Organometallic Catalysts for Intramolecular Hydroamination of Alkenes

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Abstract—Amines are invaluable precursors and necessary chemical components in industrial settings as well as pharmaceutical industries, making methods for efficient formation of C–N bonds a vital chemical process. Of these methods, the hydroamination of alkenes and alkynes, specifically the addition of an N–H bond across a carbon-carbon π-bond, is especially relevant. The hydroamination reaction is theoretically 100% atom-economical, making it a desirable synthetic route for the formation of C–N bonds. Common synthetic methods for amines are cumbersome and require multiple steps that produce waste products. However, the hydroamination reaction itself has a large negative entropy, requiring the assistance of a catalyst to promote the reaction. As such, current research focuses on the development of organometallic catalysts that can increase the efficacy of hydroamination reactions. Herein, research towards the development of an efficient catalyst for intramolecular hydroamination of alkene is reviewed.

Keywords: intramolecular reactions, hydroamination, organometallic catalysts, amines.

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1. Importance of Synthetic Routes for C–N Bond Formation

The search for new synthetic routes for the formation of C–N bonds in the past few decades has been driven by a burgeoning industrial and pharmaceutical need for more efficient and cost effective methods for the production of pharmaceuticals and pharmaceuticals precursors. While the percentage of health...
care cost on prescription drugs has only varied between 5–10% during this time, the overall expenditures of health care have grown from $26.9 billion in the 1960s to well over a trillion dollars as of 1998 [1]. Amines are common pharmaceutical precursors. A recent survey in 2005 by Dugger et al. found that approximately 15% of all bulk reactions in a chemical facility involved C–N bond formations [2]. This percentage was the highest of all bond formations, including C–C and C–O bonds, which comprised 14% and 5%, respectively. Indeed, this category was second only to CO₂H interconversions, which accounted for 26% of all bulk reactions.

A stereospecific route to C–N bond formation is important as most medicinal compounds are chiral; one enantiomer has the desired pharmacological effect, while the other is benign, or in some cases, detrimental [3]. This is true of alkaloids, which appear throughout the animal and plant kingdom and have many applications within the medical fields. For instance, Barbosa–Filho et al. reported the benefits of alkaloids in anti-inflammatory responses [4]. It has been demonstrated that many classes of alkaloids, which comprise the largest source of secondary plant substances, show anti-inflammatory effects, and as such have been used as drug models to affect these changes [5]. Newman et al. reported that between 1981 and 2002, approximately 5% of all drugs were from natural sources, while another 23% were derived from these sources [5]. Of special note, in terms of cancer related drugs, 60% were derived or from natural sources such as alkaloids. Synthetic routes have also been designed for alkaloids, but the reactions necessary to synthesize key C–N bonds in heterocycles require many reagents and adverse conditions, [6, 7] exemplifying the need for the development of new C–N synthetic routes.

2. OVERVIEW OF METHODS FOR C–N BOND FORMATION

Common methods used for C–N bond formation, Scheme 1, have drawbacks. Consequently, a number of research labs are working to develop catalysts to promote the hydroamination of alkenes. This section aims to provide an overview of the common C–N bond forming methods.

2.1. Common Methods for C–N Bond Formation

Common C–N bond formation techniques include the alkylation of ammonia, reduction of aromatic nitro compounds to form amines, reductive amination of carbonyls, and reduction of nitriles and amides, but more sophisticated techniques such as the Curtius and Hofmann rearrangements have also been established [8]. However, almost all of these reactions are multistep processes, or are so specific that they are not widely applicable.

The alkylation of amines via alkyl halides is a well-known process Scheme 1a [9]. The reaction can lead to the formation of the desired alkyamine, but multiple alkylations are common, yielding a mixture of primary, secondary, and tertiary amines as well as the fully alkylated ammonium salt [9]. Aromatic amines are commonly prepared by nitration of an aromatic ring, followed by reduction of the nitro group to form an aromatic amine, Scheme 1b [10]. Similarly, substitution reactions followed by a reduction can produce amines; for example, reaction of an alkyl halide with cyanide followed by reduction of the nitrile or the reaction of an acid chloride with an amine followed by reduction of the amide, Scheme 1c. In the case of nitriles this is limited to producing a primary amine, but the reduction of amides can yield up to a tertiary amine depending upon the substituents. Both of these reductions require a reduction using catalytic hydrogenation or lithium aluminum hydride [9, 11, 12]. Reductive amination, or reductive alkylation of amines, features a carbonyl compound reacting with ammonia, a primary amine, or a secondary amine in the presence of a hydride source or catalytic hydrogen to form the resulting amine, Scheme 1d [13, 14]. The Curtius and Hofmann rearrangements are two alternative synthesis methods. The Curtius rearrangement features an acyl azide rearranging to form an isocyanate. This can subsequently be hydrolyzed with water to form a carbamic acid, which decomposes to carbon dioxide and an amine, Scheme 1e [15, 16]. In general, regardless of the functional group directly attached to the α-carbon, the reaction gives good to excellent yields of the desired primary amine. The Hofmann rearrangement is similar in that an isocyanate is formed and then converted to the amine via the same process as described above [16]. Despite the familiarity of these synthetic approaches, each requires multiple steps and/or uses highly reactive agents in the synthetic route and are not economical; side products are produced or multiple steps are required to form the desired C–N bond. New routes for the formation of C–N bonds are needed and will be the focus of this review.