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Title: Discovering New Organocatalytic Organic Transformations Using N-heterocyclic Carbene as a Catalyst

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Keywords: Chemistry
Organic Chemistry
Heterocyclic Chemistry
N-heterocyclic carbene
Carbenes

Issue: 19-Jul-2017
Date:

Publisher: IISER-M

Abstract: The research work carried out in this thesis involves the development of new synthetic methodologies using N-heterocyclic carbene (NHC) as an organocatalyst. This thesis is divided into four chapters. Chapter 1: General introduction to N-heterocyclic carbene (NHC) catalysis. In recent years, persistent carbene chemistry has become one of the fascinating areas in organic chemistry. Among these, N-heterocyclic carbenes (NHCs) have found an important role in organocatalytic transformations, mainly in carbon–carbon, carbon–heteroatom bond formation and annulation reactions. The utility of NHCs has also been explored in other organic transformations such as; oxidation reactions, transesterification and silyl activation. The versatility of N-heterocyclic carbenes is due to their different modes of activation towards different functional groups. In this chapter, the applications of NHC as an organocatalyst for various types of organic reactions are highlighted.

Chapter 2: N-Heterocyclic carbene as a Brønsted base catalyst This chapter is sub-divided into two parts namely Part A and Part B. PART A: N-heterocyclic carbene catalyzed access to diaryl- and triarylmethyl phosphonates through the 1,6-conjugate addition of dialkylphosphites to p-quinone methides and fuchsones. Organophosphorous derivatives are found to be an imperative class of organic compounds due to their widespread applications in many areas including organometallic chemistry, medicinal chemistry and pharmaceutical industries. These are also used as metal extractants and flame retardants. Their utility has been further extended in organic synthesis as starting materials in the synthesis of olefin derivatives. Among the organophosphorous compounds, the diaryl- and triarylmethyl phosphonate derivatives have been realized as vital derivatives due to their remarkable applications in medicinal chemistry. The classical methods for the synthesis of arylated methyl phosphonates involve the Arbuzov reaction and Friedel–Crafts type of reactions. However, harsh reaction conditions and narrow substrate scope limit the applications of this protocol. In order to overcome these shortcomings, recently, many strategies have emerged for the synthesis of diaryl- and triarylmethyl phosphonates which involve FeCl₃-mediated Friedel-Crafts reaction and transition metal catalyzed coupling reactions. Although these methods involve relatively mild conditions and good regioselectivity, utilization of stoichiometric amount of FeCl₃ and metal catalysts remains challenging. Despite their extensive applications, very limited number of reports are available for the synthesis of arylated methyl phosphonates, particularly diaryl- and triarylmethyl phosphonates. Therefore, developing an alternative and more efficient method for the synthesis of these compounds remains a demanding task, especially under organocatalytic conditions. In this part of Chapter 2, we disclose NHC catalyzed atom economical 1,6-conjugate addition of dialkylphosphites to p-quinone methides and fuchsones to access diaryl- and triarylmethyl phosphonates. Optimization studies have been carried out by using NHC-CO₂ adducts as pre-catalyst for the NHC catalyzed 1,6-conjugate addition of dialkylphosphites to p-quinone methides and fuchsones. After screening different reaction conditions, IMes.CO₂ was found to be the best precatalyst for this transformation. Having optimal reaction conditions in hand, the scope and limitations of this methodology were explored by using a wide range of p-quinone methides and dialkylphosphites. Irrespective of the nature of substituents on p-quinone methides and dialkylphosphites, the corresponding diaryl phosphonates were obtained in good to excellent yields. Triarylmethyl phosphonates were obtained in low to moderate yields at 80 °C. PART B: N-heterocyclic carbene catalyzed 1,6-conjugate addition of 2-naphthol to pquinone methides: Expedient access to unsymmetrical triarylmethanes. While working on NHC catalyzed 1,6-conjugate addition of dialkylphosphites to pquinone methides we envisioned that it is possible to access unsymmetrical triarylmethane derivatives through 1,6-conjugate addition of 2-naphthol to p-quinone methides using NHC as a Brønsted base catalyst. Unsymmetrical triarylmethanes and their derivatives are remarkable synthetic targets, due to their widespread utility as building blocks in many natural products, biologically active compounds and dyes. Few of the biologically active triarylmethanes. Although numerous methods have been developed for the synthesis of unsymmetrical triarylmethanes, traditionally triarylmethanes are accessed through Friedel-Crafts type reactions of diarylmethanols or reductive dehydroxylation of triarylmethanols. Though these methods are simple and widely used the utilization of electron-rich arenes and harsh reaction conditions limit the efficacy of these protocols. To address these issues, recently, the transition metal catalyzed reactions have been developed. Ever since the extensive utility of unsymmetrical triarylmethanes, developing a simple and atom economical approach for the synthesis of unsymmetrical triarylmethanes, especially under organocatalytic conditions is always in high demand. In this part of Chapter 2, we unveiled NHC as a Brønsted base for the 1,6-conjugate addition of 2-naphthol to p-quinone methides for obtaining unsymmetrical triarylmethane

derivatives. After screening different reaction conditions, IPr.HCl was found to be the best precatalyst and dichloromethane was found to be the most appropriate solvent. Having optimized reaction conditions in hand, the scope and limitations of this methodology were further elaborated using variety of p-quinone methides as well as 2-naphthols. Regardless of the nature of substrates, the corresponding triarylmethanes were isolated in good to excellent yields. 100% atom economy and simple reaction condition are the significant features of this protocol.

Chapter 3: N-heterocyclic carbene catalyzed trimethylsilylation of terminal acetylenes and indoles using Ruppert's reagent as a silyl source under solvent free conditions. Alkynylsilicon reagents are considered important synthetic targets due to their wideranging utility in many organic transformations, such as, metal catalyzed cross-coupling reactions, alkynylation reactions and metathesis reactions. Conventionally, alkynylsilicon compounds are synthesized by deprotonation of terminal acetylenes by using strong bases such as organolithium and Grignard reagents followed by quenching with silyl electrophiles. Some other metal catalyzed or mediated protocols have also been developed to avoid some of the limitations of the traditional methods, such as utilization of strong bases and quantitative production of inorganic salts as by-products. Thence, developing an efficient and fluoride free synthetic route for the synthesis of alkynylsilicon compounds is a desirable task. It is well known in the literature that NHCs could form hypervalent complexes with silicon compounds. This concept has been applied to activate Ruppert's reagent for the trifluoromethylation of different electrophiles. Herein we report NHC-catalyzed trimethylsilylation of terminal acetylenes using CF₃ anion as a traceless base under solvent free conditions. The reaction conditions were optimized by treating phenyl acetylene and Ruppert's reagent under different conditions; to our surprise, the reaction worked pretty well under solvent free condition to produce trimethylsilylated acetylenes in excellent yields. Encouraged by the above results, we applied this strategy for indoles as well to access Nsilylated indoles. N-silylatedindoles are found to be fascinating intermediates in synthetic organic chemistry, as indoles are vital synthons in many natural product syntheses. Traditionally, Nsilylated indoles are synthesized by deprotonation of indoles by using strong bases followed by quenching with a silyl electrophile. Recently, metal catalyzed dehydrogenative Si–N coupling methods²¹ have also been developed. Under optimized conditions, most of the substituted indoles were converted to their N-silylatedindoles. Solvent free conditions, high yield of products, less reaction time, simple work-up procedure are the key features of this methodology.

Chapter 4: N-heterocyclic carbene catalyzed oxidative esterification of aldehydes with aryl boronic acids. Aryl benzoate derivatives have served as significant building blocks in many natural products and active pharmaceutical ingredients (APIs). Numerous approaches have been reported for the construction of ester functionality. Traditionally, aryl benzoate derivatives are synthesized either by acid catalyzed esterification or by transesterification reactions. Apart from these strategies, Baeyer-Villiger oxidation, organocatalytic esterification and transition metal catalyzed coupling reactions are the additional alternatives. While working on N-heterocyclic carbene catalyzed organic transformations, we envisioned that aryl benzoates could be directly accessed through NHC catalyzed aerobic oxidation of aryl aldehydes using boronic acids, especially in the absence of metal catalyst. In this chapter, the NHC-catalyzed oxidative esterification of aldehydes with aryl boronic acids are discussed. The extensive optimization studies revealed that the NHC derived from SIPr.HCl worked exceptionally well for NHC-catalyzed oxidative esterification of aldehydes with aryl boronic acids. Having the optimal reaction conditions in hand, scope and limitations of this transformation were screened by using diverse range of aldehydes and aryl boronic acids and in most of the cases the esters were obtained in excellent yields. Unfortunately, this methodology was not suitable for aliphatic aldehydes and boronic acids. Mechanistic details have been thoroughly investigated through the isotopic labelling experiment.

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