Catalytic Multicomponent Reactions Based on Isocyanides

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Due to their versatility and diversity, catalytic multi-component isocyanide-based reactions (IMCR), are very interesting and important. Isocyano group is a unique functional group due to its reactivity toward electrophiles and nucleophiles at the same atom. It participates in many multi-component reactions along with various catalysts which dramatically improve reaction conditions for the achievement of better yields, milder and benign reaction condition and in some cases better stereoselectivities. In this review, we wish to disclose the recent applications of metal, basic, acidic and many other catalytic systems in the IMCRs. In supplementary section we also updated our review with all related publications in 2010.

Keywords: Isocyanide-based reaction, Lewis acids, Bronsted acids, Ugi reaction

INTRODUCTION

The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. The outstanding position of isocyanide-based reactions can be traced back to the exceptional reactivity of the functional group of the isocyanide. No other functional group reacts with nucleophiles and electrophiles at the same atom, leading to the so called α-adduct. Other major primary reaction pathways of isocyanides are radical reactions, α-acidity, and an intrinsic high affinity toward met organic reagents and their subsequent reactions [1].

The rate of chemical reaction, in the presence of catalyst is faster and unlike other reagents, is not consumed by the reaction itself. Catalysts can be either heterogeneous and homogenous depending on whether a catalyst exists in the same phase as the substrate or not.

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In line with the tremendous renewed activity witnessed in recent years in the field of isocyanide-based reactions, remarkable new strategies have been developed based on catalyst processes. Advances in this area take advantage of the myriad of bond-forming processes that can be achieved with catalysts.

On the basis of the rapid growing number of important communications in the area of catalytic isocyanide-based reactions, we felt that it is appropriate and being useful to review the work since 2006, when the last comprehensive review, Recent Development in Isocyanide Based Multicomponent Reactions in Applied Chemistry, was Appeared [1]. Here, we wish to summarize current progress in catalytic isocyanide-based chemistry.

STEREOSELECTIVE IMCR

Although the great utility of isocyanide-based multicomponent reaction in assembling complex pharmacologically important structures in a small number of steps and with the possibility of several diverse inputs widely
recognized, the stereochemical issues still represent a challenge. In Passerini and Ugi reactions a new stereogenic center is generated but most reactions reported so far suffer from low or absence of stereoselectivity [2].

**Enantioselective Passerini Reaction**

In the classic Passerini reaction (P-3CR), an $\alpha$-acyloxy carboxamide is formed from the reaction of an isocyanide, an aldehyde, and a carboxylic acid. The mechanism involves an initial nucleophilic addition of the isocyanide on the aldehyde followed by an acyl rearrangement.

Although this reaction has been known since 1921 and is widely applied in natural product synthesis and drug discovery, but catalytic asymmetric variants are rare.

Denmark et al. described the first asymmetric Lewis base catalyzed enantioselective Passerini-type reaction (Scheme 1). The yields were good to excellent and the ee’s ranged from 70/30 to 99/1. In this reaction water is acting as the acid component [3].

Domling et al. identified the first enantioselective Passerini MCR. They screened several hundreds of combinations of Lewis acid-chiral ligands and found that a stoichiometric amount of $\text{Ti}(i\text{-OPr})_4$ in combination with TADDOL 9 turned out to give the best ee’s (Scheme 2). This system was capable of promoting reaction to afford product in low to moderate enantioselectivity [4].

![Scheme 1](image1)

![Scheme 2](image2)

\[ OCHO + NC \xrightarrow{\text{catalyst} -78^\circ\text{C}} \text{SiCl}_4 \xrightarrow{\text{sat aq. NaHCO}_3} OH \xrightarrow{\text{catalyst}} \text{N} \xrightarrow{\text{O}} \text{N} \xrightarrow{\text{O}} \text{N} \xrightarrow{n=4-6} \text{OH} \]

**Scheme 1**

\[ \text{NH} + \text{CHO} \xrightarrow{\text{THF,0}^\circ\text{C}} \text{ligand,Lewis acid} \xrightarrow{\text{ligand}} \text{NH} \xrightarrow{\text{CO}_2} \xrightarrow{\text{O}} \text{OH} \]

**Scheme 2**

\[ \text{Lewis acid} = \text{Ti}(i\text{-OPr})_4 \]