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FREE RADICAL-BASED ANNULATION OF ALKENES YIELDING FUSED CYCLOHEPTANONES

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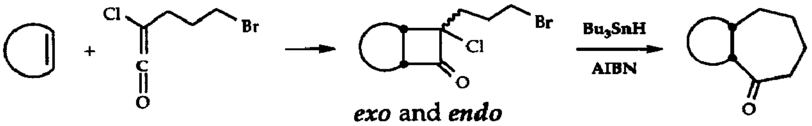
Abstract *Stereospecific annulation of cyclic alkenes for the preparation of cis-fused seven-membered ring systems was accomplished by sequential [2 + 2] cycloaddition, exo-allylation, hydrohalogenation, and free radical ring expansion. The new strategy extends our recently developed cyclobutanone-based ring expansion reactions.*

Annulation of an alkene to form a new seven-membered ring in stereospecific fashion would be a valuable adjunct to synthetic chemistry. In this paper, we report a new, high yield sequence that accomplishes this goal. Chloro(bromoalkyl)ketenes were earlier added to alkenes to form cyclobutanones and that step was followed by free radical promoted ring expansion (Scheme 1).[1-3]

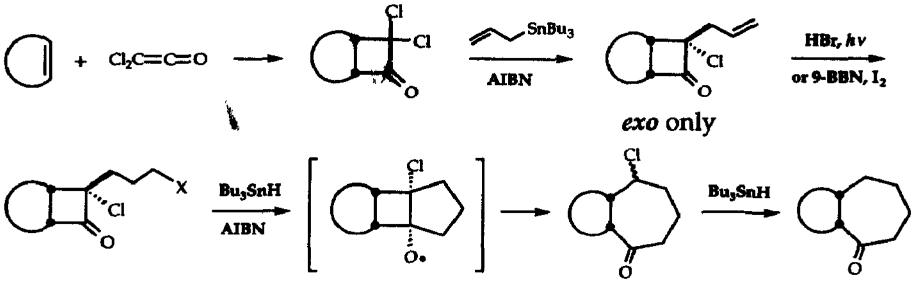
Scheme 1



Although ring expansion occurs stereospecifically and in good yield, there are two drawbacks to this approach: (i) The chloroalkylketenes react best with conjugated dienes and in lower yield with simple alkenes.[4] (ii) The ketene addition yields a mixture of *exo* and *endo* products and only the *exo* products undergo ring expansion.[2b] Both problems have now been resolved such that the new strategy has considerable synthetic promise (Scheme 2).

Dichloroketene reacts readily and in excellent yield with simple alkenes as well as with dienes to give a series of dichlorocyclobutanones.[5] With the annulated dichlorocyclobutanones in hand, it becomes a simple extension of our recently developed free radical chemistry to alkylate the dichlorocyclobutanone ring with radical acceptors.[6]

Scheme 2



We have recently shown that dichlorocyclobutanones add intramolecularly to alkenes in a free radical reaction.[6] In the present case, we observe high yield intermolecular additions to allyl tributyltin.[7] Moreover, the addition reaction proceeds to yield *only* the desired *exo*-allyl adduct as a consequence of steric constraints. Free radical hydrobromination of the allyl adduct is then followed by free radical ring expansion yielding the *cis*-fused cycloheptanone products.

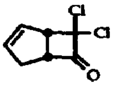
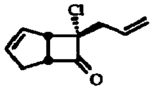
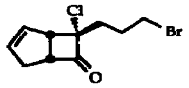
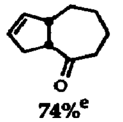
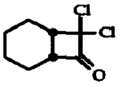
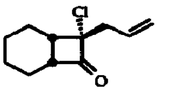
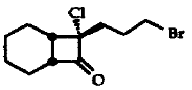
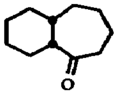
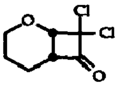
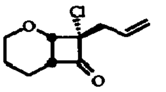
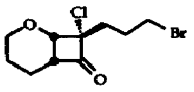
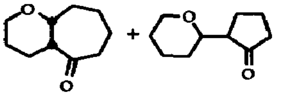
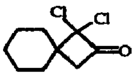
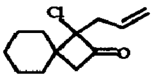
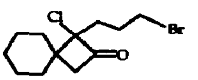
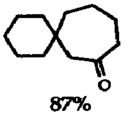
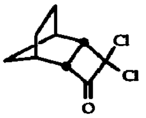
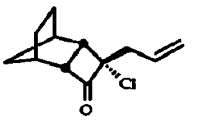
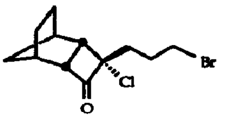
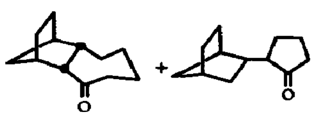
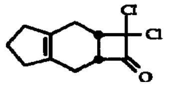
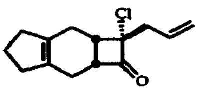
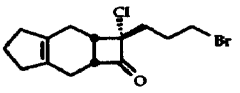
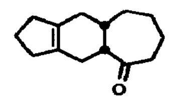
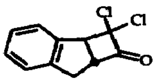
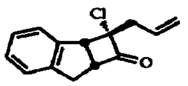
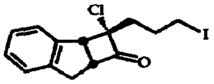
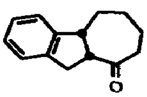
The products and yields in Table 1 attest to the versatility of the new method. In entries 1, 2 and 4, fused and spiro bicycloketones are prepared.[2a,b,d] Entry 3 demonstrates that an enol ether can be employed to provide access to the 2-oxabicyclo[5.4.0]undecan-7-one system together with a minor amount of the alternative ring-opened by-product. Bicyclic systems are likewise encompassed as indicated in entries 5 and 6. Indene as substrate yields the interesting benzoperhydroazulenone shown in entry 7.

In sum, we have here a useful straightforward method for transforming alkenes to *cis*-fused cycloheptanones.

Acknowledgment

This work was generously supported by the Institute of General Medical Sciences of the National Institutes of Health under grant GM 39825.

Table 1. Annulation of Alkenes

Entry	Dichlorocyclobutanone[a]	Allylation product[b]	*Exo*-halide[c]	Ring expansion product[d]
1		 78%	 83%	 74%[e]
2		 51%	 97%	 51%
3		 55%	 54%	 74% (79:21)
4		 50%	 60%	 87%
5		 64%	 92%	 89% (70:30)
6		 42%	 50%	 45%
7		 67%	 90%	 60%

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[a] 1.0 eq. of alkene, 1.2-1.5 eq. of Cl_3CCOCl, 2.0 eq. of zinc dust, ether, sonication 0.5-4 h, 75-90% yields. [b] 2.0 eq. of allyltributyltin, cat. AIBN, benzene, reflux 4-12 h. [c] Bromides: HBr (g), hexanes, sunlamp irradiation 0.5-3 h. Iodide: Kabalka, G.; Gooch III, E. E. J. Org. Chem. 1980, 45, 3578. [d] Slow addition of 2.5-3.0 eq. of Bu_3SnH, cat. AIBN, benzene, reflux 6-10 h. [e] Ref. 2a,b

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