Regioselective Ring-opening of Cyclopropyl Ketones with Organometallic Reagents

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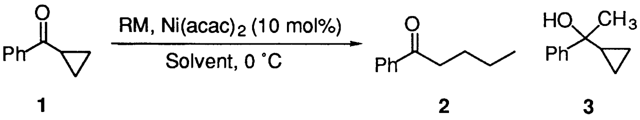
Regioselective ring-opening reaction of cyclopropyl ketones was conducted successfully, in which the reaction of cyclopropyl phenyl ketone with trimethylaluminum catalyzed by nickel acetylacetonate gave the ring-opening product in up to 76% yield.

Cyclopropanes are attractive synthetic intermediates due to their ready availability and reactivity.[1] It is well-known that cyclopropyl ketones are cleaved by a reductive process,[2] a radical process,[3] or nucleophilic reactions with heteroatoms.[4] For the acid catalyzed cleavage of cyclopropyl ketones, however, forced reaction conditions are usually employed.[5] To the best of our knowledge, although cyclopropanes possessing two electron-withdrawing groups, *e. g.*, 1-cyano-1-methoxycarbonylcyclopropane, were opened by carbon nucleophiles,[6, 7] ring-opening of simple cyclopropyl ketones was very rare.[8] We would like to report here the ring-opening reaction of simple cyclopropyl ketones with several alkyl metals catalyzed by nickel acetylacetonate.[9]

A typical procedure for the reaction of cyclopropyl phenyl ketone with trimethylaluminum catalyzed by nickel acetylacetonate is as follows: To a solution of nickel acetylacetonate (5.1 mg, 0.02 mmol) and cyclopropyl phenyl ketone (29.2 mg, 0.2 mmol) in freshly distilled tetrahydrofuran (2.0 mL) was added 2.0 M trimethylaluminum in hexane solution (1 M = 1 mol dm^{-3}, 0.5 mL, 1.0 mmol) at 0 °C under an argon atmosphere. After stirring for an additional 3 h, the reaction was quenched with 2.0 M hydrochloric acid. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting liquid was purified on silica-gel TLC (hexane : ethyl acetate = 10 : 1) to give the ring-opening product as a colorless liquid.

The reaction of cyclopropyl phenyl ketone **1** with alkyl metals was examined as a model reaction, and the results are shown in Table 1. The choice of the solvent was important for the present ring-opening reaction. Although the use of non-polar hydrocarbon solvent such as hexane and toluene afforded the mixture of the methylated products **2** and **3** in moderate yield, that of tetrahydrofuran was the most effective to afford the ring-opening product **2** in good yield with excellent regioselectivity among the other solvents (entries 1 - 6 and 8). An increased amount of trimethylaluminum improved the product yield, and the best result was obtained using 5 equivalents of trimethylaluminum (entries 7 and 8). Among the metal catalysts examined, only nickel (II) compounds induced this ring-opening reaction, but no catalytic activity was observed for nickel bromide or nickel iodide as even in THF at reflux temperature.



1 **2** **3**

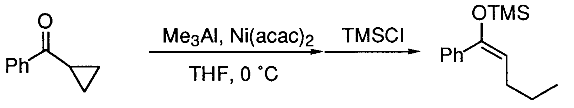
Table 1. The nickel catalyzed ring-opening reaction of cyclopropyl phenyl ketone **1**[a]

Entry	RM	Solvent	Y./% of **2**[b]	Y./% of **3**[b]
1	Me_3Al	Hexane	11	47
2	Me_3Al	Toluene	4	44
3	Me_3Al	CH_2Cl_2	14	19
4	Me_3Al	CH_3CN	5	0
5	Me_3Al	Et_2O	57	0
6	Me_3Al	1,4-Dioxane	57	0
7	Me_3Al[c]	THF	44	0
8	Me_3Al	THF	76	0
9	MeLi	THF	0	99
10	MeMgI	THF	37	0
11	Et_2Zn	THF	no reaction	
12	MeLi•Et_2Zn (1 : 1)	THF	11[d]	65[e]
13	MeMgI• Et_2Zn (1 : 1)	THF	33[f]	0
14	MeMgI•CuBr (2 : 1)	THF	25	0

[a] 5.0 eq of RM was used. [b] Isolated yield. [c] 1.0 eq of Me_3Al was used. [d] The product was 1-phenyl-1-hexanone. [e] The product was 1-cyclopropyl-1-phenylethanol. [f] The product was 1-phenyl-1-pentanone.

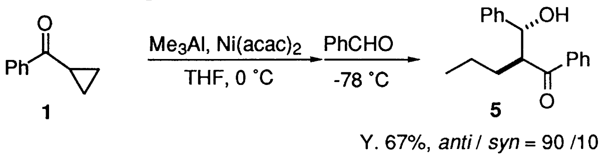
The use of methyllithium as an alkylating reagent produced exclusively the corresponding alcohol **3** by the 1,2-addition to **1** (entry 9), whereas methylmagnesium iodide afforded the ring-opening product **2** in moderate yield (entry 10).[10] Interestingly, although the use of ate complex derived from methyllithium and diethylzinc produced the corresponding ethylated adduct, the methylated adduct **2** was obtained when the methylmagnesium iodide-diethylzinc complex was used as an alkylating reagent (entries 12 and 13). Dimethylcuprate prepared from methylmagnesium iodide and cuprous bromide-dimethylsulfide complex also reacted with cyclopropyl ketone **1** to give, the ring-opening product, 1-phenyl-1-pentanone (entry 14).

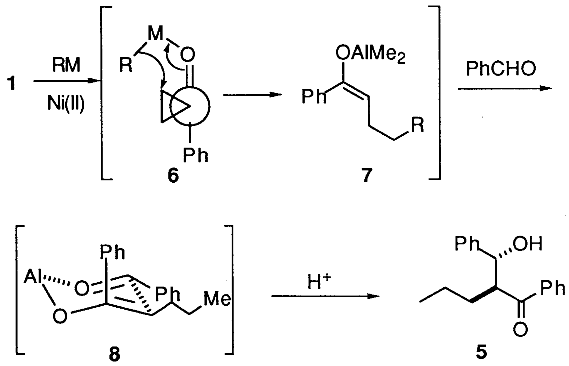
The present ring-opening reaction most probably proceeded via the formation of a metal enolate as an intermediate. In order to trap the enolate, chlorotrimethylsilane was added to the reaction mixture, and, in fact, predomiant formation of (*E*)-1-phenyl-1-trimethylsilyloxy-1-pentene **4** (>95 : 5) was observed in the ^{1}H NMR study of the crude products.



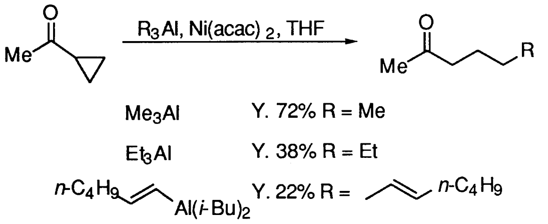
1 **4** (>95 / 5)

Addition of the enolate to benzaldehyde at -78 °C afforded the corresponding aldol product **5**, in which the *anti*-adduct **5** was predominantly formed in a ratio of *anti* : *syn* = 90 : 10. These results may explain the mechanism of the present ring-opening reaction as follows. First, an alkylmetal (alkylaluminum, Grignard reagent, alkyl lithium, and cuprate) and nickel (II) generate a low valent alkylnickel species, as indicated by change of the color of the reaction mixture from pale blue to deep red on an addition of the alkylmetal.[9b] The alkylmetal species thus obtained underwent ring-opening reaction with cyclopropyl ketone **1** through a six-membered transition state as shown in **6** to give *E*-aluminum enolate **7**. This enolate, in turn, reacted with benzaldehyde *via* a six-membered chair-like transition state **8** to give predominantly the *anti*-aldol product. The addition of 2,2,6,6-tetramethylpiperidin-*N*-oxide as a radical scavenger did not inhibit the ring-opening of the cyclopropylketone under the typical conditions, and, therefore, an anionic pathway may account for the present reaction.[11]

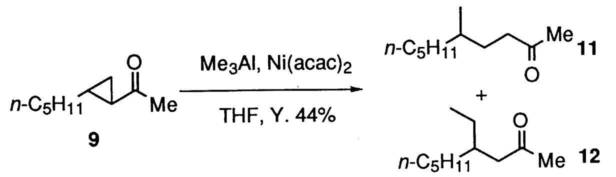


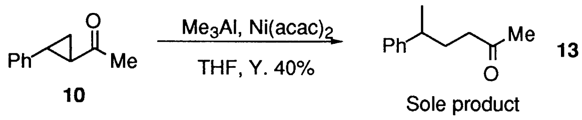


Cyclopropyl methyl ketone also reacted under these conditions to give the ring-opening alkylation product. The use of trimethylaluminum afforded 2-hexanone in good yield. Although the use of triethylaluminum or dibutyl(1-hexenyl)-aluminum instead of trimethylaluminum also gave the corresponding ring-opening products, the yields were rather poor due presumably to the lack of the nucleophilicity of the aluminum reagents.



To study the regioselectivity of the ring-opening reaction, (*E*)-2-pentyl-1-acetylcyclopropane **9** and (*E*)-2-phenyl-1-acetylcyclo-propane **10** were also examined as a substrate.[12] Although the Ni(II)-catalyzed reaction of 2-pentyl-1-acetylcyclopropane **9** with trimethylaluminum gave the ring-opening product in a ratio of **11** : **12** = 21 : 79, the use of phenyl derivative **10** afforded exclusively the ring-opening product at the benzylic position, 5-phenyl-2-hexanone **13**, with complete regioselectivity under the same reaction conditions.





In summary, the nickel catalyzed regioselective ring-opening reaction of cyclopropyl ketones using alkylaluminum reagent was successfully performed to afford the corresponding ring-opening alkylated ketones. The use of trialkyl or dialkyl-alkenylaluminum as an alkylating reagent was much more effective than that of the other alkylating reagents examined, and *anti*-aldol adduct was predominantly obtained in the addition of benzaldehyde with the *E*-enolate derived from the ring-opening reaction.

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