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Intramolecular alkene hydroamination and degradation of amidines: divergent behavior of rare earth metal amidinate intermediates†‡

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Direct N–H addition of amidines to alkenes is a highly valuable but challenging transformation that remains elusive. Now, the intramolecular hydroamidination of *N*-alkenylamidines is achieved by using a rare earth catalyst, which provides an efficient and atom-economical approach for substituted imidazolines and tetrahydropyrimidines. Moreover, a mild and efficient method for the catalytic degradation of amidines to give amines and nitriles is also developed. Additionally, amidine reconstruction followed by an intramolecular alkene hydroamidination strategy for the synthesis of substituted imidazolines and tetrahydropyrimidines from secondary enamines and inactive amidines has also been established, which may circumvent the need for some unavailable starting materials. The mechanistic studies prove that these reactions proceed *via* a key lanthanide amidinate intermediate that can undergo substrate- and amine-controlled chemodivergent transformations: intramolecular alkene insertion, nitrile extrusion, amidinate reconstruction, or a combination of the reactions. The results presented here not only demonstrate the synthetic potential and versatility of alkene hydroamidination with substrates, but also provide a good insight into the factors that promote or deter the hydroamidination of alkenes.

Introduction

The development of new methods for the efficient and atom-economical construction of C–N bonds is of great interest in organic chemistry. Intramolecular hydroamination of aminoalkenes has become a powerful tool in the synthesis of nitrogen-containing heterocycles.[1,2] Moreover, the intramolecular hydroamidation of various enamine derivatives such as *N*-protected enamines,[3] and alkenyl-substituted amides[4] and ureas,[5] has also attained maturity. However, attempts to effect the catalytic hydroamidination of alkenes have proved difficult due to a wide range of reasons, including the electrostatic repulsion between the lone electron pair on the nitrogen and the π electrons of the alkenes and the challenge in the development of related catalysts. In sharp contrast to metal–amido bonds, the metal–amidinate bonds generated readily by protonolysis or the oxidative addition of the precatalyst with amidine are generally considered to be chemically inert, and resistant toward alkene insertion and electrophilic attack.[6,7] Indeed, no insertion reactivity of the metal–amidinate linkage has ever been observed in many alkene transformations such as polymerization,[7] hydrosilylation[8a] and hydroamination[8] mediated by metal amidinate complexes. Another obstacle for the design of hydroamidination catalysts lies in the competing coordination of the neutral amidine nitrogen atoms that often coordinate more strongly to metal catalysts than alkenes, inhibiting an alternative reaction pathway with the initial alkene coordination activation and subsequent nucleophilic attack of amidines.[1,6] This is quite different from the results obtained in the case of more reactive alkynes.[9] In addition, hydroamidination has difficulty in proceeding by the initial protonation of an alkene followed by the nucleophilic attack of the amidine nitrogen pathway by using a Brønsted acid catalyst,[10] because the high basicity of amidines often leads to the preferential formation of amidinium salts over the carbenium ions.[11] Moreover, such proclivity might preclude the catalytic turnover that requires an external source of protons for the protolytic cleavage of the resulting metal–carbon bond in late transition-metal-mediated hydroamidination processes.[1d,5c]

Inevitably, amidinations of alkenes reported so far have been limited to those involving a unique combination with other processes that provide either kinetic or thermodynamic tools to activate amidines. Zhu and Chiba *et al.* demonstrated that the dehydrogenative coupling pathway relying on an oxidant is a strategic tool for the development of alkene amidinations based on *N*-allylamidines (Scheme 1a).[12,13]

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† Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

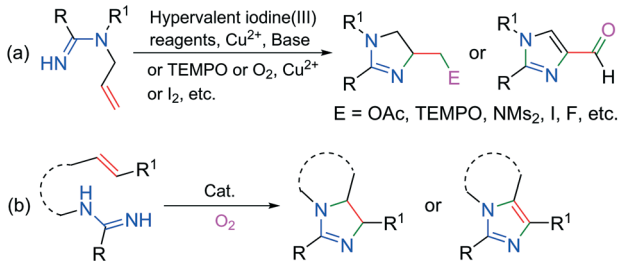
‡ Electronic supplementary information (ESI) available: Experimental details, and characterization data. CCDC 1831321. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cy01481g

Other recent efforts have been devoted to the development of new methods for the dehydrogenative [3 + 2]-annulation reactions of amidines with alkenes (Scheme 1b).[14] Bertrand *et al.* found that the protonation of bulky *N*,*N*,*N*′-trisubstituted allyl amidine with dried HCl could encourage the intramolecular proton transfer to form imidazolinium salts, but it cannot be achieved catalytically and employed for the construction of neutral 1,3-dinitrogen-containing heterocycles.[10] There remains a growing demand for the exploitation of the fundamental reactivity of amidines, including the factors that control the reactivity of metal–amidinate moieties.

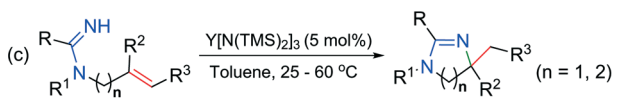
On the other hand, the degradation of amidines is of great interest from fundamental catalytic,[15] biological[16] and environmental[17] viewpoints because of the frequent existence of such structures in biologically active compounds and their role as valuable synthetic intermediates. In contrast to the extensive studies on the hydrolysis of amidines, reports on the decomposition of amidines by elimination are scarce. Recent reports of transition-metal catalyzed cyanations with RR′N–CN reagents have shed some light on the β-N elimination reactivity of the *in situ* generated metal–amidinate intermediates.[18] However, the reaction was inherently restricted to the limited CN resources. To the best of our knowledge, no catalytic and mild protocol for the direct degradation of common amidines to give amines and nitriles is reported.

In our recent studies on rare-earth catalyzed transformations of organic functional groups, we found that the Ln[N(SiMe$_3$)$_2$]$_3$ effected the cycloamidination of aminoalkenes with nitriles, which is formally equivalent to the desired hydroamidination of alkenes.[19] Considering the synthetic accessibility of amidines from other precursors such as carboxamides,[20] secondary amides,[21] thioamides,[22] or carbodiimides[23] and the importance of the intramolecular alkene hydroamidination that provides a straightforward and highly atom efficient method for the preparation of substituted imidazolines and tetrahydropyrimidines that are finding many diverse applications, with examples including natural product and drug cores,[24] synthetic intermediates,[25] heterocyclic ligands,[26,27] catalysts[28] or precursors to functionalized materials,[29] we became interested in the development of the general method for catalytic intramolecular hydroamination of *N*-alkenylamidines. Herein, we report a general method for the catalytic intramolecular hydroamidination of *N*-alkenylamidines made possible using a rare earth catalyst. Furthermore, a convenient and mild method for the catalytic degradation of amidines into nitriles and amines, and a tandem process involving amidine reconstruction and subsequent alkene hydroamidination have also been developed.

Previous work: Amidination of alkenes accompanied by oxidative dehydrogenation, only affording the oxidative amidination products



This work: First intramolecular hydroamidination of N-alkenylamidines and insight into its mechanism and versatility



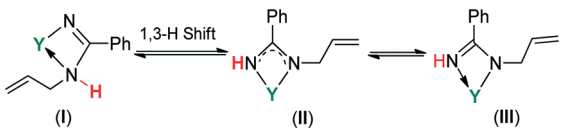
Scheme 1 Representative strategies for the amidination of alkenes. (a) Oxidative amidination. (b) Dehydrogenative coupling. (c) Direct addition (this work).

Results and discussion

Intramolecular hydroamination of *N*-alkenylamidines

In the initial experiments, we elected to employ Ln[N(SiMe$_3$)$_2$]$_3$ as the precatalyst, as it is simple and has previously exhibited a distinct performance in the catalytic addition of a C(N)–H bond across unsaturated carbon–carbon bonds.[30] It was found that treatment of *N*-allylamidine **1a** with 5 mol% of Y[N(SiMe$_3$)$_2$]$_3$ (**Y-1**) in toluene at room temperature afforded the cyclization product **2a** in 99% yield (see Table S1 in the ESI†).

On the basis of the optimized conditions, we explored the scope of the reaction for *N*-allylamidines (Table 1), *N*-methyl-*N*-allylamidines bearing various *C*-aryl and -heteroaryl substituents were appropriate substrates for this methodology, and the corresponding trisubstituted imidazolines **2a–2i** were obtained in 75–99% yields. Also, a number of synthetically useful *N*-substituents, such as alkyl, allyl, cyclohexyl and benzyl, were found to be compatible with the conditions (**2j–2m**). Remarkably, this procedure is amenable for the gram-scale synthesis of **2a** in an almost quantitative yield. To our delight, the sterically hindered disubstituted terminal alkenes gave **2q** and **2r** in high yields. Moreover, an aromatic internal alkene afforded **2s** in 87% yield. However, an aliphatic internal alkene **1t** and an *N*-monosubstituted allylamidine **1n** are ineffective substrates under these conditions. The inertness of **1n** might partly be attributed to the 1,3-H shift of the Y amidinate intermediate,[27a] leading to the stronger coordination of the metal to the N atom adjacent to the alkene unit (eqn (1)) and thus preventing the alkene insertion into the Y–N(remote) bond (*vide infra*).



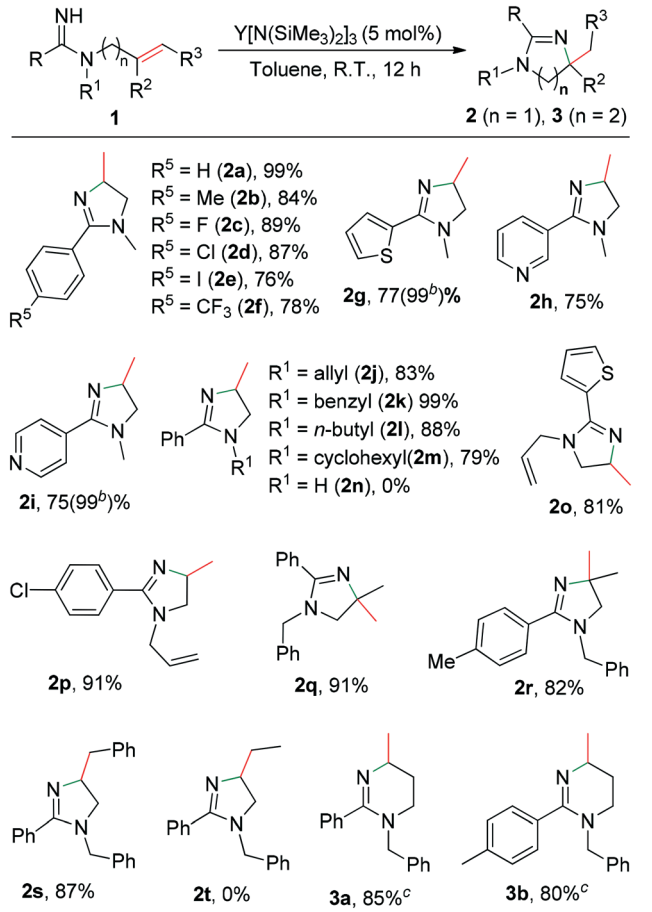
(1)

When *N*-(but-3-en-1-yl)amidines were used, the reaction also proceeded smoothly at 60 °C to afford the corresponding tetrahydropyrimidine derivatives **3a** and **3b** in good yields. The higher temperature requirement for the six-membered ring closure likely reflects a sterically controlled process.[1a]

Degradation of amidines

Surprisingly, no cyclization was observed even with prolonged heating at 100 °C when R^1 is a phenyl group (**1u**). Instead, PhCN (**4a**) and *N*-phenylallylamine were obtained (Scheme 2).

Table 1 Y-Catalyzed intramolecular hydroamination of *N*-alkenylamidines[a]



[a] Reaction conditions: 1 (0.50 mmol), **Y-1** (5 mol%), toluene (2 mL), R.T., 12 h under N_2. The yields are of the isolated products unless otherwise stated. [b] ^{1}H NMR yield. [c] 60 °C, 24 h.

In the absence of **Y-1**, no reaction occurred and **1u** was recovered intact. The spontaneous decomposition of amidines is very slow.[16] Considering the potential utility of the degradation of amidines in organic synthesis and its importance in the obliteration of the amidine-based pesticide residues which are harmful to human health and the environment, various alkene moiety-free amidines were subjected to degradation (Table 2). All *N*-methyl-*N*-phenyl amidines examined were smoothly converted to the corresponding nitriles and amines in good to excellent yields (entries 2–10). However, *N*,*N*-diethyl amidine and *N*,*N*-diisopropyl amidine degraded less readily, and a higher temperature was required (entries 11 and 12). For the less sterically demanding *N*-monosubstituted amidines, the substrates were not completely consumed even with an increased catalyst loading of 20 mol% and a longer heating time of 5 days, allowing the recovery of most of the starting material along with the desired products in low yields (entries 13–16).

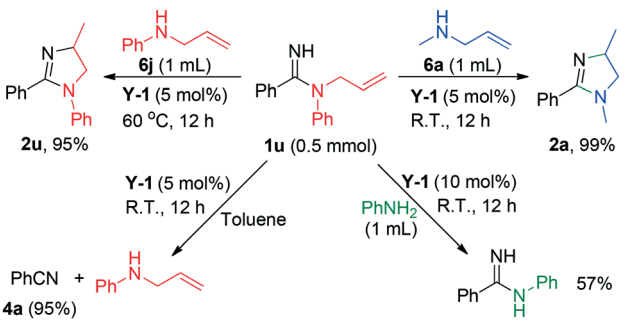
Tandem amidine reconstruction and cyclization

Given that a distinct approach relying on a β-nitrogen elimination step would offer the possibility of performing an addition of the resulting nitrile to another amine,[30d,31] we next explored a synthetic strategy based on the combination of amidine reconstruction with intramolecular alkene hydroamidination for the construction of 1,3-diazacycles. Significantly, the reaction of *N*-methyl-*N*-phenyl amidines with excess **6a**–**6e** in the presence of a catalytic amount of **Y-1** at room temperature under solvent-free conditions, enabled rapid and controlled access to the desired imidazolines in good to excellent yields (Table 3(a)). Furthermore, the tandem reaction is also effective for sterically hindered disubstituted aminoalkenes (Table 3(b) and (c)). In addition, this methodology was applicable to the synthesis of substituted tetrahydropyrimidines (Table 3(d)). Notably, the tandem amidine reconstruction/cyclization strategy for the synthesis of substituted imidazolines worked with more readily available *N*-monosubstituted amidines as well, despite the significant increase in the reaction time and temperature (Table 3(e)). This further enhances the compatibility of the present hydroamidination with the substrates.

Interestingly, it was found that using **6j** as a solvent prevented the competing nitrile extrusion of **1u** and furnished the cyclization product **2u** in 95% yield, whereas the reaction of **1u** with excess **6a** provided selectivity for the formation of **2a**. Furthermore, the treatment of **1u** with a large excess of $PhNH_2$ led to the formation of the amino-exchange product (Scheme 2). These results suggest that the selective conversion of one amidine to different types of products can be switched by using amine additive effects to control the relative rates of β-nitrogen elimination, alkene insertion, and amidinate ligand reconstruction of lanthanide amidinate intermediates, enabling the selective transformation of one less-reactive amidine precursor into a variety of 1,3-dinitrogen-containing heterocycles.

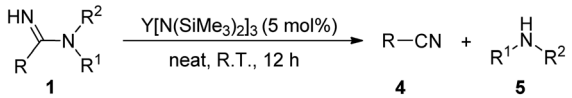
Mechanism studies

To elucidate the mechanism of the tandem amidine reconstruction/cyclization, the following reactions were investigated. The reaction of **Y-1** with 3 equivalents of **1ao** in toluene followed by recrystallization in a mixed solvent of toluene and THF afforded colorless crystals of **Y-2** in 87% yield (Scheme 3a). To our delight, the bond parameters clearly indicate that three amidinate ligands in the solid state



Scheme 2 Amine-controlled chemoselectivity switch for Y-catalyzed transformations of amidines.

Table 2 Yttrium-catalyzed degradation of amidines[a]



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Entry	Substrate R	Substrate R^1	Substrate R^2	Product	Yield (%)
1	Ph	Ph	Allyl	**4a**	95
2	Ph	Ph	Me	**4a**	93
3	*o*-MeC_6H_4	Ph	Me	**4b**	85
4	*p*-MeC_6H_4	Ph	Me	**4c**	91
5	*p*-ClC_6H_4	Ph	Me	**4d**	88
6	*p*-IC_6H_4	Ph	Me	**4e**	80
7	2-Thienyl	Ph	Me	**4f**	83
8	3-Pyridyl	Ph	Me	**4g**	87
9	4-Pyridyl	Ph	Me	**4h**	87
10	2-Naphthyl	Ph	Me	**4i**	93
11[b]	Ph	Et	Et	**4a**	67
12[b]	Ph	i-Pr	i-Pr	**4a**	75
13[c]	Ph	Ph	H	**4a**	13
14[c]	Ph	2,6-$Me_2C_6H_4$	H	**4a**	37
15[c]	*p*-MeC_6H_4	2,6-$Me_2C_6H_4$	H	**4b**	33
16[c]	Ph	2,6-$^iPr_2C_6H_4$	H	**4a**	35

[a] Reaction conditions: **1** (0.50 mmol), **Y-1** (5 mol%), toluene (2 mL), R.T., 12 h under N_2. The yields are of the isolated products. [b] 100 °C, 12 h. [c] **Y-1** (20 mol%), 100 °C, 5 days.

structure of **Y-2** feature two different tautomeric forms (Fig. 1). For one amidinate ligand the Y–N(internal) length of 2.447(2) Å is significantly longer than the Y–N(terminal) distance of 2.364(3) Å, which can formally be considered to be the donor- and σ-bonds (eqn (1), I), respectively.[32] This is similar to the situation of the yttrium *N*,*N*-disubstituted allyl amidinate intermediate, making it an advantage in the formation of a six-membered transition state required for the subsequent intramolecular addition to an alkene unit. On the contrary, the 1,3-H shift leads to the other amidinate ligands with a stronger coordination of the Y^{3+} ion to the internal N atom (average 2.380(2) Å) compared with the terminal N atom (average 2.431(3) Å) (eqn (1), III), thus preventing cyclization or nitrile extrusion. However, the ^{1}H NMR spectrum of **Y-2** in THF-d_8 implies that the hydrogen at the N atom is fluxional (one doublet at δ 5.67 ppm, J = 1.8 Hz), which is consistent with the observation that the sequential cyclization makes the reconstruction of *N*-monosubstituted amidine favorable.

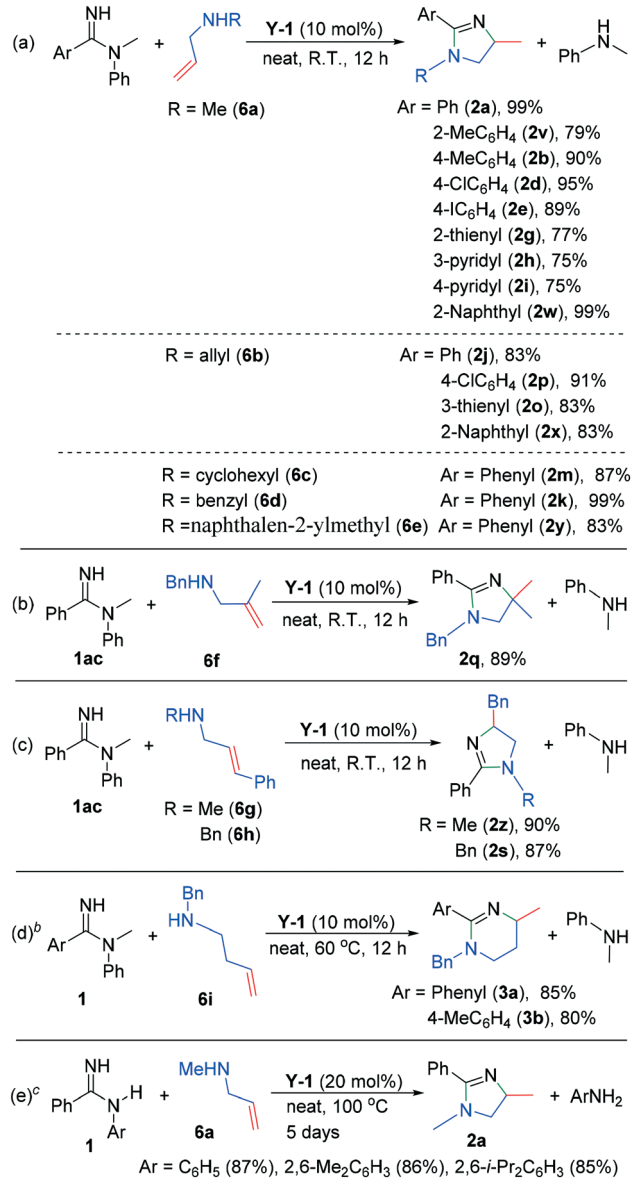
Heating a toluene solution of **Y-2** at 100 °C for 5 days followed by hydrolysis afforded PhCN and $ArNH_2$ in 43% and 35% yields, respectively (Scheme 3b). Furthermore, the reaction of **Y-2** with **6a** generated **2a** in 57% yield (Scheme 3c). The activity of **Y-2** for the catalytic reaction of **1ao** with **6a** was nearly same as that of **Y-1** (Scheme 3d). These results demonstrate that the formation and β-N elimination of yttrium amidinate intermediates are viable under the current conditions, and the liberated nitrile may reinsert into the newly formed Y–amido bond.

It is well-known that in most cases the amidinate ligands play the role of a spectator and do not participate in organometallic reactions.[6] In order to better ascertain whether **Y-1** merely plays the role of a Lewis acid catalyst or displays some specific deprotonation activity in the degradation and reconstruction of amidines, we examined the reaction of various amidines with amines or nitriles under different conditions. The treatment of **1ac** with a catalytic amount of **Y-1** in $PhNH_2$, *n*-$BuNH_2$ or Et_2NH at 60 °C allowed the isolation of the expected amino-exchange product (Scheme 4a), which provided a new method for the modification of acyclic amidines that are finding many diverse applications.[12–15,33,34] However, the amidine that lacks an NH moiety was an ineffective substrate for amidine degradation and reconstruction (Scheme 4b). It was also proven that no reaction took place under otherwise identical conditions when **Y-1** was replaced by an insufficiently basic Lewis acid $Y(OTf)_3$ or YCl_3 (Scheme 4c). These observations implied that the deprotonation of amidines to form yttrium amidinate species might be an essential step for amidine degradation and reconstruction. In addition, no product derived from tandem amidine reconstruction/cyclization was obtained when a mixture of **1a** and 4-MeC_6H_4CN in toluene was treated with **Y-1** (Scheme 4d). This would exclude the possibility that the hydroamidination proceeds through amidine degradation followed by the direct cycloaddition of nitrile with allylamine.

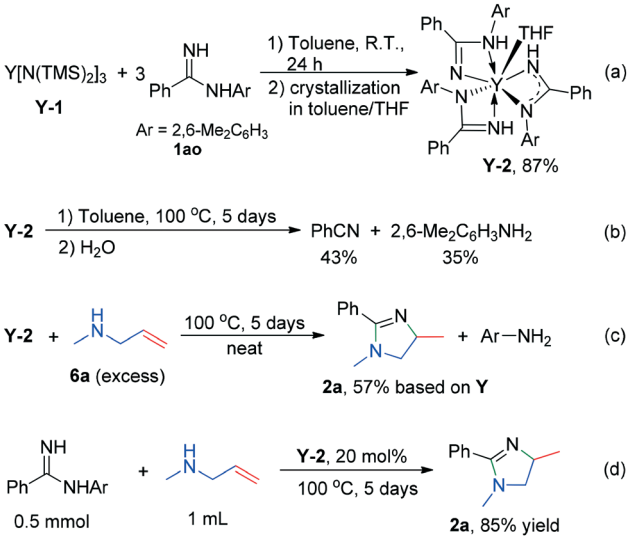
Consistent with the above observations, the ^{1}H NMR monitoring data (Fig. 2) reveal that the addition of 10 mol% **Y-1** to a mixture of **1ap** and **6a** in benzene-d_6 at room temperature led to the complete liberation of the $(Me_3Si)_2N$ ligand from **Y-1** rapidly,[19,26] and **1ap** was cleanly converted into 2,6-$Me_2C_6H_3NH_2$ and 4-MeC_6H_4CN at 100 °C within 1.5 h. The subsequent decrease of 4-MeC_6H_4CN is consistent with the formation of the target product **2b**.

Based on these results, a plausible mechanism for the tandem amino-exchange/cyclization of amidines with enamines is outlined in Scheme 5. First, an initial deprotonation of

Table 3 Tandem amidine reconstruction and cyclization[a]



[a] Reaction conditions: **1** (0.50 mmol), **Y-1** (10 mol%), **6** (1.0 mL), R. T., 12 h under N_2, isolated yields. [b] 60 °C, 24 h. [c] 100 °C, 5 days.



Scheme 3 Controlled experiments on the yttrium amidinate intermediates. (a) Isolation and structural characterization. (b) β-N elimination. (c) The feasibility of *in situ* reconstruction of amidinate ligand and sequential cyclization. (d) Catalytic activity estimation.

amidine **1** occurs to give an yttrium amidinate intermediate (**A**). **A** undergoes a β-N elimination to form the yttrium amido species **B**. Next, successive ligand substitutions afford a new amido complex **C**. Reinsertion of the nitrile fragment into the resulting Ln–N bond gives the yttrium amidinate **D**. Subsequently, the presence of a little monodentate coordination of amidinate to a Y center through the remote N atom at equilibrium driven by an alkene chelating interaction would constitute a key step of the catalysis to achieve the intramolecular addition of a C=C bond to the Ln–N(remote) bond of **E**, thus affording the 4-imidazolinylmethyl yttrium complex **F**. Finally, the predominant protonolysis of **F** with another amidine affords the corresponding substituted imidazoline product and regenerates the active intermediate **A**. It is clear that the β-N elimination and inaccessibility of a fluxional terminal N monodentate coordination of the amidinate ligands to the metal center do not favor the intramolecular alkene insertion into the yttrium–amidinate bond, and the presence of a suitable amine permits the control of the reactivity trend of the yttrium amidinate intermediates by the shift of equilibrium, enabling the occurrence of the tandem amidine reconstruction/ intramolecular alkene hydroamidination or precluding the amidine degradation.

The β-Carbon[35] and β-hydrogen[36] eliminations of late transition metal species have provided access to unique organic transformations that would otherwise be difficult to achieve. However, the C–N bond transformations involving the β-N elimination of the metal complex intermediate as an

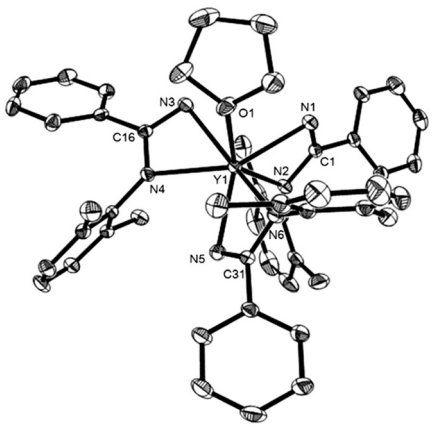
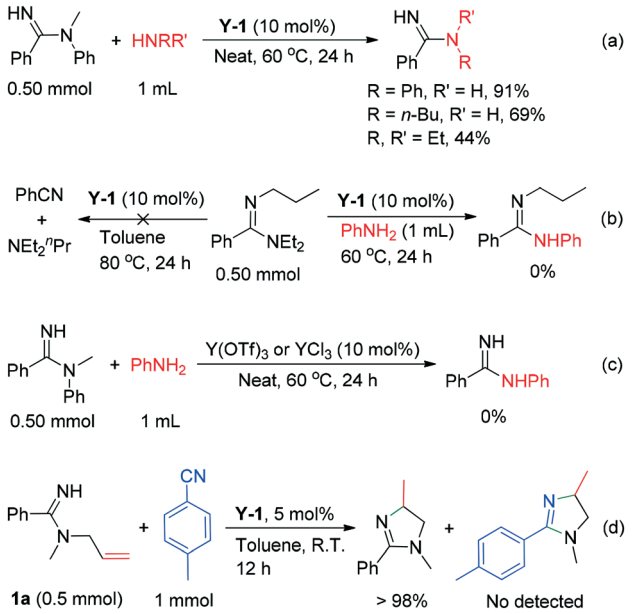


Fig. 1 Molecular structure of **Y-2**. Thermal ellipsoids are shown at 30% probability. Selected bond lengths (Å): Y1–N1 2.414(3), Y1–N2 2.366(2), Y1–N3 2.447(3), Y1–N4 2.395(2), Y1–N5 2.364(3), Y1–N6 2.447(2).



Scheme 4 Factors influencing reconstruction of amidines: (a) amine property. (b) Initial deprotonation of amidines playing a key role. (c) The role of catalyst basicity. (d) Cyclization proceeding *via* intramolecular addition of *N*-allyl amidinate yttrium complex rather than dipolar cycloaddition of nitrile to allylamine.

elementary step remain relatively little explored.[37] In particular, taking into consideration the limited knowledge in rare earth metal-based β-elimination events[38] and the prospective impact of C–N activation, we believe that the results will trigger an increasing interest in using the β-elimination of organometallic complexes of early transition metals as a key step for the design of new catalytic reactions.

Conclusions

In summary, the intramolecular hydroamidination of *N*-alkenylamidines is achieved by using a rare earth catalyst. Significant substrate flexibility and a simple and atom-economical procedure make this an attractive method for the synthesis of substituted imidazolines and tetrahydropyrimidines. Furthermore, mild methods have also been developed to allow for facile deamidination to release amine and nitrile, and for the selective transformation of amidines to those bearing different substituents at the N atom *via* an unusual β-N elimination of the yttrium amidinate intermediate. As an alternative approach for 1,3-dinitrogen-containing heterocycles, the tandem amidine reconstruction/cyclization strategy may circumvent the need for unavailable starting materials, which further enhances the compatibility and versatility of the alkene hydroamidination with the substrates. The results presented here not only demonstrate the synthetic potential and versatility of the lanthanide-catalyzed hydroamidination of alkenes, but also unravel that the selective conversion of one amidine into different types of products can be switched by using amine additive effects to control the relative rates of β-nitrogen

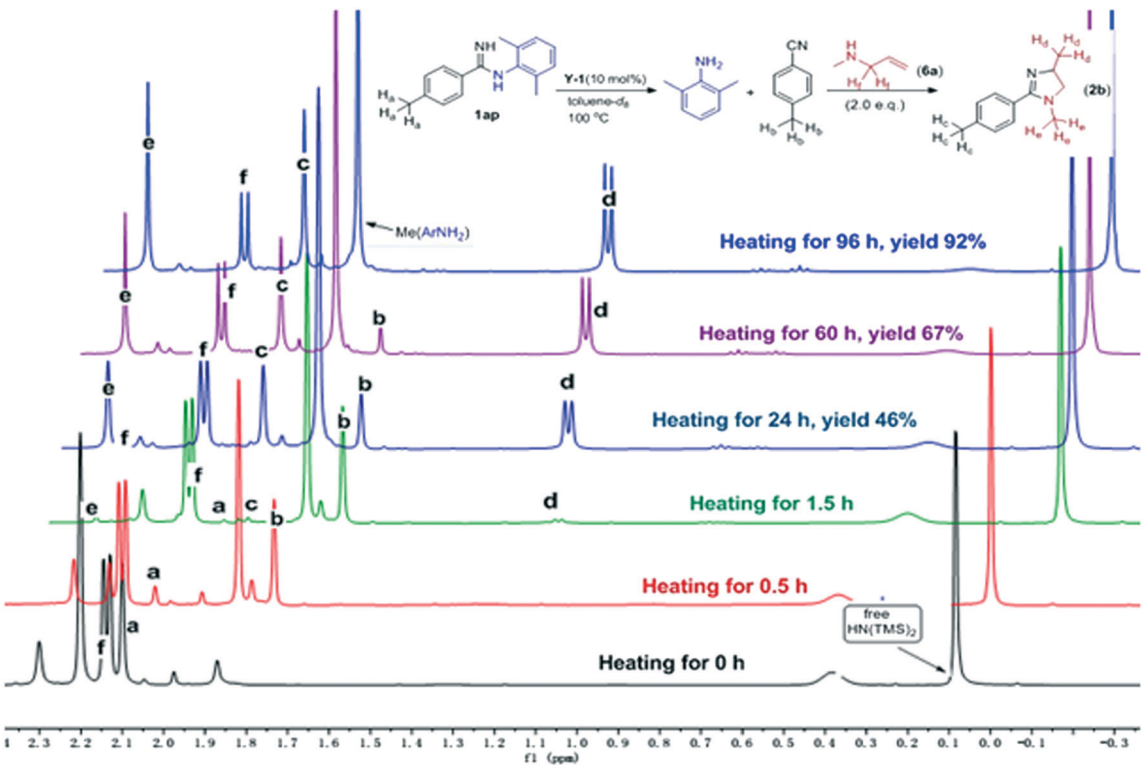
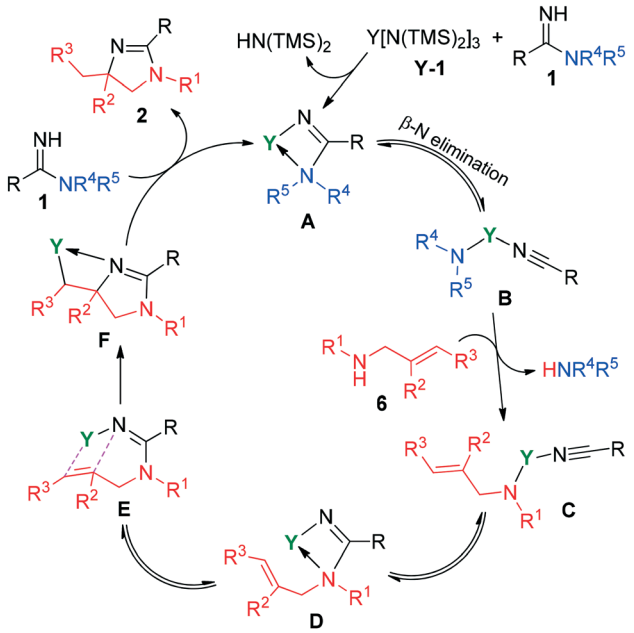


Fig. 2 ^{1}H NMR spectra for the progress of the reaction of **1ap** with **6a** using **Y-1** as the catalyst.



Scheme 5 Proposed mechanism for the tandem amino-exchange/cyclization of amidines with enamines.

elimination, alkene insertion, and amidinate ligand reconstruction of lanthanide amidinate intermediates in a mechanistically complex process. Further studies on synthetic applications are now in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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