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Samarium(II) Iodide Promoted Intramolecular Coupling between Carbonyl Groups and Activated Olefins Under Sterically Crowded Environment

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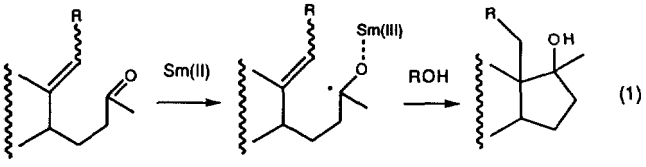
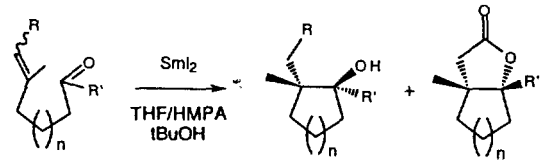
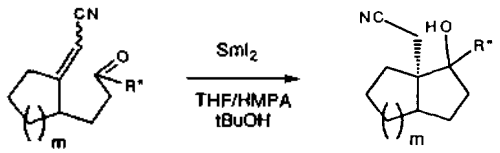
We have reported that intramolecular radical addition to properly activated olefins can be successfully employed in the construction of carbon centers under sterically crowded environment.[1] Since it is well known that the reaction of samarium(II) iodide[2] with the carbonyl group of ketones or aldehedes generate ketyl radicals, it would be interesting to investigate the addition ability of ketyl radicals to olefins under sterically crowded environment. The transformations of interest can be represented by the following equation (1).



(1)

The results of the investigation were shown in Table 1. Our study was focused only on the olefins with activating groups, that is, electron withdrawing groups such as alkoxycarbonyl (entries 1-4) or nitrile (entries 5-10) groups. The yields obtained for the corresponding five membered ring forming cases were not poor ($n=1$, entries 1 and 2). The cyclization in which six membered ring would form ($n=2$, entries 3 and 4), however, proceeded ineffectively. In particular, the coupling between the ketone group and the olefin ($R'=CH_3$) was not successful (entry 4). It has been known

Table 1. Samarium(II) iodine promoted cyclization to construct a quaternary carbon center

Entry[a,b]	Educt	Product (Yield)	
			
1	$n=1$, $R=CO_2Et$, $R'=H$	**1** (75%)	–
2	$n=1$, $R=CO_2Et$, $R'=CH_3$	**2** (68%)	–
3	$n=2$, $R=CO_2Et$, $R'=H$	–	**3** (43%)
4	$n=2$, $R=CO_2Et$, $R'=CH_3$	(0%)	–
5	$n=2$, $R=CN$, $R'=H$	**4** (45%)	–
6	$n=2$, $R=CN$, $R'=CH_3$	(0%)	–
			
7	$m=1$, $R''=H$	**5** (61%)	
8	$m=1$, $R''=CH_3$	**6** (61%)	
9	$m=2$, $R''=H$	**7** (71%)	
10	$m=2$, $R''=CH_3$	**8** (74%)	

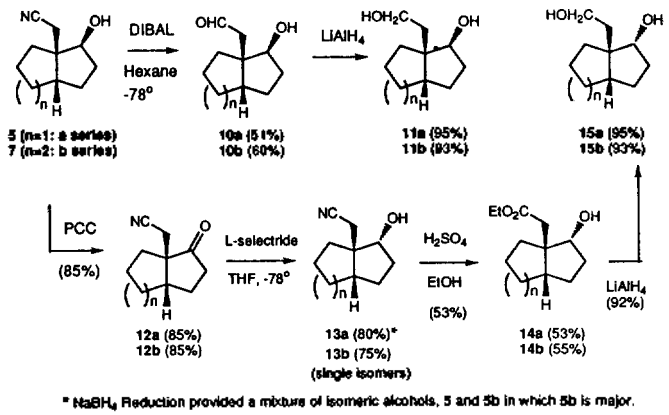
[a]E/Z ratio of the starting materials (>9 : 1) (entries 1-6). [b]E/Z ratio of the starting materials (7 : 3 to 15 : 1) (entries 7-10).

that the rate of the free radical addition to olefins is much more increased when olefin is activated with the nitrile group than with the alkoxycarbonyl group.[3] This is what exactly observed when CO_2R was replaced with CN. From the entry 5 it can be learned that the 6-heptenyl radical type cyclization can be realized albeit in low yield. The coupling between the ketone and the olefin is, however, not yet feasible (entry 6).

The difference in the cyclization rates upon replacement of the olefin activating group from CO_2R to CN is clearly shown in the case of producing fused ring products (entries 7-10). The cyclizations were, in fact, not possible for the olefins substituted with alkoxycarbonyl groups. It could be, however, efficiently achieved even under sterically crowed environment with olefins activated with nitrile groups.

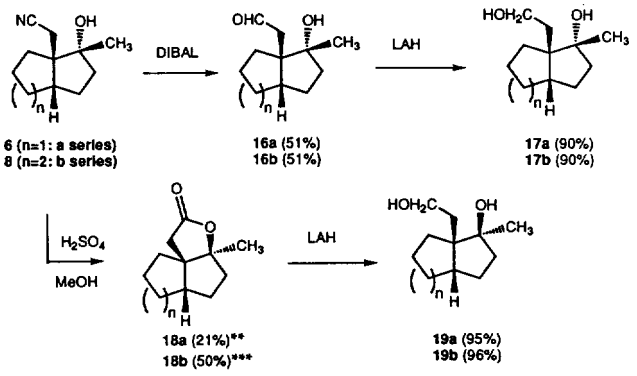
A critical point that should be addressed is the stereoselectivity of the products formed. In each case single isomer was observed exclusively. The excellent stereoselectivity has been frequently reported in the samarium(II) iodide promoted couplings, especially in the intramolecular carbonyl-olefin couplings in which the predominant formation of *trans*-products was observed.[4] The *trans* stereochemistry of the products **1** and **2** is also supported since no lactone was formed. The cyclized product **3** has, however, a *cis* stereochemistry since it was proved to be a lactone. The *trans* stereochemistry of **4** was also assumed, although the stereochemistry was nor rigorously determined in this case.

This stereochemical aspect became more fascinating, considering the products obtained in the cases shown in entries



* $NaBH_4$ Reduction provided a mixture of isomeric alcohols, 5 and 5b in which 5b is major.

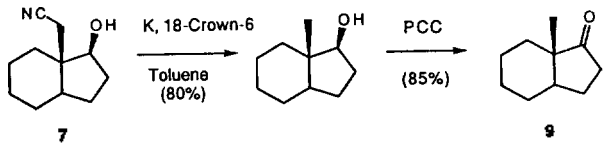
Scheme 1. Determination of the stereochemisty of **5** and **7**.



**Lactone 18a was obtained in 20~30% yield along with elimination products(~30%).
***Lactone 18b was obtained in 50% yield along with elimination products(~10%).

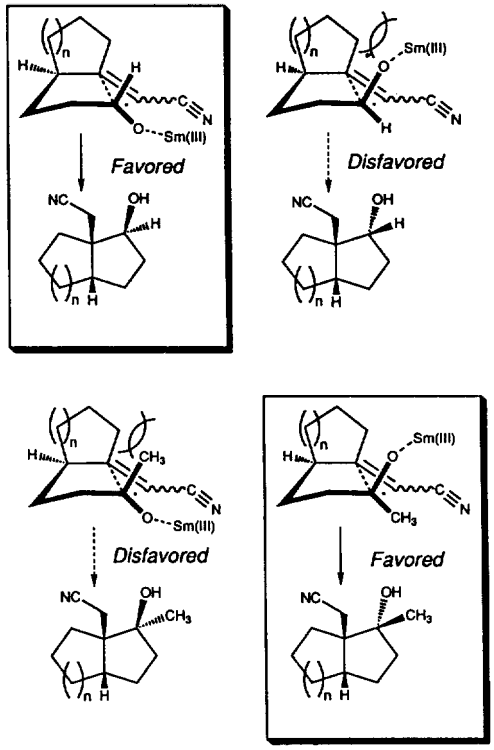
Scheme 2. Determination of the stereochemisty of **6** and **8**.

7-10. The ring juction stereochemistry was clarified by the sequence shown in the following equation.



The nitrile group of alcohol **7** was removed according to the procedure reported.[5] After PCC oxidation ketone **9** was obtained. Identificaiton of the ring junction stereochemistry was achieved by the comparison of the ^1H NMR chemical shift of the methyl group of **9**, which was identical with the value reported for the *cis* hydrindane structure (δ 1.03).[6] The *trans* methyl would have a chemical shift of 0.88 (δ). The ring junction stereochemistry of **8** was assumed to be *cis*. In the case of the cyclized products **5** and **6**, *cis* stereochemistry for ring junctions can be easily accepted due to the 5/5 ring system.

The stereochemical relationship of the newly formed carbon centers (in the products **5**, **6**, **7**, and **8**) was determined unambiguously according to the sequences shown in Scheme 1 and 2. Determination of the stereochemistry of **5** is achieved as the following sequence (Scheme 1 ; 5/5 ring fused system, $n=1$: a series). Reduction with DIBAL followed by LAH reduction provided **11a**. On the other hand, oxidation of **5** provided ketone **12a**. Reduction of the ketone **12a** with



Scheme 3. Transition state analysis.

L-Selectride generated a single isomer **13a**. After hydrolysis of nitrile **13a** the resulting hydroxy ester **14a** was reduced. The fact that ester **14a** was not isolated as a loctone proved the stereochemical relationship, that is, *trans* between hydroxyl and CH_2CN. The diol **15a** obtained turned out to be different from the diol **11a**. This sequence fix the stereochemisty of **5** as shown in Scheme 1-*cis* relationship between hydroxyl and CH_2CN. This is of interest, since generally the predominant formation of the *trans* products has been claimed from the similar cases previously reported. The stereochemistry of **7**, which also turned out to be a *cis* relationship, was determined by the same sequences shown in Scheme 1 (6/5 fused system, $n=2$: b series).

For the cases with an additional methyl group (that is, **6** and **8**), similar sequences were sucessfully applied to determine the stereochemistry (Scheme 2). For the determination of the stereochemistry of alcohol **6** (5/5 fused system, $n=1$: a series), two successive reductions (DIBAL and LAH) of **6** was performed to provide **17a**. On the other hand, acid hydrolysis of **6** afforded a lactone **18a**. The alcohol **19a**, which was obtained by the LAH reduction of **18a**, was a different alcohol from **17a** and this observation proved that the stereochemical relationship of **6** be *trans* between hydroxyl and CH_2CN as shown in Scheme 2. During the acid hydrolysis elimination followed by the addition caused epimerization of the stereogenic center. In fact, approximately 30% of the elimination product was also identified in this hydrolysis step. The stereochemistry of **8**, which was also a *trans* relationship (OH *vs* CH_2CN), was determined by the same sequence (6/5 fused system, $n=2$: b series) as decribed above.

These outstanding stereoselectivties for the formation of **5**, **6**, **7**, and **8** could be rationalized by a transition state

analysis shown in Scheme 3. Without methyl (in the case of **5** and **6**), between two possible transition states one with H located on the ring, which would lead to the product stereochemistry observed, is favored over the case with O-Sm (III) moiety on the ring. In the cases of the substrates with methyl (**7** and **8**), the transition state with O-Sm(III) part placed on the ring is favored over the transition state with methyl on the ring due to the steric interaction caused by the methyl group.

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