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Cycloamidination of Aminoalkenes with Nitriles: Synthesis of Substituted 2-Imidazolines and Tetrahydropyrimidines

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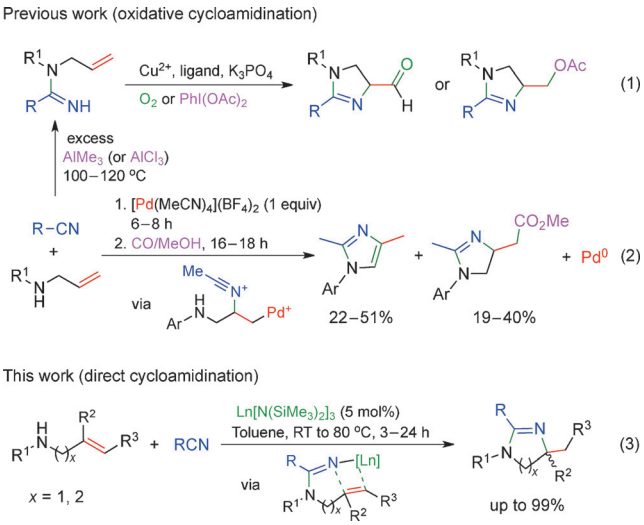
Abstract: *The first catalytic cycloamidination of aminoalkenes with nitriles has been achieved by using rare-earth complexes. This reaction is equivalent to the desired intramolecular hydroamination of alkenylamidines, and allows a new direct access to substituted 2-imidazolines and tetrahydropyrimidines in high yields under operationally simple reaction conditions. Moreover, the methodology is also efficient for synthesis of symmetric and unsymmetric bridged diimidazolines. Compared with the traditional stepwise-mediated synthetic approaches, the present method avoids the use of additives and harsh reaction conditions, and thus leads to a completely different product distribution. Mechanistic data suggest that the reaction involves the initial NH activation by lanthanide complex followed by nitrile insertion into a Ln–N bond to form an amidinate lanthanide intermediate which undergoes the cyclization.*

Tandem insertions of two distinctly different functionalities into a N–H bond represent an efficient, atom-economical, and highly desirable route to nitrogen-containing molecules.[1–3] Recent pioneering work reported by the groups of Xie and Demir showed that Ti^{IV}[3a] and Au^{I}/Zn^{II}[3b] could catalyze the tandem insertions of nitrile and alkyne into a N–H bond to form substituted isoindoles, isoquinolines, imidazoles, and pyrroles. Despite the importance of this methodology, the corresponding tandem insertion of alkenes and nitriles into a N–H bond has not been realized because of the lower reactivity and electron density of alkenes compared with those of alkynes.[4] Typically, the attainment of this goal for alkenes requires a multistep process [Scheme 1, Eq. (1)]. The major obstacles originate from: 1) in most cases the alkene hydroamination is mutually incompatible with the amidination of nitriles, thus making the control of related cascade sequences difficult in a one-pot operation;[5,6] 2) catalytic addition of a secondary aminoalkene to a nitrile to give the amidine remains elusive;[6,7] 3) the hydroamination between amidines and alkenes is challenging.[8] Although several strategies such as aminooxygenation,[6] iodoamidination,[8a] hydroamidiniumation,[8c] and aerobic [3+2]-annulation,[9] have been developed for cyclization of alkenylamidines to form imidazoline derivatives, they are based on the combination with another process. There remains a demand for exploitation of the direct alkene hydroamidination which enables realization of predictable chemoselectivity.



Scheme 1. Comparison of the prior work to the current work.

Hegedus and co-workers found that the reactivity of CH_3CN toward N-allylanilines could be enhanced by stoichiometric amounts of a highly electrophilic palladium species and CO [Scheme 1, Eq. (2)].[10] However, the reaction gives access only to a limited scope of substrates. Further, the factors that affect the relative rates of competing mechanistic pathways in this reaction (e.g., β-hydride elimination versus CO insertion), including the feasibility of its catalytic version, are not well understood. Herein, we describe the first examples of lanthanide-catalyzed direct hydroamination/cyclization of aminoalkenes with nitriles [Scheme 1, Eq. (3)], which provides a straightforward and versatile method for atom-economical synthesis of a variety of 2-imidazoline and tetrahydropyrimidine derivatives which have many diverse applications, including natural product[11] and drug[12] cores, organic synthesis,[13] precursors to functionalized molecules,[14] and important ligands[8d,15] in organometallics.

In our preliminary studies, we examined cyclization between N-methyl allylamine (**1a**) and benzonitrile (**2a**). It was found that the reaction of **1a** with **2a** in toluene in the presence of 5 mol% $Yb[N(SiMe_3)_2]_3$ at room temperature afforded the desired **3aa** in almost quantitative yield (for structure see Scheme 2; see the Supporting Information).

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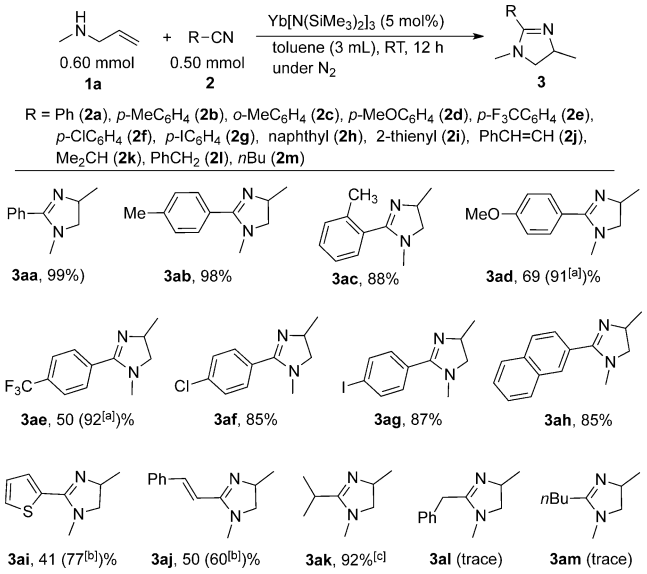
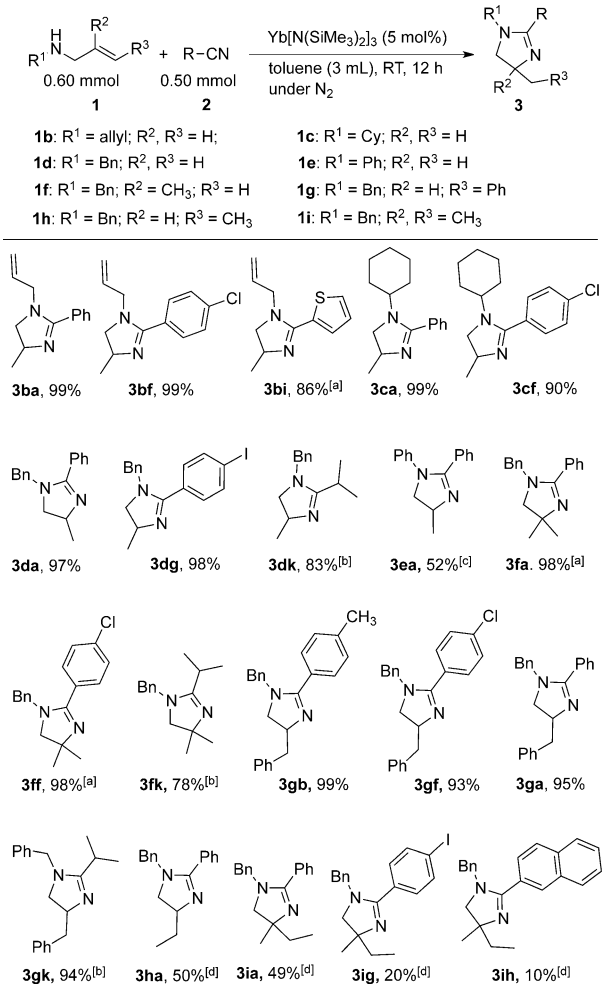


Scheme 2. Scope of nitriles in the lanthanide-catalyzed cyclization with **1a**. Yields are those of isolated products unless otherwise stated. [a] 40 °C, 24 h. [b] 60 °C, 24 h. [c] Yield determined by ^{1}H NMR spectroscopy.



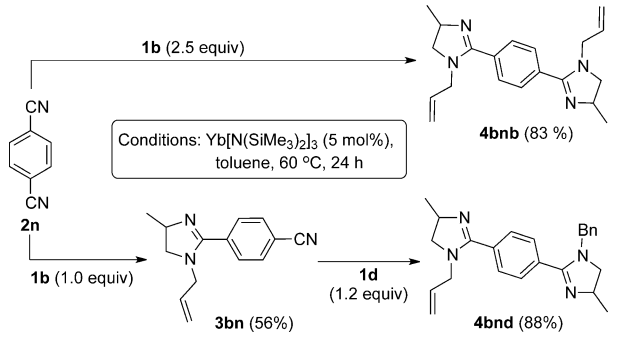
Scheme 3. Synthesis of multisubstituted imidazolines. Yields are those of isolated products unless otherwise stated. [a] 60 °C, 24 h. [b] **1** (0.50 mmol), **2k** (0.60 mmol), 60 °C, 24 h. [c] 40 °C, 24 h. [d] **1h** (0.50 mmol), **2a** (1.0 mmol), 60 °C, 24 h.

On the basis of the optimized reaction conditions, we firstly explored the scope of the reaction to nitriles. As shown in Scheme 2, the catalytic system is tolerant to many functional groups such as halides, F_3C, MeO, and thienyl. Aryl nitriles bearing electron-donating and electron-neutral substituents afforded **3aa**–**ad** in 88–99 % yields. An aromatic nitrile with a strong electron-withdrawing CF_3 group gave **3ae** in 92 % yield. Products bearing halogens (**3af**, **3ag**) were obtained in good yields. Naphthyl and 2-thienyl nitriles could also be cyclized under the current reaction conditions (**3ah**, **3ai**). In general, the presence of strong coordinating atoms on the nitriles has a slightly negative impact on the catalytic reaction because of their competing coordination to the highly Lewis-acidic Ln^{3+} ions, thus relatively high reaction temperatures (40–60 °C) are required. Surprisingly, cinnamonitrile also afforded **3aj** in 60 % yield, which is in contrast with the well-known Michael addition of amines to α,β-unsaturated nitriles, thus forming exclusively the anti-Markovnikov hydroamination products.[5a,b] Isopropyl nitrile readily participates in this catalytic cyclization process (**3ak**), but **2l** and **2m**, with more active hydrogen atoms, afforded only trace amounts of the products, presumably because these nitriles can quench the Ln–C/N bond.[16]

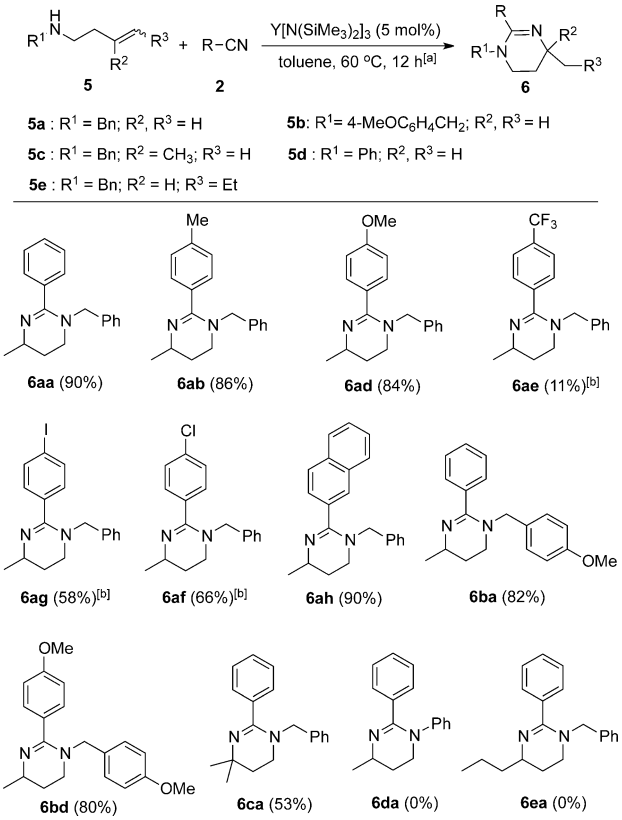
This catalytic cyclization also appears to be general in regard to allylamine substrates (Scheme 3). A number of synthetically useful N substituents, such as alkyl, allyl, cyclohexyl, and benzyl, were found to be compatible with the reaction conditions. Moreover, this procedure is amenable to the gram-scale synthesis of **3ba** in almost quantitative yield. To our delight, the sterically hindered **1f** gave **3fa**,**ff**,**fk** in high yields. Despite significant advances in metal-catalyzed hydroamination, the cyclohydroamination of acyclic internal alkenes is generally difficult, thus obstructing their applications in the construction of azacycles bearing the key substituents.[17] Remarkably, the aromatic internal alkene **1g** afforded **3ga**,**gk** in excellent yields, while an aliphatic internal olefin is less reactive and requires harsher reaction conditions (**3ha**). In particular, the reaction with the trisubstituted alkene **1i** afforded **3ia**,**ig**,**ih**, which would be difficult to prepare otherwise,[18] albeit in low yields. The structures of **3ag** (see Figure S1 in the Supporting Information) and **3dg** (see Figure S2) were further confirmed by the X-ray crystal diffraction analysis.[19]

Bearing in mind the importance of ansa-bridged diimidazolines as ligands in adjusting organometallic reactivity and catalytic behavior,[15] we then became interested in the reactions of **2n** with **1** (Scheme 4). Treatment of **2n** with 2.5 equivalents of **1b** afforded the dicyclization product **4bnb** in 83 % yield, while reaction of **2n** with one equivalent of **1b** afforded **3bn** as the main product. **3bn** reacted with **1d** to afford the desired unsymmetric dicyclization product **4bnd**.

Encouraged by the above results, we next explored the use of the reaction in synthesis of tetrahydropyrimidines. As shown in Scheme 5, the reactions of **5a** with electron-neutral and electron-rich aryl nitriles proceeded smoothly, thus giving



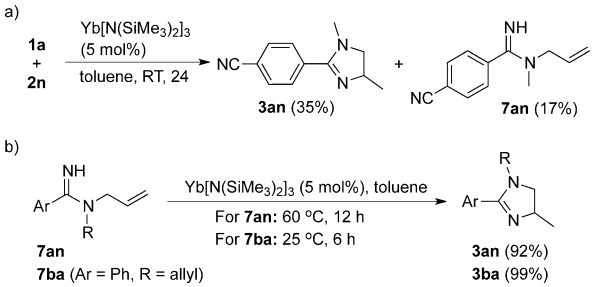
Scheme 4. Dicyclization of terephthalonitrile.



Scheme 5. Synthesis of substituted tetrahydropyrimidines. [a] Reaction conditions: **5** (0.60 mmol), **2** (0.50 mmol), $Y[N(SiMe_3)_2]_3$ (0.025 mmol), toluene (3 mL), 60 °C, 12 h under N_2. Yield is that of the isolated **6**. [b] 80 °C, 24 h.

6aa,**ab**,**ad** in good to excellent yields, but the electron-deficient aryl nitriles were markedly less reactive than those with the Me or OMe moiety, and required a higher reaction temperature (**6ad** versus **6ae**, **6af**). **5b** also afforded the desirable products in good yields (**6ba**, **6bd**). For the sterically hindered **5c**, **6ca** was obtained in 53 % yield. However, the aminoalkenes with an N-phenyl substituent (**5d**) or 1,2-disubstituted alkene (**5e**) are ineffective substrates under these reaction conditions. The diminished activity for six-membered-ring closure likely reflects a sterically controlled process.[20]

Having established that the cycloamidination of **1** with **2** is catalyzed by $Ln[N(SiMe_3)_2]_3$, we focused on elucidating the reaction mechanism. Firstly, we studied both the preference for addition of the nitrile to the amine, and the intermediacy of rare-earth amidinates (Scheme 6). It was found that the



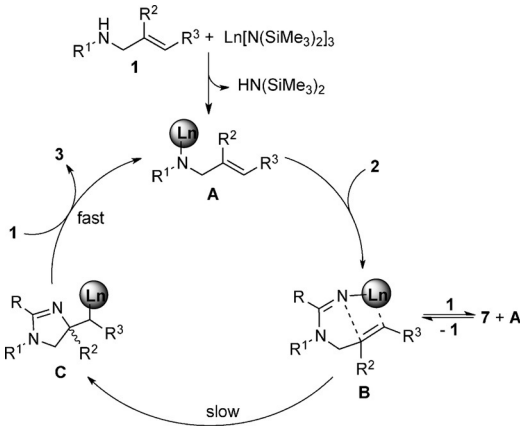
Scheme 6. Mechanistic studies.

single C–N-forming intermediate **7an** could be isolated in 17 % yield when the reaction of **1a** with **2n** was carried out at room temperature (Scheme 6a). Remarkably, **7an** was completely converted into **3an** when subjected to a higher reaction temperature. As far as we are aware, transformation of **7an** into **3an** represents the first example of the metal-mediated hydroamidination of alkenes.[1,20] To draw more support, we also carried out the reaction of **7ba**,[6b] the cyclization took place selectively and quantitatively (Scheme 6b).

Secondly, we monitored the reaction between **1b** and **2a** in a [D_6]benzene solution, in the presence of the paramagnetic precatalyst $Y[N(SiMe_3)_2]_3$, by ^{1}H NMR spectroscopy (see Figure S3). The results reveal that addition of 10 mol % $Y[N(SiMe_3)_2]_3$ to a mixture of **1b** and **2a** immediately generates **3ba** with the partial liberation of $(Me_3Si)_2N$ ligands (a new peak at $\delta = 0.10$ ppm) from the precatalyst. The presence of two sets of signals in the coordinated $(Me_3Si)_2N$ region ($\delta = 0.55$ and 0.40 ppm) together with the appearance of minor amounts of new olefinic ($\delta = 5.08$–5.25 and $\delta = 5.78$–5.95 ppm) and alphatic ($\delta = 4.19$–4.25 ppm) C–H resonances indicate the formation of more than one active Ln species in the catalytic cycle. The reaction is complete after 3 hours. Consistent with this, in the ^{1}H NMR spectrum of the catalytic conversion of a [D_6]benzene solution of **7ba** into **3ba**, no signal at $\delta = 0.55$ ppm was observed, but the doublet peaks at $\delta = 0.40$ ppm remained (see Figure S4). This data implies that the signal at $\delta = 0.55$ ppm might originate from an yttrium amido complex bearing $(Me_3Si)_2N$ ligands, while the stronger doublet peaks at $\delta = 0.40$ ppm could be attributed to the protons of the $(Me_3Si)_2N$ ligand of the yttrium amidinate intermediate. Furthermore, the intermolecular substrate protonolysis of the precatalyst was also observed by the ^{1}H NMR spectrum when a [D_6]benzene solution of **1b** was treated with 0.1 equivalents of $Y[N(SiMe_3)_2]_3$ (see Figures S5 and S6). In addition, the kinetic isotope effects (KIE) of 2.33 for the cyclization of the N-deuterated **1b** is also within the normal range (2.3–5.2) observed for NH activation of aminoalkenes by organolanthanides.[1a] How-

ever, utilization of $Yb(OTf)_3$ as a replacement of $Yb[N(SiMe_3)_2]_3$ was ineffective.

Based on the results described above, a reasonable pathway for the formation of **3** is shown in Scheme 7. The reaction is likely initiated by the deprotonation of aminoalkenes by metal species. Coordination and sequential insertion of one nitrile into the Ln–N bond of **A** gives the key lanthanide



Scheme 7. Possible mechanism for the formation of **3**.

amidinate intermediate **B**. Subsequently, the intramolecular addition of a C=C bond to the Ln–N bond of **B** leads to the cyclization, thus affording the 4-imidazolinylmethyl lanthanide complex **C**. Finally, predominant protonation of **C** with another allylamine affords the cyclization product **3** and regenerates the active intermediate **A**. The isolation of **7al** and a higher concentration **B**, compared with **A**, in the ^{1}H NMR spectroscopy (see Figure S3) suggest that alkene insertion into the resulting lanthanide–amidinate bond might be the rate-determining step in the catalytic cycle.[19]

In conclusion, we have developed a new, highly efficient, atom-economical, and convenient method for the synthesis of a variety of imidazolines and tetrahydropyrimidines by lanthanide-catalyzed direct cycloamidination of aminoalkenes and nitriles. Importantly, compared with traditional stepwise-mediated synthetic approaches to 1,3-dinitrogen-containing heterocycles from aminoalkenes and nitriles,[6,9] the present method not only avoids the use of additives, but also leads to a completely different product distribution. Mechanistic studies shed light on the possible reaction pathway. The results reported here open up a new prospective and allow new tactics in aminoalkene-based coupling events. We are currently expanding its scope by using additional reaction partners and are synthesizing a variety of small-molecule arrays.

Experimental Section

General procedure for synthesis of **3**: A mixture of $Yb[N(SiMe_3)_2]_3$ (16.3 mg, 0.025 mmol, 5 mol%), allylamine (0.60 mmol), and nitrile (0.50 mmol) in toluene (3 mL) was stirred at room temperature under N_2. The reaction mixture was quenched with water (2 mL) after completion of the reaction. The solution was extracted with ethyl acetate (3×5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated. The pure 2-imidazoline **3** was obtained by flash column chromatography on silica gel with ethyl acetate/TEA (20:1) as the eluent.

Acknowledgments

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