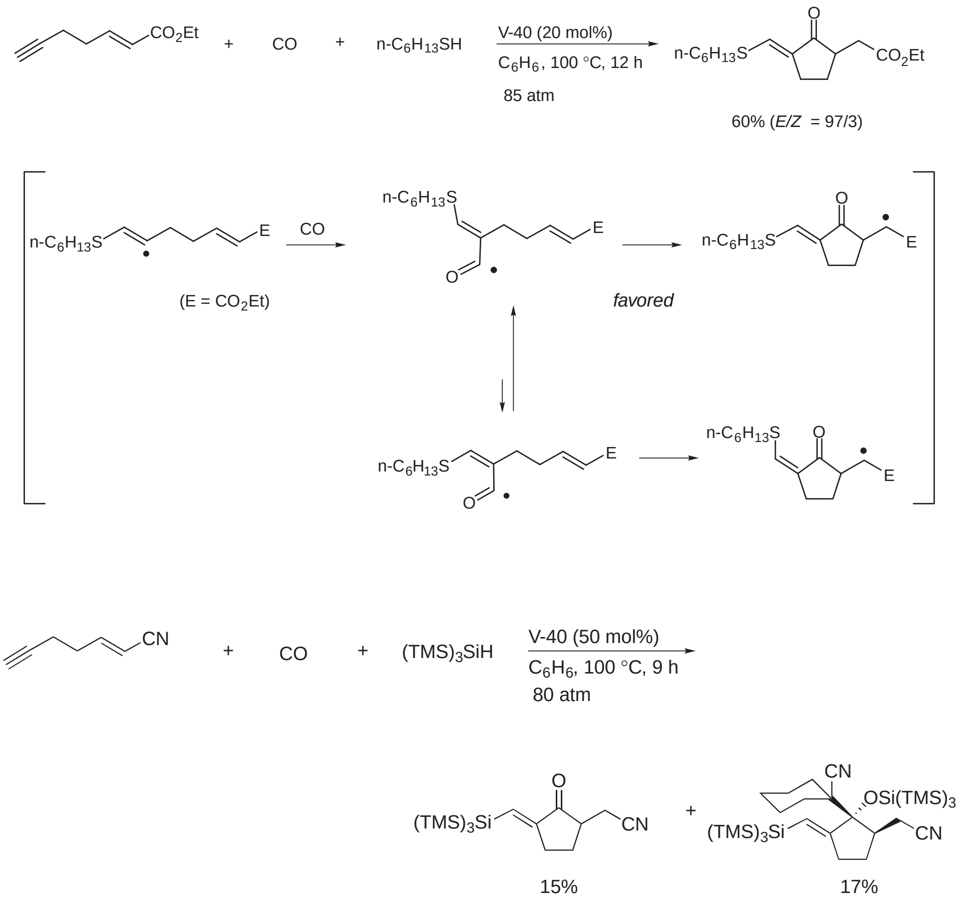
3.2 Intramolecular Trapping of α,β-Unsaturated Acyl Radicals. Carbonylation of 3-*t*-butylthio-attached vinyl iodide under standard tributyltin hydride/AIBN mediated radical reaction conditions gave α,β-unsaturated γ-thiolactone as the sole carbonylation product (Scheme 11).[12] Only the *Z*-form of the α,β-unsaturated acyl radical can undergo an S_Hi cyclization reaction at sulfur with the release of a *t*-butyl radical, however no α,β-unsaturated aldehyde derived from the *E*-form of α,β-unsaturated acyl radical was formed. In this regard, the rapid isomerization between two isomeric α,β-unsaturated acyl radicals via α-ketenyl radicals is proposed since the initial carbonylation should give an *E*, *Z* mixture of α,β-unsaturated aldehydes.

Tandem radical cyclization and carbonylative tandem cyclization of the alkyne provided the round-trip radical rearrangement product exclusively in 68% yield (Scheme 12).[13] In this reaction, we suspect that the initial carbonylation of the vinyl radical produces mainly the (*E*)-unsaturated acyl radical, but this readily equilibrates with the *Z* isomer via the α-ketenyl radical. The cyclization of the *Z*-form of the radical and cleavage then provides the final product.

We examined the tandem carbonylative radical cyclization of 1,5-enynes using hexanethiol as a radical mediator and V-40 (1,1′-azobis(cyclohexane-1-carbonitrile) as a radical initiator.[21] The reaction proceeds smoothly to give the corresponding cyclopentanone in 60% yield (Scheme 13). The almost exclusive formation of *E* isomer suggests that (*E*)-α,β-unsaturated acyl radical preferentially participates in the cyclization. The favorable disposition of the thio group trans to the carbonyl group is consistent with previously reported radical carbonylation of alkynes using thiols, leading to β-thio-attached (*Z*)-α,β-unsaturated aldehydes[22] and the thiocarbonylation



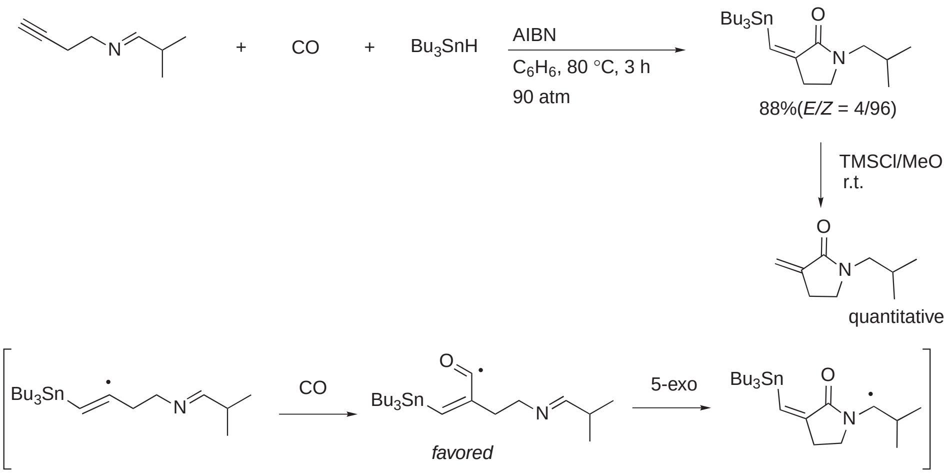
Scheme 12. Carbonylative tandem radical cyclizations involving α,β-unsaturated acyl radicals.



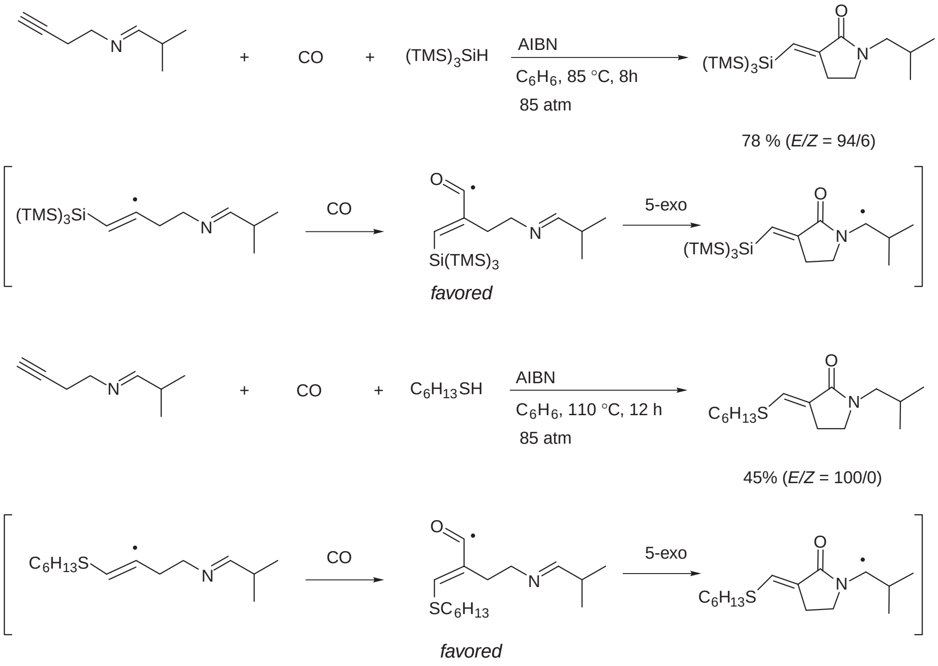
Scheme 13. Cyclizative thio- and silylcarbonylation of 1,5-enynes involving a β-heteroatom-attached α,β-unsaturated acyl radicals.

of azaenynes (vide infra). On the other hand, the corresponding silylcarbonylation using TTMSS instead of hexanethiol gave a similar product but in low yield. The reaction using TTMSS suffers from poor chain propagation, since the product, a β-silyl-substituted enone serves as a trap for oxophilic $(TMS)_3Si$ radicals,[23] resulting in the formation of 3-silyl-1-siloxyallyl radicals, which were eventually coupled with the initiator radicals.

Radical cyclization onto imine N=C bond has a potential as a means for the synthesis of nitrogen-heterocycles,[24,25] how-



Scheme 14. Cyclizative stannylcarbonylation of 2-aza-1,5-enyne involving β-stannyl-attached α,β-unsaturated acyl radical.

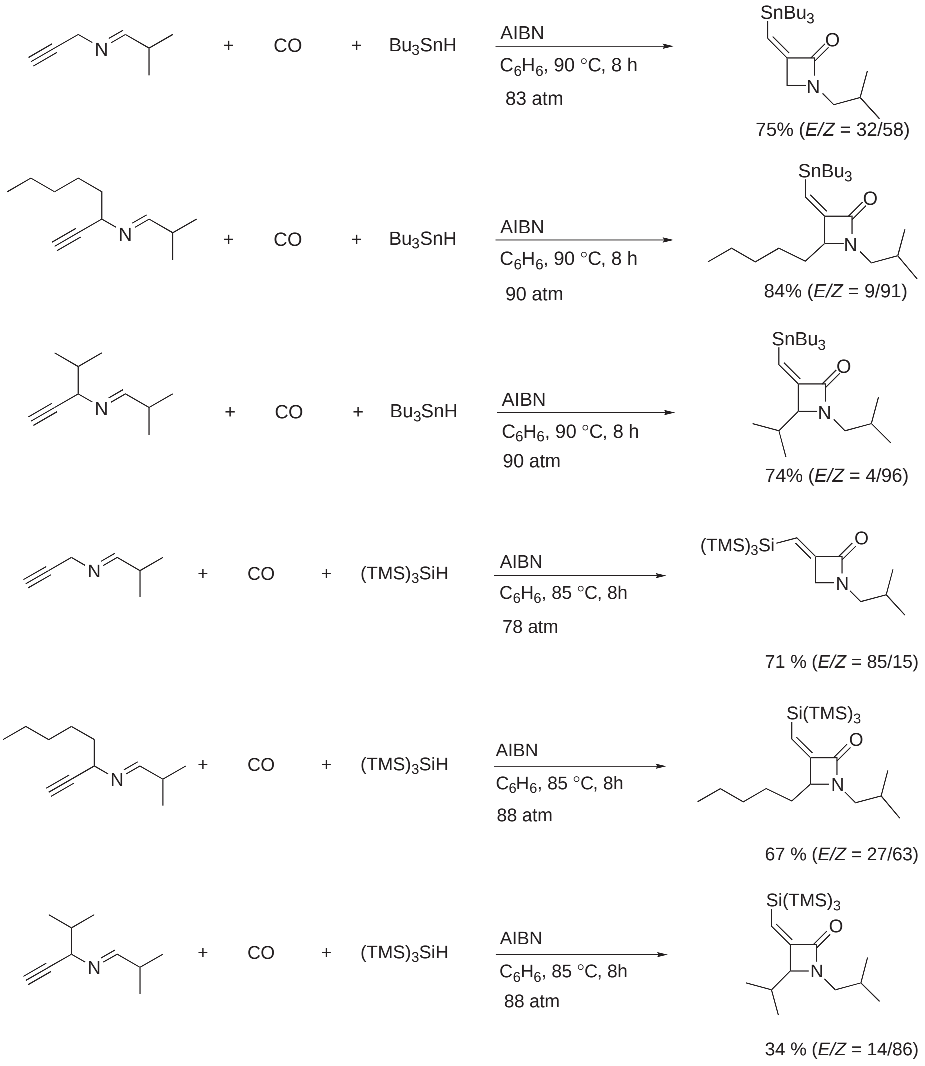


Scheme 15. Cyclizative silyl- and thiocarbonylation of 2-aza-1,5-enyne involving β-heteroatom-attached α,β-unsaturated acyl radicals.

ever, selective cyclization onto imine nitrogens is generally difficult to achieve.[26] We have previously reported that 5-exo/6-endo acyl radical cyclization onto imine N–C bond proceeded regioselectively onto nitrogen to give γ-lactams.[27] We examined the case of α,β-unsaturated acyl radicals by using azaenynes as the substrates. Under free radical reaction conditions, the stannylcarbonylation of azaenynes proceeds efficiently accompanied by regioselective cyclization onto the nitrogen atom to give lactams in good yield (Scheme 14).[28] Polar interactions between α,β-unsaturated acyl radicals and imine N=C bonds are likely responsible for increasing the ease of these reactions.[29]

We also examined similar cyclizative radical carbonylations of azaenynes using TTMSS and hexanethiol as a radical meditaor which leads to α-silyl- and thiomethylene lactams, respectively.[30] Scheme 15 summarizes the results of the synthesis of γ-lactams. Stannylcarbonylation gave the *Z*-isomer in high selectivity, whereas the two variants gave *E*-isomers in high or exclusive selectivity. Molecular orbital calculations of the five-membered ring products (G = SnH_3, SiH_3, and SMe, hydrogen at N) at the B3LYP/DZP level predict that the *Z*-isomer is more stable than the *E*-isomer when Sn is involved, and the *E*-isomer is more stable when sulfur is involved, in good agreement with the experimental results. Although a significant energetic difference between the *E* and *Z* isomers is not apparent for the silicon-containing product, pronounced steric effects associated with the bulky $(TMS)_3Si$ group reasonably accounts for the origin of the *E*-selectivity observed for the α-silylmethylene lactam.

Scheme 16 summarizes the results of the synthesis of α-(tributylstannyl)methylene and β-(tris(trimethylsilyl))methylene β-lactams. The stereochemical results for β-lactam forma-



Scheme 16. Cyclizative stannylcarbonylation and silylcarbonylation of 2-aza-1,4-enynes.

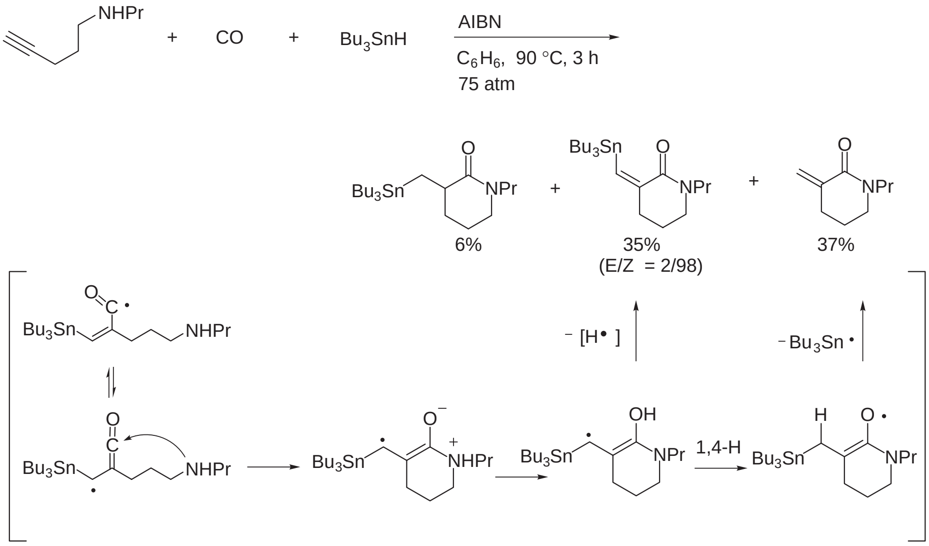
tion with respect to the newly formed C–C double bonds depends on the substitution pattern at the propargylic position. Thus, if the substituent is anything but hydrogen, tributyltin and $(TMS)_3Si$ groups tend to be disposed *syn* to the carbonyl group to avoid $A^{1,3}$ strain.

4. Trapping of α-Ketenyl Radicals by Amines

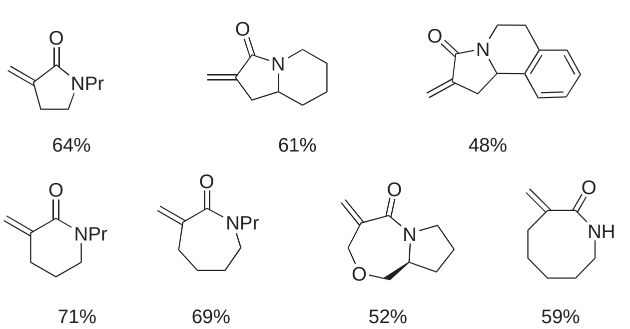
4.1 Intramolecular Trapping. It is well known that ketenes react with nucleophilic reagents to provide access to a wealth of carbonyl compounds.[31] The intramolecular trapping of α-ketenyl radicals by an amino group was successfully carried out using a radical carbonylation system comprised of ω-alkynylamines in which tributyltin hydride was used as a radical mediator and AIBN as a radical initiator.[32] For example the tin-mediated radical reaction of 4-pentynylpropylamine with CO gave three six-membered ring lactams (Scheme 17). Major products were the α-methylene lactam and the α-stannylmethylene lactam, with the α-stannylmethyl lactam being formed as a minor product. This minor product is most likely obtained by the hydrostannylation of the initially formed α-methylene lactam. In this reaction system, the elusive α-ketenyl radical may be trapped by an internal amine functionality to give the 3-hydroxyallyl radical. The subsequent 1,4-H shift can convert the 3-hydroxyallyl radical to the 1-oxoallyl radical,[33] which then undergoes β-scission of the carbon–tin bond to give the α-methylene ketone with liberation of a tributyltin radical. The formation of a tin-attached unsaturated lactam requires a formal oxidation step. One possibility is the abstraction of hydrogen from the hydroxyallyl radical by AIBN, which has been proposed by Bowman and Beckwith in a somewhat related system.[34]

Although two major products were obtained, combined with the subsequent protodestannylation procedure for the α-stannylmethylene lactam, the α-methylene lactam was obtained in 71% yield after isolation by silica-gel column chromatography. Scheme 18 lists the products obtained by two step procedure comprising cyclizative stannylcarbonylation and protodestannylation. Both primary and secondary amines work well in the cyclizative carbonylation reactions. Using alkynes containing cyclic amine moieties as the substrates, bicyclic α-methylene lactams can be prepared easily using this the procedure.

4.2 Intermolecular Trapping. In principle, the α-ketenyl radicals that are generated should be susceptible to intermolec-



Scheme 17. Nucleophilic trapping of α-ketenyl radical by an internal amino group.



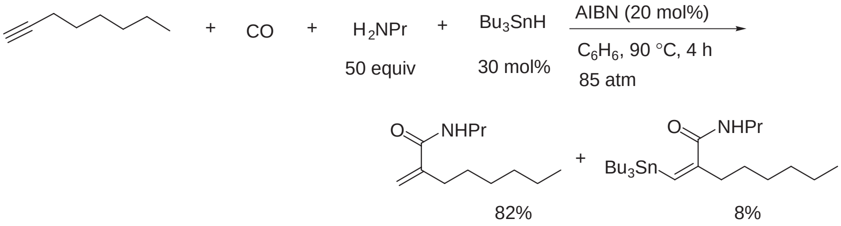
Scheme 18. Synthesis of α-methylene lactams from alkynylamines and carbon monoxide.

ular trapping by an amine. We also hypothesized that the formation of α-methylene lactams which do not contain a tributyltin unit suggests that the reaction should take place in the presence of a catalytic amount of tributyltin hydride. Indeed, when we examined the AIBN-initiated reaction of 1-octyne, CO, and tributyltin hydride (30 mol %) in the presence of a large excess of propylamine (50 mol equiv), the desired carbonylation reaction proceeded smoothly to give *N*-propyl-2-hexylacrylamide in 82% yield (Scheme 19).[35] In this reaction, a small amount of α-stannylmethylene amide was formed, which was easily converted to α-methylene amide by a protodestannylation procedure. In the DFT calculations, the 1,4-H migration is predicted to be exothermic by 80.0 kJ mol^{-1} and a five-membered cyclic transition state is suggested.

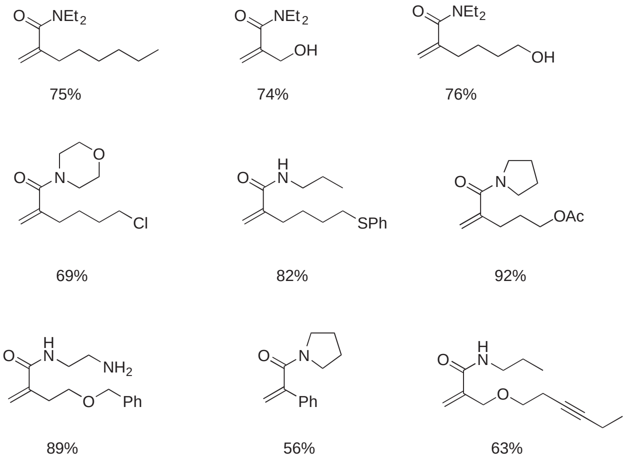
A variety of primary and secondary amines proved work well for the ketenyl radical trapping reaction leading to α-substituted acrylic amides (Scheme 20). In the case of a substrate containing two alkynyl groups, the reaction proceeded chemoselectively at the terminal alkyne to provide the corresponding amide. Scheme 21 illustrates a hybrid radical/ionic chain mechanism, in which an ionic reaction participates in propagation of the free radical chains. So far, the acrylic amide synthesis method using transition metals have been developed, however, the regioselective of the product could not be controlled.[36]

Conclusion

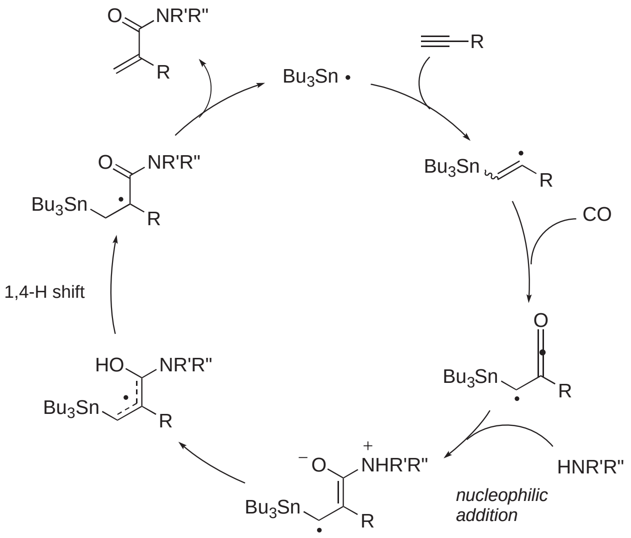
Radical carbonylation reactions have found wide applications for the synthesis of carbonyl compounds and this Account specifically focused on the unique aspects of the carbonylation of vinyl radicals in which α,β-unsaturated acyl radicals and α-ketenyl radicals are produced as key intermediates. Experimentally observed selective transformations via *Z*-form α,β-unsaturated acyl radical suggest that a rapid isomerization of the *Z*- and *E*-form α,β-unsaturated acyl radicals via α-ketenyl radicals occurs. Consistent with the experimental results, ab initio and DFT MO calculations predict that α,β-unsaturated acyl radicals and α-ketenyl radicals are not canonical forms but, rather, are interconvertible isomers at temperatures that are typically used in radical reactions. The method used to generate α,β-unsaturated acyl radicals by the carbonylation of vinyl radicals has an advantage of the facile generation of α,β-unsaturated acyl radicals including polar functionalities. The intramolecular trapping of α-ketenyl radical by imines and amines, when successful, gives a wide range of lactam rings.



Scheme 19. Intermolecular nucleophilic trapping of α-ketenyl radical by an amine.



Scheme 20. Synthesis of α-substituted acrylic amides from terminal alkynes, CO, and amines.



Scheme 21. Chain cycle of hybrid/radical ionic reaction involving α-ketenyl radical.

A new method for the carbonylation of alkynes with amines, which is being carried, catalyzed by tributyltin radicals, has been developed.

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Award recipient

Ilhyong Ryu received his B.S. from Nagoya University in 1973. He then moved to the Graduate School of Engineering, Osaka University, where he received his Ph.D. in 1978 under the direction of Professors Noboru Sonoda and Shinji Murai. After serving as of a JSPS postdoctoral fellow and a research associate at Osaka University, he was appointed Assistant Professor at Osaka University, Faculty of Engineering, in 1988. During this period, he also had the experience of working with Professor Howard Alper for a year (1991–1992) as a Visiting Scientist at the University of Ottawa. In 1995, he was promoted to Associate Professor at Osaka University. He moved to Osaka Prefecture University as a Full Professor in 2000. He was a Visiting Professor at the Australian National University (2000) and Université Pierre et Marie Curie (2002). He has been the recipient of the Progress Award in Synthetic Organic Chemistry, Japan (1990) and the Chemical Society of Japan Award for Creative Work (2004). He was approved as a Fellow of the Royal Society of Chemistry (2005). His research interests include new synthetic methodologies based on free radical species, new catalytic transformations, the utilization of new reaction media, and micro devices in organic synthesis.

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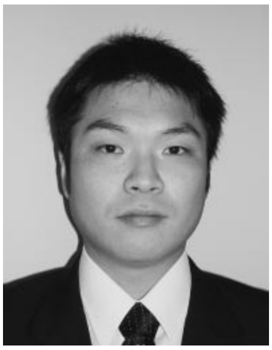

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