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LETTERS

1,4 Additions with lithium bis(methylenecyclopropyl)cuprate

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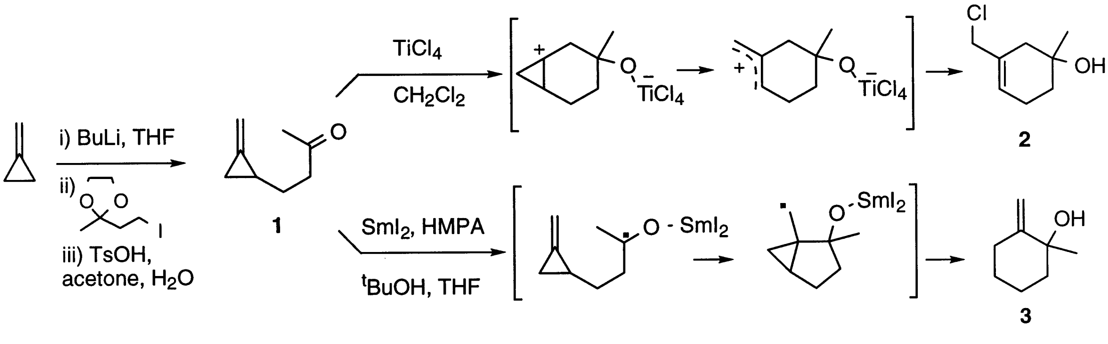
Abstract—Addition of lithium bis(methylenecyclopropyl) cuprate to α,β-unsaturated ketones provides an efficient route to methylenecyclopropyl ketones which on treatment with $TiCl_4$ give a range of cyclised products. © 2000 Elsevier Science Ltd. All rights reserved.

Methylenecyclopropane derivatives have been used extensively in synthesis and in a range of novel transformations including cycloaddition reactions,[1] radical based annulation reactions[2] and radical cyclisation reactions.[3] Most recently it has been shown that, mediated by Lewis acids, methylenecyclopropanes can be coupled to ketones, both inter-[4] and intramolecularly.[5] Thus, we have shown that treatment of methylenecyclopropyl ketone **1** with $TiCl_4$ gives the cyclohexenol **2** as the major product (Scheme 1).[5a] Alternatively, treatment of ketones such as **1** with samarium iodide leads to methylene cyclohexanol **3** via a radical ring expansion pathway.[3a]

In this earlier work,[5b] ketone **1** was prepared by alkylation of lithiated methylenecyclopropane with an iodo ketal (Scheme 1), and indeed the alkylation of lithiated methylenecyclopropane has proven to be one of the most useful methods for the preparation of substituted methylenecyclopropanes.[6] However, and perhaps rather surprisingly, there have been very few reports of the preparation of organocuprates derived from lithiated methylenecyclopropane,[7] nor of the use of such a reagent in 1,4-addition reactions.[8] We now report that lithium bis(methylenecyclopropyl)cuprate undergoes clean 1,4-addition to a range of α,β-unsaturated ketones to give methylenecyclopropyl ketones, which, in turn, can be cyclised with $TiCl_4$ to give a range of cyclised products.

The desired cuprate was prepared by addition of methylenecyclopropane to a solution of BuLi in THF at −30°C, warming to room temperature and recooling to −25°C, followed by cannular addition of the resulting lithiated methylenecyclopropane to a suspension of CuI in THF, also at −25°C. Michael addition was



Scheme 1.

Keywords: methylenecyclopropane; cuprate; Lewis acid.

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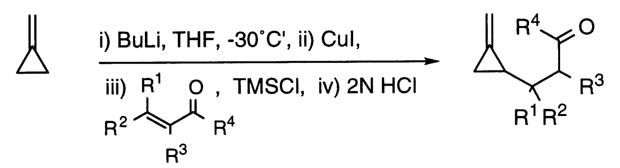
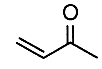
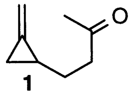
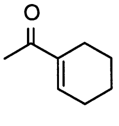
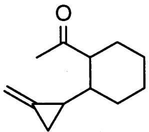
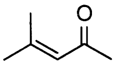
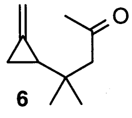
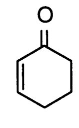
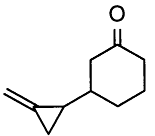
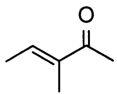
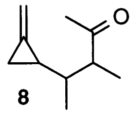
Table 1.



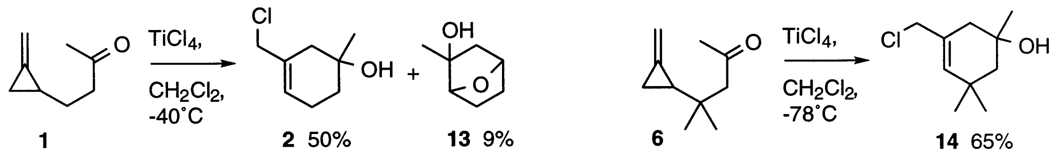
substrate	product	yield	ratio of diastereoisomers	substrate	product	yield	ratio of diastereoisomers
 **4**	 **1**	79%		 **9**	 **10**	76%	5:5:3:1
 **5**	 **6**	71%		 **11**	 **12**	95%	1:1
 **7**	 **8**	59%	3:3:2:1				

carried out using slow addition of a mixture of α,β-unsaturated ketone and trimethylsilyl chloride[9] to the cuprate at −78°C. After acid hydrolysis and column chromatography, the ketone products were isolated in good yields (Table 1).

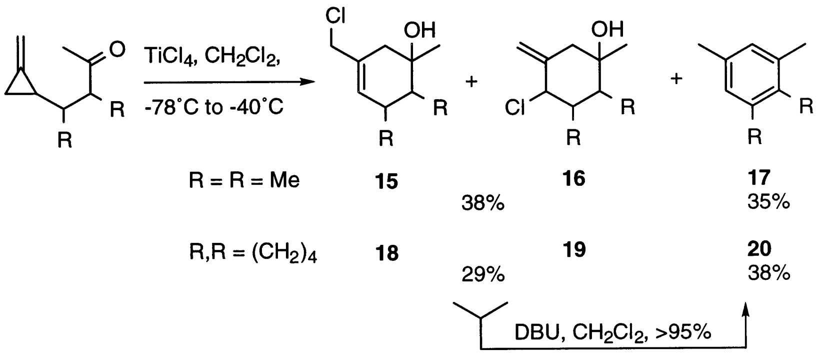
Addition to methyl vinyl ketone **4** gave the previously described ketone **1** in 79% yield. Likewise, addition to the hindered enone **5** proceeded in good yield. Addition to enones **7** and **9** gave mixtures of four diastereoisomeric ketones in each case with little stereoselectivity, and addition to cyclohexenone **11** gave a 1:1 mixture of the two possible diastereoisomers. Attempted addition to chalcone or to the α,β-unsaturated esters methyl crotonate and methyl acrylate did not give any of the desired products under the conditions described above.

Lewis acid mediated cyclisation of the ketones was carried out using $TiCl_4$ in CH_2Cl_2. As previously described,[5b] cyclisation of ketone **1** under optimal conditions, at −40°C, gave cyclohexenol **2** in 50% yield, accompanied by the bicyclic ether **13** in 9% yield (Scheme 2). Cyclisation of ketone **6**, however, proceeded rapidly at −78°C to give cyclohexenol **14** in 65% yield, reflecting the influence of the gem-dimethyl on the cyclisation (Thorpe–Ingold effect).

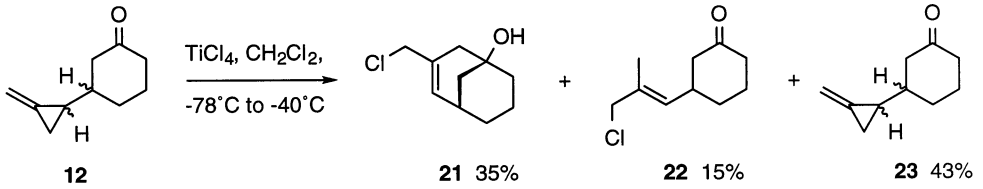
Cyclisation of the diastereoisomeric mixtures of ketones **8** and **10** both gave good overall yields of cyclised products (73 and 67%, respectively), but as complex mixtures of diastereoisomeric cyclohexenes, methylenecyclohexanes and highly substituted aromatics, a third of these clearly resulting from elimination of H_2O and



Scheme 2.



Scheme 3.



Scheme 4.

HCl from the first two (Scheme 3). Indeed treatment of the mixtures of **15** and **16**, or **18** and **19**, with DBU, cleanly transformed them into the corresponding aromatic products **17** and **20**, respectively.

Cyclisation of ketone **12**, on the other hand, yielded the anticipated bicyclic alcohol **21** in 35% yield, the allyl chloride **22** and starting ketone, but as a single diastereoisomer (Scheme 4). Clearly only one of the diastereoisomeric ketones is able to cyclise under the reaction conditions used, but does so very efficiently.[10]

In conclusion, lithium bis(methylenecyclopropyl) cuprate adds cleanly to enones and provides a simple route to highly substituted methylenecyclopropyl ketones, which have not previously been readily accessible. The cyclisation of such ketones using Lewis acids has been examined and this extends the scope of this methodology for the preparation of functionalised cyclohexanols, and potentially of highly substituted aromatics.

Acknowledgements

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