ENHANCING THE ACCESS TO α-TERTIARY CARBINAMINES VIA THE DOUBLE ADDITION OF ORGANOMETALLICS OF ABUNDANT METAL ONTO C-N BONDS UNDER MILD CONDITIONS

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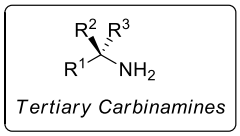
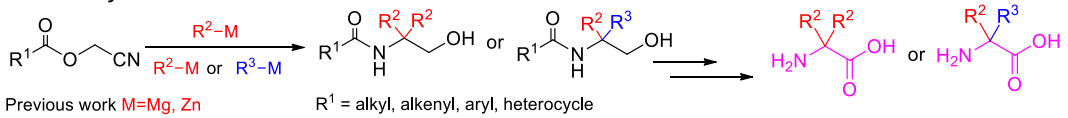


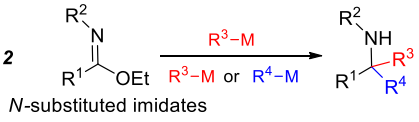
The tertiary carbinamine is a crucial structural moiety predominantly found in various complex bioactive molecules. It constitutes a fundamental component of non-natural amino acids. Over several decades, numerous classical methods to synthesize tertiary carbinamines have been reported. However, some of these methods prove to be unsuitable for the introduction of aryl, alkenyl, or alkynyl substituents. Further exploration of novel reagents and reaction conditions promises to enhance the synthetic toolbox to access this vital structural moiety, fostering innovation in drug discovery and chemical biology. The approach of using organometallics for the double addition onto nitriles is one of the promising methods which encounter challenges with the second addition due to the weak reactivity of the metallated imine intermediate.[1]

Scheme ***1***



To tackle these challenges, the double addition of Grignard reagents onto acylcyanohydrins has been developed as a straightforward approach to tertiary carbinamines (Schema **1**).[2] This method capitalizes on the intramolecular migration of the acyl group to form an acylated imine intermediate which is electrophilic enough to undergo the second addition. This approach offers advantages such as mild conditions, a simple protocol, readily available starting materials and organometallic reagents, to yield hydroxyamides that serve as precursors of quaternary amino acids. Furthermore, chiral models have been successfully synthesized by employing two Grignard reagents with different reactivities.[3] In order to develop stereoselective control, efforts are underway to stabilize intermediates using less commonly employed organometallics, such as organoaluminum reagents known for their nucleophilic and Lewis acid properties. In the first part of this communication, the study of the addition of alkynylalanes onto acylcyanohydrins will be presented. On the other hand, imidates are well-known as substrates with the potential for undergoing double addition of organometallics such as organolithiums, organomagnesiums, and organozincs reagents to provide *N*-protected α-tertiary carbinamines (Schema **2**). However, the controlled step-by-step double addition of two different organometallics to provide the chiral compounds was quite challenging, except when the triorganosilyllithium or the alkynyllithium reagents were used to carry out the first addition, followed by the addition of the organomagnesium or alkynyllithium reagents[4]. Therefore, the variety of substituents of the asymmetric compounds was limited. The second part of this communication will discuss the success of adding two different Grignard reagents onto imidates to achieve the secondary carbinamine and the preliminary study of the addition of the organomagnesiums reagents onto ketimidates for the access to tertiary *N*-substituted carbinamines.

Scheme ***2***



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