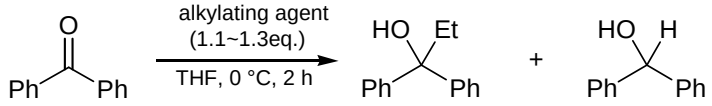
Highly Efficient Alkylating Agent

Tertiary alcohols are synthesized industrially on large scale by addition of alkylating agents to ketones, and are mainly used as starting materials in the preparation of pharmaceuticals and agricultural chemicals. Although Grignard reagents are frequently used as alkylating agents in these reactions, an excess amount of Grignard reagents is required. Furthermore, aldol adducts, reduction products, and pinacol derivatives are generated as by-products and adequate control of reaction is difficult even at low temperatures. Taken together, these problems render the synthesis of the desired tertiary alcohols selectively and in high yields, difficult.

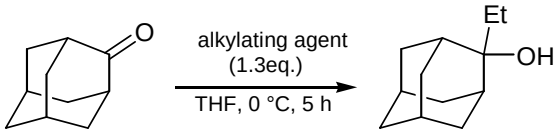
Previously, Ishihara *et al.* have found that the desired tertiary alcohols may be obtained in high yields by using magnesium-ate complexes $RR'_2MgLi \cdot LiCl$ prepared from Grignard reagents (1 eq.) and organolithium reagents (2 eq.). The corresponding reactions proceed smoothly and without the generation of by-products which normally accompany the corresponding reactions utilizing the Grignard reagent alone. It is considered that this is because the ate complexes concerned are more nucleophilic and less basic than the parent Grignard reagents. However, this method still requires the use of 2 molar equivalents of expensive organolithium reagents although a stoichiometric amount of the Grignard reagents can be used. Clearly, the development of more efficient alkylating agent is desirable .

More recently, Ishihara *et al.* re-examined this reaction using various metal-ate complexes. As a result, they discovered that tertiary alcohols may be synthesized in high yields with minimum side reactions by the addition of a substoichiometric amount of zinc chloride to the Grignard reagents. They rationalized this observation by invoking the formation of highly active zinc-ate complexes $R_3ZnMgCl$ *in situ* in an efficient catalytic cycle. They have applied this method the alkylation of various ketones.



alkylating agent	tertiary alcohol [Y. (%)]	reduction product [Y. (%)]
EtMgCl	25	71
EtMgCl + $ZnCl_2$ (10mol%)	84	15

In the alkylation of 2-adamantanone, which is typically considered to be difficult since reduction occurs in preference to the desired alkylation when only Grignard reagents are used, the yield of desired product was improved greatly by using this protocol. Furthermore, addition of lithium chloride increased the yields up to 81%. 2-Alkyl-2-adamantanol is a useful photoresist material, so it is anticipated that this method will be of great utility in various fields.



alkylating agent	Y. (%)
EtMgCl	29
EtMgCl + $ZnCl_2$ (10mol%)	58
EtMgCl + $ZnCl_2$ (10mol%) + LiCl	81

Keywords *: Grignard reagents, alkylation of ketones and aldimines*

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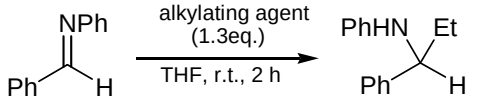
Furthermore, it was also reported that this reaction is applicable to the related, but much less reactive aldimines and that the addition reaction proceeds efficiently.



alkylating agent	Y. (%)
EtMgCl	41
EtMgCl + $ZnCl_2$ (10mol%)	81

In this way, the reactions mentioned above constitute simple and practical methods for the generation of tertiary alcohols, which can be performed under mild conditions, and which are also useful industrially. The original paper by Ishihara *et al.* qualified as the 1st "Most-Accessed Articles" in the category of communications for the *Journal of the American Chemical Society* (Web Edition) from July to September, 2006.

TCI is happy to make available the following zinc chloride-activated Grignard reagent which is convenient to use for the above alkylation.

E0778 Ethylmagnesium Chloride (*ca.* 0.8mol/L in Tetrahydrofuran) activated with Zinc Chloride (*ca.* 10mol%) 250g

References

1) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.*, **2006**, *128*, 9998.
2) M. Hatano, S. Suzuki, K. Ishihara, *Kagaku*, **2007**, *62 (3)*, 16.