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LETTERS

Intramolecular Ketyl-Olefin Cyclization Mediated by Magnesium Metal

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Abstract: *Ketones tethered to carbon-carbon multiple bonds at δ-position are treated with magnesium metal to provide cyclized products which stem from addition of ketyl radical to olefinic or acetylenic bonds.*

Keywords: intramolecular cyclization; ketyl radical; magnesium

Radical cyclizations *via* intramolecular addition of carbon radical to multiple bond have been extensively demonstrated as useful tools in organic synthesis.[1] Among these, intramolecular ketyl-olefin cyclizations are relatively new and have many advantages especially of high diastereoselectivity at newly formed carbon-carbon bond of the cyclic product compared to simple radical cyclizations.[2] In order to achieve intramolecular ketyl-olefin cyclizations, methods to create ketyl radical via electrochemical,[3] photohemical,[4] and low valent metals[5] have been employed. Recently Sm(II)[6] and organotin[7] in aprotic solvent have been extensively exploited for ketyl-olefin cyclization relative to other low valent metals. However, both reagents are known to have drawbacks in its economy and covenience.[2d] In an effort to overcome these drawbacks and expand its utility, magnesium in methanol has been demonstrated in our laboratory as a convenient single electron transfer reagent for a number of reductive reactions.[8] In contrast to abundant examples of Sm(II) or organotin mediated ketyl-olefin cyclization reactions, precedent of magnesium induced intramolecular cyclization *via* unequivocal addition of ketyl radical to multiple bond were not found except one example.[9] In order to clarify this uncertainty, ketone tethered to olefin inert to magnesium would be a substrate of choice. Motivated both by drawbacks of conventional electron transfer reagent and by scarcity of precedents, ketyl-olefin cyclization by magnesium was studied with ketones tethered to olefin inert to magnesium.

Various ketones (**1-10**) containing carbon-carbon multiple bonds at the δ-position were subjected to 10 equivalent magnesium metal in dry THF and 20 equiv of absolute EtOH in the presence of catalytic amount of $HgCl_2$ at room temperature to afford the corresponding cyclized products in various yields (10-96%) as shown in Table I. A mixture of geometric isomers of cyclopentanone **1** (*Z/E*; 1/1.2) subjected to our previous reductive cyclization condition (10 equiv magnesium metal in dry methanol at –23 °C for 5 h) proceeded smoothly to provide bicyclic alcohol **1t** as a single *trans* stereoisomer[10] in 96% yield, regardless of the configuration of the double bond as noted previously.[8b] This result contrasts with that of the SmI_2-mediated cyclization, in which a

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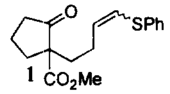
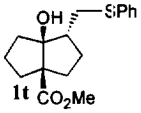
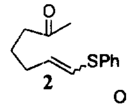
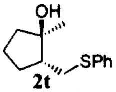
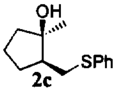
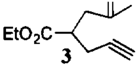
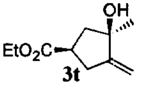
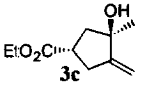
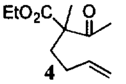
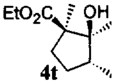
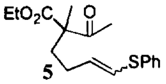
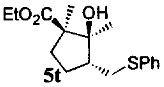
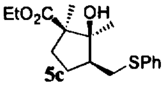
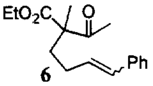
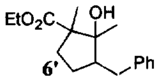
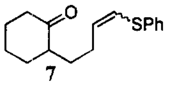
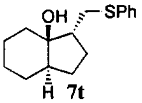
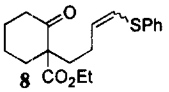
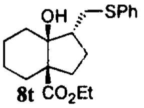
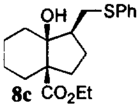
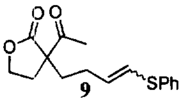
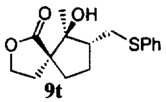
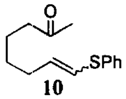
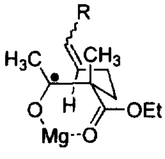
dramatic change in diastereoselectivity was observed depending on the configuration of double bond.[11] This seems to be due to the large electronic repulsion between the oxygen atom and the sulfur atom in the transition state. In stark contrast to cyclopentanone **1**, linear aliphatic ketone **2** and **10** did not proceed under the same condition, and starting material was recovered completely. Ketyl radical from cyclopentanone, in which carbonyl group is slightly activated due to ring strain and chelation effect of CO_2Et comparing to aliphatic ketones, is generated more easily in the mild reaction condition than that from aliphatic ketones.

Table 1. Intramolecular Ketyl Radical Cyclization of Ketones Tethered to Carbon-Carbon Multiple Bonds with Mg/THF-EtOH/cat. $HgCl_2$.

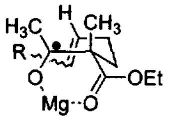
Substrates	Cyclized Products[a]		Yields (%)[b,c]
 **1**	 **1t**		96[d]
 **2**	 **2t**	 **2c**	49 (8.8 : 1)[e]
 **3**	 **3t**	 **3c**	31 (1.9 : 1)[e]
 **4**	 **4t**		70
 **5**	 **5t**	 **5c**	93 (17 : 1)
 **6**	 **6'**		63[f]
 **7**	 **7t**		55
 **8**	 **8t**	 **8c**	77 (10 : 1)
 **9**	 **9t**		10
 **10**			–[g]

[a] t: trans, c: cis. [b] Isolated yields. [c] Ratio in the parenthesis is t/c. [d] 10 eq Mg/MeOH, -23 °C. [e] A rest of the product was reduced alcohol. [f] Diastereomeric mixture. [g] Only reduced alcohol was obtained.

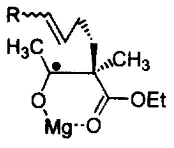
In order to effect the reaction we attempted desulfonylation condition which was developed previously.[8c] Substrates **2** and **10** were completely converted under modified conditions (10 equiv Mg, 20 equiv EtOH in THF, cat HgCl$_2$, at room temperature) where EtOH was used as a proton source in THF solvent. Without HgCl$_2$ and/or EtOH the reaction was not initiated at all. Linear aliphatic ketone **2** afforded monocyclic alcohol as a mixture of *trans* **2t** and *cis* **2c** in 49% yield (**2t**/**2c**; 8.8/1) along with simply reduced alcohol in 50% yield. Interestingly, ε-alkenyl ketone **10** gave only the simply reduced alcohol quantitatively without any trace of cyclized product. It seems that reduction of carbonyl group is more favorable than 6-*exo-trig* cyclization reaction. δ-Alkynyl ketone **3** afforded a product mixture consisting of the expected allylic alcohol **3t** and **3c** (31%, **3t**/**3c**; 1.9/1 was determined by ^{1}H NMR),[10] γ-butyrolactone (31%) resulting from lactonization of the corresponding alcohol formed by simple reduction of carbonyl group, and unreacted starting material (18%). δ-Alkenyl ketone **4** provided **4t** as a single diastereoisomer in 70% yields. The same kind of high diastereoselective cyclization of ketone **4** was also achieved with SmI$_2$ in 75% yield.[12] The reaction seems to go through the same kind of chelated transition structure as in the SmI$_2$-mediated reaction. A mixture of geometric isomers (*Z*/*E*; 1/1) of 2-phenylthioalkenyl ketone **5** gave the cyclized product in 93% yield with high diastereoselectivity (**5t**/**5c**; 17/1).[13] Strikingly, the cyclic adduct was not obtained at all with the SmI$_2$.[12] When the substituent was changed from phenylthio to phenyl as in **6** both diastereoselectivity and chemical yield decreased significantly comparing with **5**. As mentioned for the case of **1**, absence of sulfur atom might have weaken stereoelectronic repulsion in the transition state so that bias to *cis* confirmation increases. Three transition states can be postulated to explain *cis* relationship between OH and CO$_2$Et of the product from β-keto esters shown as below.[12]



A



B



C

Transition state **A** and **B** is more favorable than that of **C** because **C** cannot attain the correct orbital alignment without significant distortion and ensuing strain. The stability of **A** is reinforced by steric interactions directing the developing methylene center away from the face of the molecule with the large chelated ring and by the electronic repulsion between the oxygen atom of the nucleophilic ketyl and the sulfur atom. Cyclohexanone **7** gave a single diastereomer **7t** in 55% yield along with a simply reduced alcohol in 43% yield. The relative stereochemistry between the hydroxy group and the (phenylthio)methylene group and that between the hydroxy group and ring juncture hydrogen were determined as *trans*.[10] Cyclohexanonecarboxylate **8** gave the expected cyclic diastereomers **8t** and **8c** (**8t**/**8c**; 10/1) in 77% yield. It is interesting to note that similar substrate without phenylthio group does not cyclize with SmI$_2$.[12] γ-Latone **9** afforded a spiro adduct **9t** as a single diastereomer albeit in disappointingly low yield. The rest of by products were intractable. Although relative stereochemistry of adduct **9t** was difficult to assign by ^{1}HNMR, it may be assumed based upon the above results and our previous studies,[8a] that a *cis* relationship exists between the hydroxy group and the lactone ester moiety.

In summary, magnesium metal can be used for ketyl-olefin cyclization generating unambiguous ketyl radical which undergoes intramolecular addition to multiple bond. It is efficient, economic, and complementary to SmI_2-mediated reaction.

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9. Magnesium in methanol promotes reductive cyclization of ketones tethered to olefin substituted with electron withdrawing ester or nitrile group, however, it is uncertain that whether the reaction proceed through addition of ketyl to olefin or allyl anion to carbonyl group (see ref 8a).
10. The structure and relative stereochemistry of **1t** as well as other products were elucidated by 2-D COSY and 1-D NOE difference spectra.
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13. The starting ketone **5** was synthesized in 99% yield (*Z*/*E*; 1/1) by the reaction of ethyl 2-methylacetoacetate with 1.1 equiv 90% acrolein in diethyl ether at room temperature followed by Wittig reaction without further purification of the intermediate aldehyde.