

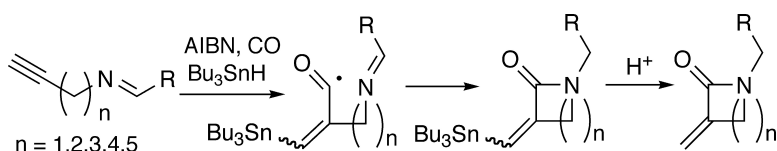
Communication

**Broad-Spectrum Radical Cyclizations Boosted by Polarity Matching.
 Carbonylative Access to β -Stannylmethylene Lactams from Azaenynes and CO**

Ilhyong Ryu, Hironari Miyazato, Hiroki Kuriyama, Kazutoshi Matsu, Mami Tojino, Takahide Fukuyama, Satoshi Minakata, and Mitsuo Komatsu

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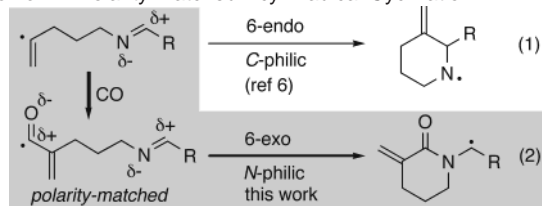
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Radical cyclization chemistry has provided powerful means to construct both carbocycles and heterocycles.^{1,2} For radical cyclizations to be generally applicable, two hurdles need to be surmounted: (i) levels of regioselective control in cyclization modes and (ii) broad applicability covering small to medium ring cyclizations. In this regard, we are interested in the possibility of providing a kinetic boost to radical cyclizations by introducing a polar component. We previously reported that complete 5-exo cyclization of acyl radicals onto imine nitrogens can be accomplished by this method.³ Herein we report that by employing an α,β -unsaturated acyl radical as the attacking radical and an imino group as the acceptor, a radical cyclization process can be developed which has unusual generality. Cyclizations occur with high regioselectivity favoring the *N*-philic mode for the synthesis of 4-, 5-, 6-, 7-, and 8-membered rings. The radical cyclization was conveniently accomplished by using a tin hydride mediated carbonylation system using azaenynes as the substrates, which led to α -stannylmethylene lactams, precursors for α -methylene lactams (Scheme 1).

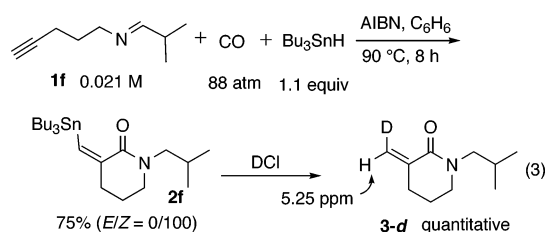
Scheme 1. Polarity-Matched Acyl Radical Cyclization



The *N*-philic cyclization of acyl radicals is counter-intuitive, since acyl radicals generally behave as nucleophilic radicals toward C–C double bonds.^{4,5} Unlike the case of acyl radicals, the corresponding 5-exo cyclization of vinyl radicals onto N–C double bonds is highly inefficient, suggesting that the combination of a nucleophilic vinyl radical and the nitrogen atom of imines is polarity-mismatched.^{6,7} The radical instead preferred to react via 6-endo cyclization onto the carbon (eq 1). By adding carbon monoxide to this same reaction, we envisioned that in situ conversion of the “polarity-mismatched” vinyl radical/imine combination to a “polarity-matched” α,β -unsaturated acyl radical/imine combination would result in efficient cyclization leading to the α -amino radical of α -methylene-substituted δ -lactams (eq 2).

The carbonylative 6-membered ring forming reaction was affected using azaenynes such as **1f** under stannyl carbonylative conditions to give α -stannylmethylene δ -lactam **2f** in good yield (eq 3). The *Z*-geometry of the product was further confirmed by NMR

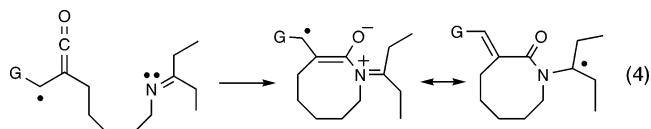
analysis of the product **3-d** resulting from destannylation with deuterium chloride (DCl), which is known to proceed with retention of configuration.⁸



Using azaenynes with various carbon chains, we then examined the generality of the cyclization of unsaturated acyl radicals onto N–C double bonds (Table 1). Most radical cyclizations suffer from a rather limited spectrum of cyclization modes, for example, 5-exo and 6-exo cyclizations, while systems in which smaller and larger rings are efficiently formed are scarce. Surprisingly, the polarity matched cyclization reaction described herein has an unusual scope, including 4-exo, 5-exo, 6-exo, 7-exo, and even 8-exo cyclizations. Thus, a variety of β -lactam derivatives were prepared (runs 1–4),⁹ and carbonylative 5- to 8-membered ring cyclizations also proceeded in good yield (runs 5–9). On the other hand, carbonylative cyclization of **1j**, which yielded 9-membered ring lactam **2j**, occurred in a very low yield (run 10). In this case, the compound resulting from hydrostannylation of **1j** as well as unreacted **1j** was detected.

Vinylstannanes are versatile functional groups, and we examined several destannylation reactions of the products **2**, which are also shown in Table 1. For example, treatment of **2h** with HCl (Me₃SiCl, MeOH, rt, 1 h) gave the corresponding α -methylene lactam **8** quantitatively. Iodination of *E* and *Z* isomers of **2a** with molecular iodine (I₂, ether, 0 °C, 1 h) gave the corresponding *E* and *Z* form of α -iodomethylene lactams **4(E)** and **4(Z)** quantitatively.¹⁰ Stille coupling reaction of **2b(Z)** with PhI (cat. Pd₂(dba)₃, DMF)¹¹ proceeded to give the stereo-retained phenylation product **5(Z)**.

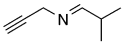
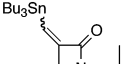
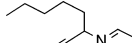
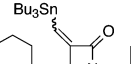
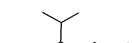
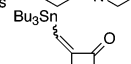
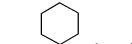
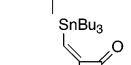
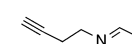
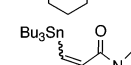
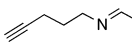
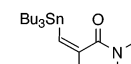
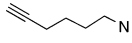
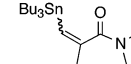
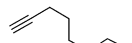
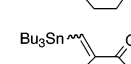
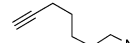
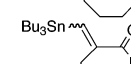
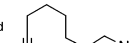
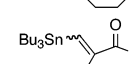
We think that the unusual scope of the present cyclization may originate from the unique ability of the α,β -unsaturated acyl radical to behave as an α -ketenyl radical,¹² which would serve as an efficient *polar* partner of an imino functionality (eq 4).



It should be noted that stereochemical results of β -lactam formation with respect to newly formed C–C double bonds

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Table 1. Stannylcarbonylation of Azaenyne 1 Leading to α -Stannylmethylene Lactams and Some Destannylation Reactions^a

run	azaenyne 1	conditions	lactams 2	yield ^b (E/Z) ^c
1		0.05 M CO 83 atm 90 °C, 8 h	 4(E) (from 2a(E)) 4(Z) (from 2a(Z))	75% (32/68) quantitative quantitative
		I ₂ , ether 0 °C, 1 h		
2		0.05 M CO 90 atm 90 °C, 8 h	 5(Z) (from 2b(Z))	84% (9/91) quantitative
		Ph-I cat. Pd ₂ (dba) ₃ DMF, r.t., 3 days		
3		0.02 M CO 90 atm 90 °C, 8 h		74% (4/96)
4		0.05 M CO 90 atm 90 °C, 8 h	 6(Z)	40% (0/100) 80% (0/100)
		Ph-I cat. Pd ₂ (dba) ₃ DMF, r.t., 4 days		
5		0.02 M CO 90 atm 80 °C, 8 h		88% (4/96)
6		0.021 M CO 88 atm 90 °C, 8 h	 3	75% (0/100) quantitative
		Me ₃ SiCl, MeOH r.t., 1 h		
7		0.01 M CO 80 atm 90 °C, 8 h	 7(E) (from 2g(E))	69% (19/81) 92%
		Ph-I cat. Pd ₂ (dba) ₃ DMF, r.t., 8 h		
8		0.02 M CO 85 atm 90 °C, 8 h	 8	61% (52/48) quantitative
		Me ₃ SiCl, MeOH r.t., 1 h		
9		0.02 M CO 90 atm 90 °C, 8 h	 9	61% (82/18) quantitative
		Me ₃ SiCl, MeOH r.t., 1 h		
10 ^d		0.02 M CO 85 atm 115 °C, 8 h		10% (47/53)

^a Conditions: **1** (0.5 mmol), Bu₃SnH (0.55–1 mmol), AIBN (19–37 mol %), benzene, CO (80–90 atm). For a typical procedure, see the Supporting Information. ^b Isolated yields by flash chromatography on silica gel. ^c Determined by ¹H NMR of crude reaction mixture. ^d V-40 (1,1'-azobis(cyclohexane-1-carbonitrile)) was used as a radical initiator.

depended strongly on the substitution pattern at the propargylic position (runs 1–4). Thus, if the substituent is anything other than hydrogen, the tributyltin group tends to be disposed syn to the carbonyl group to avoid A^{1,3} strain.

In summary, free-radical mediated stannylcarbonylation of azaenyne provides a general $[n + 1]$ -type annulation approach leading to α -stannylmethylene lactams. The cyclization is unprecedented in its breadth, covering 4-exo, 5-exo, 6-exo, 7-exo, and 8-exo modes. Polar interactions between α,β -unsaturated acyl radicals and imine N=C bonds are likely responsible for increasing the ease of these reactions. We believe that the concept of “polarity matching” will greatly increase the scope of radical reactions and provide an arena for the development of new radical reactions. Study along this line is currently underway in our labs, as is the elucidation of the cyclization transition state of the present reaction.

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Supporting Information Available: General experimental procedures including spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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