6. G. Stork and K. Nakatani, *Tetrahedron Lett.*, **29**, 2283-2286 (1988).
7. D. Rodphaya, J. Sekiguchi, and Y. Yamada, *J. Antibiotics*, **39**, 629-635 (1986).
8. D. F. Taber, R. E. Jr. Ruckle, and M. J. Hennessy, *J. Org. Chem.*, **51**, 4077-4078 (1986).
9. J. Djonlagic, M. O. Sepulchre, M. Sepulchre, N. Spassky, and M. S. Jacovic, *Makromol. Chem.*, **189**, 1485-1492 (1988).

Construction of Contiguous Quaternary Carbon Centers by Intramolecular Addition of Tertiary Radicals to Activated Olefins

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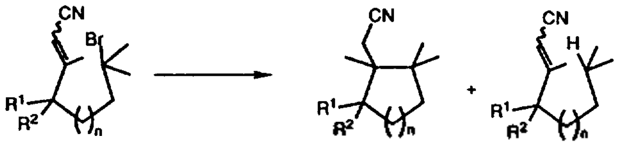
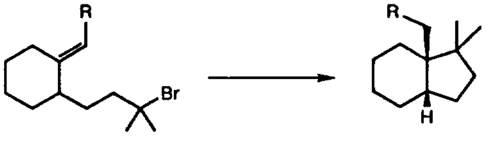
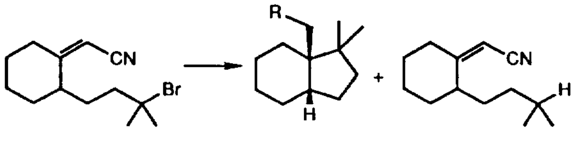
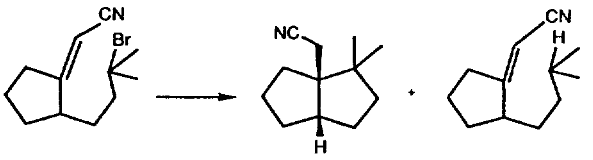
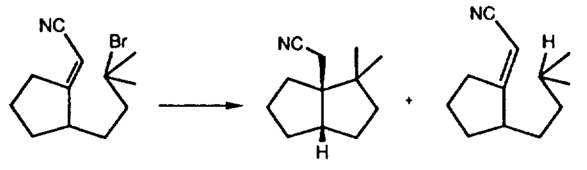
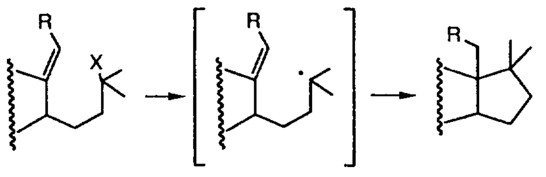
Even though various synthetic methodologies have been developed, construction of quaternary carbon centers still remains a challenging task to synthetic chemists.[1,2] Addition of free radicals to alkenes has enjoyed increasing popularity for the formation of carbon-carbon bonds due to its advantages over the ionic reactions. Free radical addition to alkenes, however, has been noted for its sensitivity to steric environment. For example, the radical cyclization rates are decreased as steric hindrance at the site of attack is increased. Free radical addition to alkenes for the construction of sterically congested environment have hardly been systematically investigated.[2d,3] Here we report a successful free radical addition in intramolecular mode for the formation of *contiguous* quaternary carbon centers. We envisioned that smaller SOMO-LUMO energy gap employing tertiary alkyl radicals and olefins having electron withdrawing groups which has lower LUMO energy might overcome the constraints created by steric congestion. This will add another option for the construction of contiguous quaternary carbon centers in addition to the method *via* the Michael reaction[2a] and *via* the addition on benzyllithium to carbon-carbon double bonds.[2c]

We have investigated the intramolecular cyclization *via* the radical intermediates directly generated from the corresponding tertiary bromides[4] to construct the contiguous quaternary carbon centers represented by the Eq. (1).

Table 1. Radical Cyclization to Construct Contiguous Quaternary Carbon Centers[6]

Entry	Bromide	Stereochemistry of olefin	Product(Yield)	
				
1	n=1, R^1=H, R^2=H,	(*E*)	(75%)	–
2	n=2, R^1=H, R^2=H,	(*E*)	(64%)	(15%)
3	n=1, R^1=CH_3, R^2=H,	(*Z*)	(62%)	(13%)
4	〃	(*E*)	(32%)	(22%)
5	n=1, R^1=CH_3, R^2=CH_3,	(*E*)	(73%)	–
				
6	R=CN	(*E*)	1 (88%)	
7	R=Ph	(*E*)	(45%)	
				
8		(*Z*)	(50%)	(30%)
				
9		(*Z*)2	(63%)	(7%)
				
10		(*E*)	(43%)	(20%)



(1)

The results of the cyclizations are summarized in Table 1. All the substrates for radical cyclization were prepared by the Witting reaction of the corresponding ketones. (*E*)- and (*Z*)-isomers separated by HPLC.[5] Cyclizations[6] usually proceeded in good yields despite the disadvantages in steric environment. All the cyclization proceeded in 5- or 6-*exo*-trigonal modes and we were unable to detect the products from 6-*endo*- or 7-*endo*-trigonal cyclization. Activation of the terminal site of the double bond is required and nitrile group is much superior to phenyl and alkoxycarbonyl (entries 6 *vs.* 7) (*vide infra*). The formation of five-membered ring (entry 1) is a little more facile than the case of six-membered ring (entry 2), providing cyclization products in reasonable yields. Generation of three contiguous quaternary carbon centers was proven to be feasible as shown in entry 5. The introduction of a methyl group adjacent to the carbon sp^2 center to which the radical attacks may lead to the diastereoselective radical addition due to 1,3-allylic strain.[7] The reaction yielded an inseparable mixture of cyclized products as well as a reduced product in both cases (entries 3 and 4). ^{1}H-NMR analysis of the cyclized product mixtures reveals that the ratios of the diastereomers formed were good in both cases (>*ca.* 8 : 1).[8] It is also interesting to note that the rate of cyclization depends on the alkene stereochemistry to some extent (entries 3 *vs.* 4, 6 *vs.* 8, and 9 *vs.* 10), even though the origin for the rate differences is not clear at the moment. The cyclization which leads to the fused ring products proceeded as expected (entries 6-10). Five membered ring annulations onto preexisting five-and six-membered rings proceeded as desired. Formation of the hydrindanes was efficiently achieved from the corresponding bromides (entries 6 and 8). The hydrindane **1** is a single isomer. Switching to Ph group for the activation, the cyclization rate was considerably slowed down (entry 7, 45% yield) and a single isomer was also formed in this case. No cyclization was observed on switching R group to CO_2Et (entry not shown). Thus, the activating group at the terminal site of the double bond is found to be crucial for successful cyclization at the sterically congested site.

Control of the ring-junction stereochemistry, especially in the formation of hydrindane system, has been a subject of interest. The ring-junction stereochemistry of hydrindane formed in the case of entry 6 was unambiguously determined as *cis* (as the structure shown in entry 6 of Table 1) by X-ray structural analysis of the corresponding carboxylic acid **1a** obtained by acid hydrolysis of **1**.[9] In the case of entry 7, a *cis*-hydrindane was also presumed to be formed.[10]

The facile formation of 5/5 ring system was also observed (entries 9 and 10). Construction of bicyclic compounds by radical addition to *exo*-double bonds provides a unique opportunity to evaluate the empirical rules made by Clive and coworkers regarding to the stereochemical consequences for ring-fusion geometry.[11] Our successful cyclization described here confirms the validity of the Clive's empirical rules, that is, this rule can now be applied to 5-*exo*-[*exo*-n] cases, where n=5 and 6.[12,13] It seems also appropriate to mention that the nitrile group introduced for the activation of the double bond for radical attack, provides an additional advantage for further synthetic manipulation. Also the nitrile group can be easily removed by treatment of potassium in toluene in the presence of 18-crown-6.[14]

In conclusion, the intramolecular radical addition to properly activated olefins can be successfully employed in the construction of carbon centers with sterically crowded environment. Further exploration of the radical cyclization method is under progress.

References

1. S. F. Martin, *Tetrahedron* **36**, 419 (1980).
2. For recent examples for the construction of *contiguous* quaternary carbon centers, see (a) R. A. Holton, A. D. Williams, and R. M. Kennedy, *J. Org. Chem.*, **51**, 5480 (1986); (b) S. Yamago and E. Nakamura, *J. Chem. Soc., Chem. Soc., Chem. Commun.*, 1112 (1988); (c) A. Krief and P. Barbeaux, *Synlett*, 511 (1990); (d) C. E. Schwartz and D. P. Curran, *J. Am. Chem. Soc.*, **112**, 9272 (1990).
3. Recently a report on the addition of *tert*-butyl radical to activated alkenes appeared. See G. A. Russell, C.-F. Yao, R. Rajaratnam, and B. H. Kim, *J. Am. Chem. Soc.*, **113**, 373 (1991). A report on a transannular cyclization *via* radical intermediate generated by alkoxy radical fragmentation has been appeared. See C. W. Ellwood and G. Pattenden, *Tetrahedron Lett.*, **32**, 1591 (1991).
4. The tertiary bromides were prepared by treating the corresponding tertiary alcohols with TMSBr. Iodides can also be employed, however, they gave lower cyclization yields presumably due to their instability.
5. Characterization of the (*E*)- and (*Z*)-isomers was achieved by ^{1}H-NMR analysis and NOESY.
6. Reaction conditions: A solution of tributyltin hydride (1.2 equiv) and AIBN (catalytic amount) in benzene was added during 10 h by syringe to a solution of the bromides in benzene (0.02 M) at reflux.
7. For the recent relevant example, see (a) M. Ihara, K. Yasui, N. Taniguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, **29**, 4963 (1988); (b) M. Ihara, K. Yasui, N. Taniguchi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans.*, 1, 1469 (1990); (c) M. Ihara, K. Yasui, N. Taniguchi, and K. Fukumoto, *ibid.*, 2771 (1990).
8. Stereochemistry of the cyclization products is under investigation.
9. We are grateful to Dr. Jong Hwa Jeong of the Inorganic Chemistry Lab of Korea Institute of Science and Technology (KIST) for performing the X-ray crystal structure determination of **1a**. Crystal data: $C_{13}H_{22}O_2$, FW=210.316; space group P1; $a=6.607(1)$, $b=8.350(1)$, $c=11.362(2)$ Å; $\alpha=90.72(1)$, $\beta=98.46(2)$, $\gamma=106.38(2)°$; $V=593.8(2)$ Å^3; $Z=2$; d(calcd)=1.176 g/cm^3, Crystal size 0.10×0.33×0.43 mm^3. The final R (R_w) value was 0.0417 (0.0483) for 1120 ($I>3\sigma(I)$) reflections.
10. Spectral data: **1** ^{1}H-NMR (300 MHz, $CDCl_3$) δ0.98 (s, 3H), 1.03 (s, 3H), 1.24-1.68 (m, 12H), 2.14 (m, 1H), 2.18 and 2.58 (AB, 2H, $J=17$ Hz); ^{13}C-NMR(75 MHz, $CDCl_3$) δ38.14 (CH_2CN), 41.17, 44.46 and 45.50 (4° carbons), 119.04 (CN). **1a** (carboxylic acid obtained from hydrolysis of **1**) mp. 129-131℃; ^{1}H-NMR (300 MHz, $CDCl_3$) δ.0.90 (s, 3H), 1.38 (s, 3H), 1.67 (m, 12H), 2.05 (m, 1H), 2.17 and 2.64 (AB, 2H, $J=13$ Hz), 10.5 (brs, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.26 (COOH); **2** ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.09 (s, 3H), 1.10-2.10 (m, 11H), 2.26 and 2.32 (AB, 2H, $J=17$ Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 40.0 (CH_2CN), 119.6 (CN).
11. For leading references on controlling ring-junction stereochemistry of hydrindanes via radical cyclization: see (a) D. L. J. Clive, H. W. Manning, and T. L. B. Boivin, *J. Chem. Soc., Chem. Commun.*, 972 (1990), and references therein; (b) S. Satoh, M. Sodeoka, M. Sasai, and M. Shibasaki, *J. Org. Chem.*, **56**, 2278 (1991); (c) G. Stork and

M. Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).

12. (a) A. Y. Mohammed and D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 588 (1986); (b) D. L. J. Cliver, D. R. Cheshire, and L. Set, *J. Chem. Soc., Chem. Commun.*, 353 (1987).
13. Clive and coworkers only mentioned on 5-*exo*-[*endo*-n] system, where n=5, 6, and 7.
14. T. Ohsawa, T. Kobayashi, Y. Mizuguchi, T. Saitoh, and T. Oishi, *Tetrahedron Lett.*, **26**, 6013 (1985).