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Stereoselective Construction of Functionalized Bicyclic Carbocycles Through Metal-Halogen Exchange-Initiated Sequential Conjugate Addition Reactions

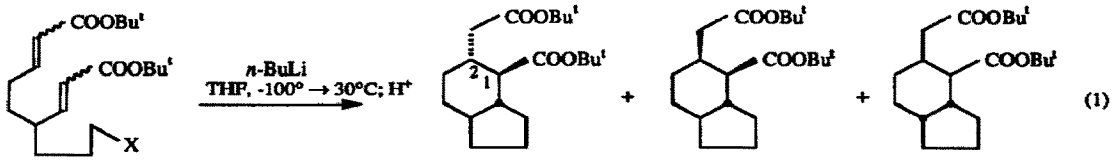
Manning P. Cooke, Jr. * and D. Gopal

Department of Chemistry, Washington State University, Pullman, Washington 99164

Abstract: **Rapid metal-halogen exchange reactions have been used to initiate the stereoselective formation of trans-bicyclo[4.3.0]nonane and strained trans-bicyclo[3.3.0]octane derivatives through sequential intramolecular conjugate addition reactions. Stereoselectivity has been controlled in anionic olefin addition reactions as well as in corresponding radical cyclizations through control of acceptor olefin stereochemistry.**

One of the more important approaches to carbocyclic construction involves intramolecular reactions of carbon-carbon multiple bonds with reactive carbon centers.[1] Cyclization reactions of carbocations[2] and radicals[3] have received much attention while their carbanionic counterparts have received relatively little.[4,5] The cyclization of 5-hexenyllithium and related systems have recently been studied,[5] but in general such cyclizations are relatively slow, require accelerating agents such as TMEDA,[5d,h,j,k] proceed only with unsubstituted terminal olefins, generate organolithium products not compatible with the presence of many internal groups and which are difficult to preserve. We have recently shown that lithium-iodine exchange reactions of primary iodides occur very rapidly at low temperatures and often may be conducted in the presence of carbonyl-containing functional groups[6] including esters, allowing such exchange reactions to be used to trigger intramolecular Michael addition reactions leading for 3, 4, 5 and 6-membered rings.[7] We now wish to report the facile formation of functionalized trans-bicyclo [4.3.0] nonane and strained trans-bicyclo [3.3.0] octane derivatives through metal-halogen exchange-initiated sequential conjugate addition reactions in which stereoselectivity is achieved through control of acceptor olefin geometry.

Substrate E,E-**1a** has been found to cyclize in high yield (97% GC, 85% isolated) through reactive intermediate lithium derivative **1b** upon treatment with *n*-BuLi (-100° → -30°C, THF)[8] giving, after protonation of resulting enolates, a 13:1:4 mixture of isomeric bicyclo[4.3.0]nonane derivatives, 2[9a], 3[9b] and



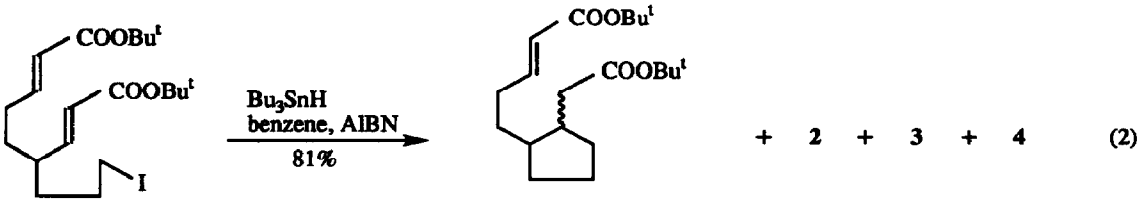
1a (X = I)
b (X = Li)

E,E-1a[13] —97%→ 2+3+4 (13:1:4)
Z,E-1a —91%→ 2+3 (12:1)
Z,Z-1a —94%→ 2+3+4 (0.8:1)

4[10] (eq. 1). While this cyclization is quite efficient, the low stereoselectivity was disappointing especially with regard to ring juncture stereochemistry (t/c = 3.5) in light of the fact that structurally analogous 4-methyl-5-hexenyllithium cyclizes to give 1,2-dimethylcyclopentane with nearly 14:1 trans selectivity.[5d] Lower selectivity in the ring junction-forming conjugate addition reaction likely arises from transition-state changes brought about by the increased exothermicity of the addition to an olefin bearing a carbanion stabilizing group and is a reflection of a transition-state that is less restrictive than the concerted ones proposed for addition reactions of unactivated olefins.[5e, 11]

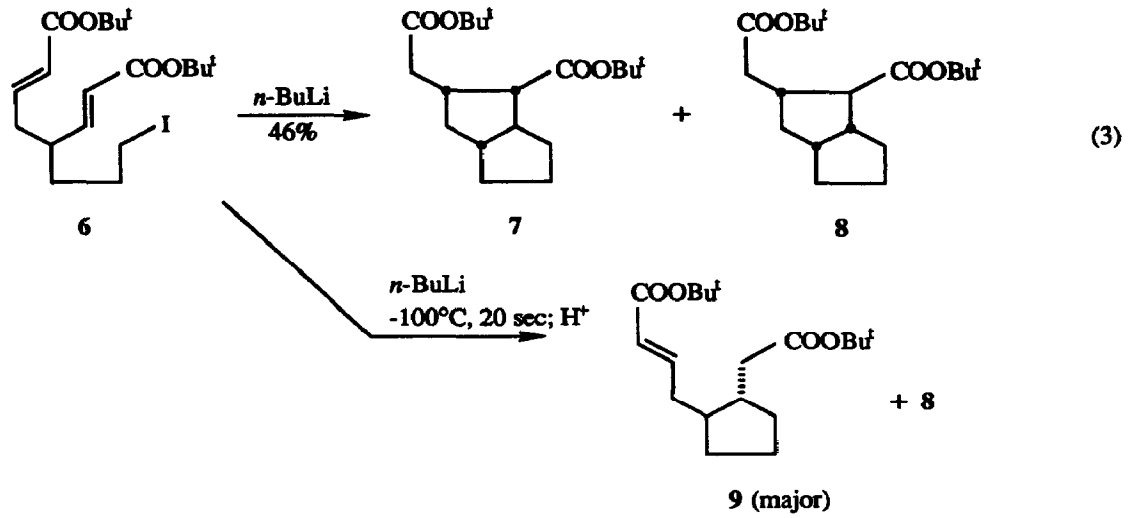
A recent model study from this laboratory[7c] suggested that Z-olefin stereochemistry should destabilize the rotamer leading to cis ring-junction products through increased 1,3-allylic strain[12] and to our delight cyclization of the analogous Z,E isomer[13] of **1a**, gave in 91% yield, a 12:1 mixture of **2** and **3** with essentially no cis ring-junction products (**4**) being formed. Stereochemistry at C-1 and C-2 is also a function of terminal acceptor olefin stereochemistry; cyclization of Z,Z-**1a**[13] gives **2** and its C-2 epimer **3** in 94% yield with **2/3** = 0.8. These results may be rationalized by considering that with terminal E-acceptor geometry, the dominance of all-trans **2** is the result of an expected chair transition state in which the relevant substitutents are all equatorially disposed. With terminal Z-acceptor geometry, chair transition states leading to **2** and **3** both possess severe 1,3-allylic interactions and have ester and enolate oxygen atom orientations which preclude a closed cyclic structure containing Li^+ chelation.[14] However, a more favorable twist-boat transition-state devoid of serious 1,3-allylic stain does exist leading to **3** and allows for possible intramolecular counterion chelation.

In contrast to these anionic cyclizations, inferior results were obtained in the radical mode. Treatment of E,E-**1a** with Bu_3SnH gave in 81% yield a 2:3:1 mixture of bicyclic and and monocyclic products with bicyclic products consisting of a 3:1 mixture of **2** and **3**, small amounts of **4** and monocyclic **5** as a 9:1 mixture of trans/cis isomers (eq. 2). The sizable amount of monocyclic **5** formed is likely a result of the competitive

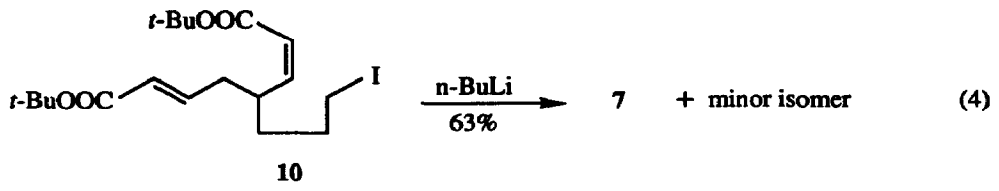


quenching by Bu_3SnH of the relatively non-nucleophilic radical center generated in the first cyclization reaction---a radical which reacts at a reduced rate with the remaining electron-deficient olefin.[3d] Similar results are obtained with Z,E-**1a**[13], but in this case only the trans-isomer of monocycle **5** is formed demonstrating the power of acceptor olefin geometry control in achieving high stereoselectivity in radical cyclizations as well.[7c]

To our surprise, treatment of **6** with *n*-BuLi (eq. 3), as above (eq. 1), also gave bicyclic products (46%, **7**[15a], **8**[15b] and two isomers of unproven stereochemistry, 22:20:1:1) even though in this case the second



cyclization reaction generates the strained[16] trans-bicyclo[3.3.0]octane system.[17] Rapid addition of *n*-BuLi to **6** followed by rapid quenching (-100°C, < 20 sec, MeOH) gave, in addition to **8** (but only traces of **7**), large amounts of trans-monocycle **9** (86% of volatiles) unattended by any of the corresponding cis-isomer, indicating that the second Michael addition is exceptionally rapid in the case of the cis ring-junction isomer.[18] Incorporation of Z-olefin geometry in the first acceptor (**10**) to preclude formation of any cis ring-junction product led, in 63% yield, predominantly to **7** along with 7% of a stereoisomer of unknown stereochemistry at C-1 and C-2 (eq. 4).



In summary, we have demonstrated the feasibility of tandem lithium-iodine exchange-initiated conjugate addition reactions in the stereoselective construction of functionalized bicyclic ring systems---even strained ones---which contain multiple stereocenters. Rapid metal-halogen exchange reactions combined with intramolecular Michael addition reactions leading to stabilized (enolate) anions considerably expand the scope of anionic cyclization reactions and avoid many of the difficulties encountered in the cyclization reactions of unactivated olefins.

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8. Typical of subsequently described anionic cyclization reactions, a vigerously stirred solution containing 193 mg (0.43 mmol) of **1a** was treated over 30 sec at -100°C with 0.3 mL (0.48 mmol) of 1.6 N *n*-BuLi (hexane). After 15 min, the temperature was allowed to gradually rise to -30°C over 1 h whereupon 0.2 mL HOAc was added followed by 3 mL of saturated $NaHCO_3$. Solvent removal, pentane-water extraction and chromatography (SiO_2,CH_2Cl_2) gave 118 mg (85%) of a 13:1:4 mixture (capillary g.c. prior to purification) of **2**, **3** and **4**. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.91; H, 10.00.
9. Stereochemistry established by X-ray crystallographic analysis of (a) the corresponding diacid, m. 172-174°C; (b) of the corresponding diol, mp 89-90°C.
10. Stereochemistry at C-1 and C-2 has not been firmly established.
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12. A model identical to **1a** but with a γ-ethyl substituent has been found to cyclize with greater than 300:1 trans-selectivity.[7c]
13. The stereochemical designators refer to the central and terminal olefin, respectively.
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15. Stereochemistry established by X-ray crystallographic analysis of (a) the corresponding diacid, mp 171-174°C; (b) of the corresponding diol, mp 78-80°C.
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17. The formation of this same ring system through the cyclization of an unactivated dienyllithium intermediate has recently been reported.[5l, m]
18. In all cases, the initial cyclization step is extremely rapid at -100°C (< 10 sec), but in the case of E,E-**1a**, for example, $t_{1/2} \approx 15$ min at -100°C for the (second) Michael addition leading to 6-membered ring-formation.

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