Preparation of New Magnesium Carbenoids Aiming Inhibitors of HIV-1 Protease Synthesis

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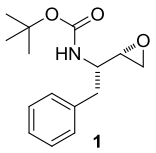
INTRODUCTION

Inhibitors of HIV-1 protease were developed to act specifically on this enzyme class, with high affinity and high complementarity to the catalytic site of the protein, intrinsically competing with the natural substrates.[1] The (2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-phenylbutane (**1**) and its diastereomer of configuration (2*R*,3*S*) (**2**) are key intermediates in the preparation of some important antiretroviral compounds such as saquinavir, amprenavir, atazanavir and lopinavir.[2]



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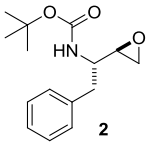

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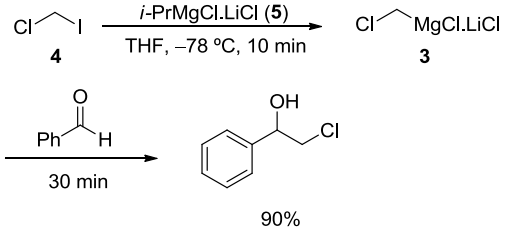
Thus, in this work we have investigated a new method for the stereoselective preparation of these chiral intermediates using organomagnesium reagents complexed with lithium chloride.

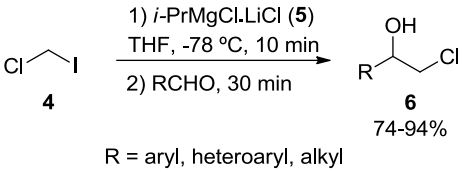
RESULTS AND DISCUSSION

Initially, we studied the preparation of the mixed lithium-magnesium carbenoid $ClCH_2MgCl.LiCl$ (**3**) through the reaction between chloroiodomethane (**4**) and *i*-PrMgCl.LiCl (**5**) (turbo Grignard).[3] The best reaction conditions were determined by the reaction of magnesium carbenoid and benzaldehyde leading to the corresponding chlorohydrin in 90% yield (Scheme 1).



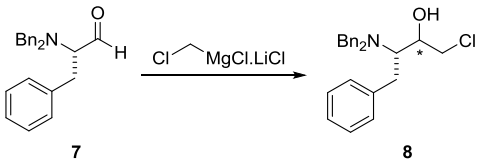
Scheme 1

The reagent **3** works well with different types of aromatic, aliphatic and heterocyclic aldehydes, leading to the formation of the corresponding chlorohydrins in good yields (Scheme 2).



Scheme 2

In recent studies the reagent of type **3** was tested with the aldehyde derivative of *L*-phenylalanine (**7**) leading to the corresponding chlorohydrins (**8**), in a good diastereomeric excess (determined by LC-MS analysis).



Scheme 3

The absolute configuration of the synthesized compounds is now under investigation by Nuclear Magnetic Ressonance (NMR).

CONCLUSION

Chloromethylmagnesium compounds of type **3** are very selective reagents and show a great potential for preparation of chlorohydrins. Furthermore, it can be an alternative to the synthesis of important intermediates of inhibitors of HIV-1 protease.

ACKNOWLEDGEMENTS

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