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ARTICLE

Simple $ZnEt_2$ as catalyst in carbodiimide hydroalkynylation: structural and mechanistic studies

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Expanding the possibilities of use of simple and available $ZnEt_2$ as catalyst, the hydroalkynylation of carbodiimides with a variety of alkynes to obtain unsaturated substituted amidines is described in this work. Different stoichiometric studies allow to propose that amidinate complexes are intermediates in this catalytic process, produced by easy activation of the C-H bond of the alkyne, formation of alkynyl derivatives followed by a carbodiimide insertion step. Kinetics studies allowed the generation of a rate law for the hydroalkynylation of *N,N'*-diisopropylcarbodiimide with phenylacetylene which is second order in [carbodiimide], first order in [catalyst] and zero order in [alkyne], with a negligible PhC≡CH/PhC≡CD isotopic effect, consistent with a rate-determining state involving carbodiimide insertion. The hydroalkynylation reaction has been coupled with isocyanate (and isothiocyanate) insertion and intramolecular hydroamination to obtain imidazolidin-2-ones (or thione). The structures of different plausible intermediates have been determined by X-ray diffraction studies.

Introduction

Metal catalysis has a great impact in industrial processes including the production of "commodities" and fine chemicals. Nevertheless, the commercial use of the least abundant transition metals (e. g, Pd, Rh, Ru, Ir) in catalytic processes, as well as the growing trend in modern catalysis research towards the use of derivatives of the lanthanoids, show some disadvantages due to their low availability, high prices, or toxicity, which implies additional purification processes, especially when the final product has a pharmaceutical use. Hence, part of the actual research is focused, on the one hand, on their replacement by cheaper and less toxic metals with simple ligand systems, and, on the other hand, on the discovery of new protocols with such metals.[1] Therefore, the use of inexpensive, biocompatible and environmentally benign zinc compounds can be of great interest.[2] For example, well-known diethylzinc is a commonly used transmetallation reagent,[3] with an affordable price which makes it a very attractive precursor for applications in catalytic synthesis. In general, $ZnEt_2$ has been used as a precursor for well-defined or in situ formed complexes in a literature dominated by polymerization chemistry.[4] In contrast, the examples of use of this compound without auxiliary ligands are rare.[5]

Alkynes are among the most valuable functional groups in organic synthesis since they can be transformed to build new C-C or C–N bonds by catalytic methods.[6] On the other hand, carbodiimides are members of the heterocumulene family and they are part of a plethora of NH addition reactions mediated by metal complexes to obtain guanidines.[7]

Amidines, analogous to guanidines but with a CN_2 core, are synthesized by different methods involving amides, thioamides or nitriles.[8] Propiolamidines (or propargylamidines) (RN=C(C≡CR')(NHR)), which contain a C–C triple bond, introduce a new factor of potential reactivity, which can be exploited in the synthesis of complex organic heterocycles.[9] Although these molecules can be obtained by nucleophilic attack of alkynyllithium derivatives to carbodiimides, the yields are often low and the work–up, involving hydrolysis of the obtained amidinate salts, could lead also to the hydrolysis of the final moisture–sensitive amidine product.[10] As a new strategy, a wide variety of metal catalysts have successfully been employed in the atom–economic synthesis of these propiolamidines by addition of terminal alkynes to carbodiimides. Pioneering work was carried out by Süss–Fink who employed a bimetallic Ru–Co cluster to obtain propiolamidines at high temperature.[11] Since then, the majority of the few and recent studies has focused on rare–earth metal catalysis.[10,12] Outstandingly, carbonylpropiolamidine derivatives with potential biological applications were also prepared under mild conditions *via* a copper–catalysed multicomponent reaction (MCR) between terminal alkynes, acid chlorides and carbodiimides.[13]

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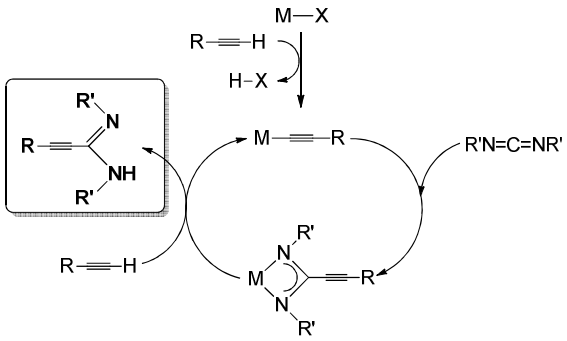
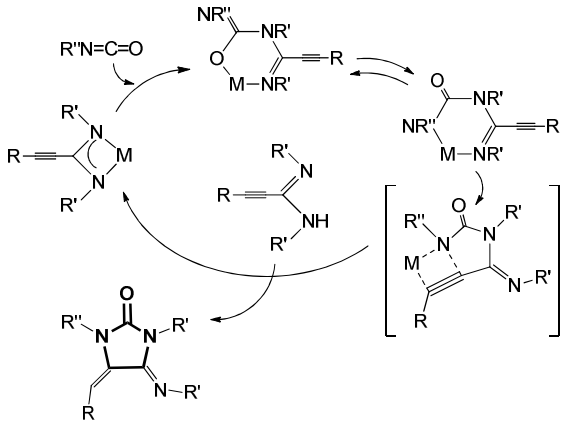
A valuable alternative has been tabled by using main group metal catalysts. On the one hand, simple lithium hexamethyldisilazide ($LiN(SiMe_3)_2$) opened the way to these earth–abundant elements, allowing to obtain propiolamidines in practically quantitative yields.[14]



Scheme 1. Proposed catalytic synthesis of propiolamidines.



Scheme 2. Proposed catalytic coupling and cyclization of propiolamidines and isocyanates.

For example, a calcium amido–β–diketinimato complex catalysed the reaction between phenylacetylene and carbodiimide, in a process where the catalyst lost the ligands to give the real undetected active species.[15] Finally, the related work of Coles with magnesium reagents, as well as the use of homoleptic heavier alkaline earth amido compounds by Hill, are good benchmarks for the research on simple and available catalysts for this efficient C–C bond formation reaction.[16]

In all cases, these catalytic reactions were proposed to proceed *via* propiolamidinate intermediates, produced by the insertion of a carbodiimide molecule into a reactive metal–acetylide bond. The catalytic cycle restarts by protonolysis with acetylene to release the propiolamidine as shown in Scheme 1.

Recently, Hill has reported the preparation of imidazolidinones, and other similar heterocycles, using a strontium amido derivative as an efficient catalyst.[17] The synthesis of these cyclic ureas are of special interest as they are found in many biologically active molecules, including potent anti–HIV agents.[18] Many of these heterocycles can be synthesized by other catalytic methods based in less abundant transition metals or by multistep processes with their respective undesired subproducts.[19] In the elegant process described by Hill, the reaction takes place *via* a consecutive formation of propiolamidine, the addition of an isocyanate and the consequent intramolecular hydroamination (Scheme 2).

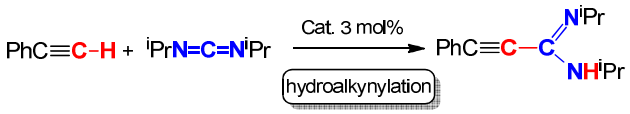
In the last years, our laboratory has been actively engaged in developing the catalytic guanylation of amines employing $ZnEt_2$.[20] In these processes, $ZnEt_2$ activates amine N–H bonds to obtain reactive amido species towards the carbodiimide insertion. Although references about Zn–catalysed reactions involving the functionalization of alkynes are well documented,[6g] to the best of our knowledge no cases of the use on those hydroalkynylation reactions have been reported so far. As part of our ongoing research regarding the chemistry of $ZnEt_2$ as a catalyst, we now focused our attention into the use this simple compound in the catalytic activation and addition of terminal alkynes to carbodiimides to obtain substituted propiolamidines. Propiolamidinate zinc complexes have been obtained and fully characterized, and proposed as plausible intermediates. Mechanistic studies are also presented to propose a catalytic cycle. Finally, the reaction was coupled to the addition of isocyanates (and isothiocyanate) allowing the synthesis of substituted imidazolidinones through intramolecular hydroamination of intermediate ureas.

Results and Discussion

Catalytic hydroalkynylation studies

As stated previously, $ZnEt_2$ **1** shows excellent results for the construction of C–N bonds of guanidines.[20] Encouraged by these results we decided to expand the scope of this catalyst into the realm of C–C bond formation.

Table 1. Optimization of the reaction conditions



Entry	Catalyst	Solvent	T (°C)	t (h)	Yield (%)[a]
1	$ZnEt_2$	Toluene-d_8	25	24	24
2	$ZnEt_2$	Toluene-d_8	70	1	51
3	$ZnEt_2$	Toluene-d_8	70	7	65
4	$ZnEt_2$	Toluene-d_8	70	16	75
5	$ZnEt_2$	Toluene-d_8	70	24	90
6	$ZnEt_2$	THF-d_8	70	24	48
7	$ZnEt_2$	CD_2Cl_2	70	24	0
8	$ZnMe_2$	Toluene-d_8	70	24	75

[a]Yields obtained *via* spectroscopic ^1H NMR. Reactions carried out using 0.5 mL of solvent, 0.5 mmol of PhC≡CH, 0.5 mmol of DIC, and 0.015 mmol of catalyst (3 mol%).

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The effectiveness of **1** in the catalytic addition of terminal alkynes to carbodiimides was initially investigated on an NMR scale in toluene−d_8 using *N,N'*−diisopropylcarbodiimide and phenylacetylene, as a model reaction (Table 1). A control reaction confirmed that the propiolamidine was not formed in the absence of **1**. In contrast, a catalyst loading of 3 mol% yielded 24% of the amidine [^{i}PrN=C(C≡CPh)(NH^{i}Pr)] **2a** after 24 h at room temperature (Table 1, entry 1). More respectable yields were obtained with increased temperature and reaction times (Table 1, entries 2−5), with good yields (~90%) at 70 °C and 24 h. An important solvent effect was observed when the more polar THF−d_8, with greater coordination ability, or CD_2Cl_2 were employed. In the latter case, the reaction was inhibited (Table 1, entries 6 and 7). Finally, the use of the closely−related, but more expensive $ZnMe_2$ did not lead to higher yields (Table 1, entry 8).

Table 2. Hydroalkynylation of carbodiimides.

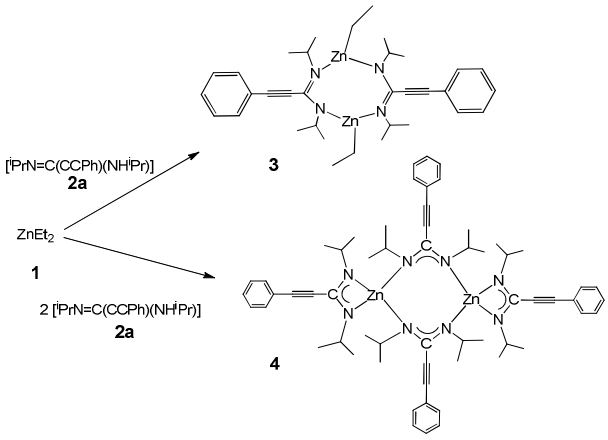
Entry	Alkyne	Carbodiimide	Yield (%)[a]
1	PhC≡CH	DIC	**2a**/90
2	PhC≡CH	DCC	**2b**/89
3	PhC≡CH	EtNCN^{t}Bu	**2c**/55
4	*p*FC$_6$H$_4$C≡CH	DIC	**2d**/83
5	*p*CF$_3$C$_6$H$_4$C≡CH	DIC	**2e**/90
6	*p*CF$_3$OC$_6$H$_4$C≡CH	DIC	**2f**/85
7	*p*MeOC$_6$H$_4$C≡CH	DIC	**2g**/90

[a]Yields obtained *via* spectroscopic ^{1}H NMR. Reactions carried out using 0.5 mL of solvent (toluene-d^8), 0.5 mmol of alkyne, 0.5 mmol of carbodiimide, and 0.015 mmol of catalyst (3 mol%), at 70 °C, for 24 h.

Further studies were performed with a range of terminal alkynes and carbodiimides (Table 2). All reactions went smoothly providing the corresponding propiolamidines. Like *N,N'*−diisopropylcarbodiimide (DIC), *N,N'*−dicyclohexylcarbodiimide (DCC) also reacts with phenylacetylene with good conversions, whereas the steric demand of bulkier *N,N'*−EtNCN^{t}Bu slightly affects the yield (Table 2, entries 1−3). The reactions using alkynes with electron−withdrawing or donor substituents at the phenyl ring occur also with good yields (Table 2, entries 4−7). It is worth noting that catalyst **1** displayed remarkable functional group tolerance and groups such as F or OR were unaffected under the reaction conditions used. This catalytic activity is comparable to that reported using magnesium alkyls or strontium amides as precatalysts.[16]

Stoichiometric and Mechanistic studies

The knowledge of the catalytic mechanisms is of the utmost importance because it helps design new catalysts and leads to further synthetic developments. In this context, to gain mechanistic insights into this catalytic process, a series of stoichiometric reactions were carried out. From Scheme 1, it seems reasonable to assume from previous reports that the catalytic cycle starts with the initial metalation of the terminal carbon of the alkyne,[6f] to form a reactive zinc acetylide which, after insertion of the corresponding carbodiimide *via* an associative bond metathesis, affords amidinate intermediates.[16a] Unfortunately, reactions of $ZnEt_2$ with PhC≡CH give, in addition to ethane, a very insoluble white solid, likely due to the formation of polymeric aggregates of Zn(C≡CPh)$_2$ or ZnEt(C≡CPh).[21] Surprisingly, addition of excess of PhC≡CH and DIC results in the redissolution of this precipitate to form complex mixtures which, after warming at 70 °C for several hours, yield the corresponding amidine **2a**. These facts allow us to conclude that additional alkyne or carbodiimide form soluble adducts with the polymeric alkynyl species, as was previously observed with phosphanes or THF coordinated to ZnEt(C≡CPh).[22]



Scheme 3. Synthesis of zinc propiolamidinates.

In fact, labile coordination of carbodiimide to an yttrium complex has been proposed as intermediate in catalytic hydroalkynylation,[12d] and two zinc complexes with coordinated carbodiimide have been isolated.[23] The requirement of this coordination to the metal center could be the origin of the observed negative effect of THF on the catalytic activity (Table 1, entry 6).

Among the known routes to obtain new guanidinate or amidinate complexes, the direct reaction between the proligand and a metal complex containing ligands that are susceptible to cleavage by protonolysis has been widely used.[24] As an alternative to obtain these amidinate complexes as plausible central active species, stoichiometric reactions of $ZnEt_2$ and preformed amidine **2a** were performed in 1:1 and 1:2 metal:amidine ratios (Scheme 3).

In the first case, ^{1}H NMR spectroscopy showed complete conversion after a few minutes at room temperature. This new complex **3** shows a simple pattern in its spectra (See Figure S1). In addition to phenyl protons, methyl and methine protons of the isopropyl groups appear as a doublet and a septuplet at δ 1.37 and 4.25 ppm, respectively, along with a triplet and a quadruplet, at δ 1.67 and 0.82 ppm, respectively, assigned to a Zn−ethyl moiety, a finding that indicates the structure of a very symmetric complex of formula [ZnEt{C(C≡CPh)(N^{i}Pr)$_2$}] **3**. It should be noted the excellent selectivity of the process towards the heteroleptic

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mono–chelated complex, stable in solution for days, under inert atmosphere.

Fortunately, suitable X–ray quality crystals of **3** were obtained from a saturated solution in hexane. The molecular structure and the atomic numbering scheme are shown in Figure 1. The complex appears to be a dinuclear eight–membered metallacycle system in solid state, which adopts a boat–type conformation in which every zinc metal center bears a terminal ethyl group and an amidinate ligand acting as bridging monodentate μ–κ^1–κ^1 donor in remarkable contrast with most amidinate complexes, which typically adopt a chelate mode.

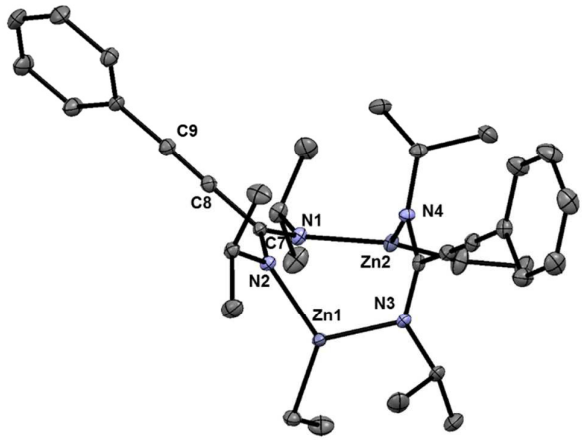

Figure 1. Molecular structure of compound **3**: H atoms are omitted for clarity and ORTEP ellipsoids are plotted at 50% probability level.

The chelate coordination was ruled out since the Zn1–N1 distance of 2.893 Å (and Zn2–N3, 2.838 Å) exceeds the typical distance for a dative Zn–N bond of 2.4 Å.[25] As a result of this coordination mode, the zinc atoms adopt a trigonal–planar coordination geometry (sum of bond angles at Zn1 360°; Zn2 359.5°). We would like to note that, although pseudotetrahedral is the habitual coordination mode in zinc amidinate complexes in the solid state,[26] very few examples of zinc amidinate complexes with trigonal coordination have been previously described, usually with bulky substituents on nitrogen atoms.[23,26b,f,g,i] The bond lengths Zn1–N2 or Zn2–N1 (2.007 and 2.004 Å, respectively) are comparable with those of $[\{EtC(N^iPr)_2\}ZnEt]_2$.[23b] Finally, the amidinate ligands show a uniform delocalization in the CN_2 core (C7–N1 1.342 Å, C7–N2 1.320 Å, sum of bond angles at C7 360°).

When a 1:2 metal:amidine ratio was used, the complete conversion of the starting reagents takes place after 2h at room temperature. ^{1}H NMR spectra in C_6D_6 show, at the end of the reaction, three similar doublets and their corresponding septuplets, assigned to three inequivalent isopropyl groups, a pattern hard to fit with the expected symmetric bisamidinate complex $[Zn\{C(C{\equiv}CPh)(N^iPr)_2\}_2]$ (see Figure S2). To obtain more information about the real structure of this new complex, suitable X–ray quality crystals were obtained from a saturated solution in hexane. Diffraction studies (Figure 2) reveal a dinuclear compound with two types of amidinate ligands, one coordinated in a chelate κ^2– fashion and the other one bridging both metal nuclei in a μ–κ^1–κ^1– fashion, which produces a distorted pseudotetrahedral coordination around the zinc atoms, with a bite angle for the chelate ligand of 65.1° and a N1–Zn1–N3 angle of 130.2°. Like compound **3**, complex **4** shows delocalization at the amidinate core in both chelate and bridging ligands (C–N ~1.33 Å, sum of bond angles at C1 and C31 ~ 360°).

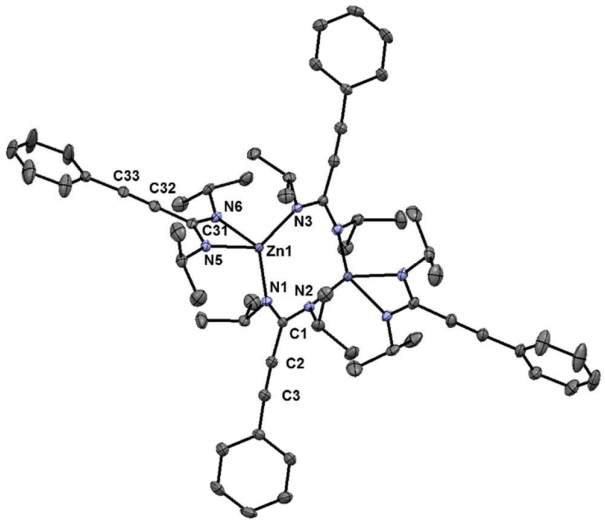

Figure 2. Molecular structure of compound 4: H atoms are omitted for clarity and ORTEP ellipsoids are plotted at 50% probability level.

The distribution of the ligands in complex **4** explains the presence of only two of the three sets of signals assigned to isopropyl groups observed in the ^{1}H NMR spectra. When these C_6D_6 solutions where heated, a reversible decrease in intensity of two of the doublets and the concomitant increase of the less shielded one was observed. In fact, a thermodynamic equilibrium between two different species was reached at room temperature, lying towards a symmetric species upon heating. This behavior was studied in more detail and the equilibria were monitored by ^{1}H NMR variable temperature experiments (See Figure S3). Changes in the relative intensity of methyl protons were followed, this allowing us to calculate K_{eq} at different temperatures. The thermodynamic parameters ΔH^0 of 95.5 kJ.mol^{-1} and ΔS^0 of 278.9 J.mol^{-1}K^{-1} were obtained from the corresponding van't Hoff plot, wich allowed us to calculate a value for ΔG^0 of 12.0 kJ.mol^{-1} at 298K (See Figure S4).

These results are in accordance with an associative process at lower temperatures, to obtain the characterized dinuclear compound, albeit low energy is needed to produce the inverse, dissociative, process to give a mononuclear compound with two equivalent amidinate ligands (shown as chelate ligands, although a hemi–labile form cannot be completely ruled out), as depicted in Scheme 4. This kind of equilibrium has not been observed previously in propiolamidinate systems,

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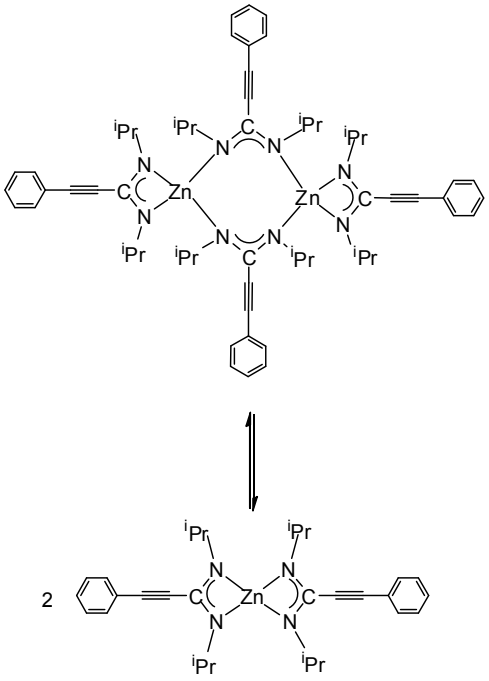
although a similar equilibrium was found in a magnesium dimer compound with $[CMe(N^iPr)_2]^-$ ligands and the rearrangement of the propiolamidinate units from a chelating into a bridging binding mode has also been postulated in the synthesis of zinc clusters.[27,26g]



Scheme 4. Equilibrium between dimeric and monomeric forms of **4**.

Although different examples of propiolamidinate complexes of rare–earth and group 2 metals are known, [10,12c,d,g,i,15,16a,c,28] these are the first examples of fully characterised zinc propiolamidinates and promising candidates with potential applications in catalysis and materials chemistry as analogous guanidinate complexes.[26j,29] In fact, ^{1}H NMR monitoring of the reaction of an equimolar mixture of DIC and PhC≡CH in the presence of 3 mol% of complexes **3** or **4** indicated the catalytic formation of amidine **2a** in ~80% yield after 24 h at 70 °C, showing a similar efficiency to that found for compound **1**. This confirms the involvement of amidinate intermediates in the catalytic cycle (vide supra). When carrying out the reaction between complex **4** and two equivalents of PhC≡CH, in C_6D_6 solution in a NMR tube, a fast transformation takes place, to obtain a new compound (or mixture of compounds), the main feature of which being a broad peak near δ 9 ppm, along with broad peaks assigned to phenyl and isopropyl groups, and free alkyne, as observed in its ^{1}H NMR spectra (See Figure S5). Surprisingly, when PhC≡CD (99% deuterated) was used, that peak was considerably reduced, the rest of the spectrum remaining unaltered.

In order to stablish the exact structure of this new compound, suitable X–ray quality crystals were obtained from a toluene–pentane solution. Diffraction studies (Figure 3) reveal a four–coordinate Zn center, with two σ–bonded alkynyl and two neutral amidine ligands, the latter coordinated through the N=C nitrogen atom, with a C1–N1 bond distance (1.306Å) slightly shorter than that of the C1–N2 bond (1.352 Å). The Zn–C≡C angles (174.30°) were very close to the linearity necessary to form a σ–bonded alkynyl ligand.

A reasonable mechanism for the formation of **5** involves initial π–interaction between free alkyne and the Lewis acidic center of complex **4**. Such coordination could to enhance the acidity of the C–H bond. The Brönsted basicity of the labile non–coordinated N atom of the amidinate ligands prompts deprotonation of the alkyne–CH bond affording coordinated amidines and the alkynyl–zinc groups. This proposal is reminiscent of the C–H bond activation occurring in frustrated Lewis pairs (FLP) for terminal alkynes (Scheme 5).[30]

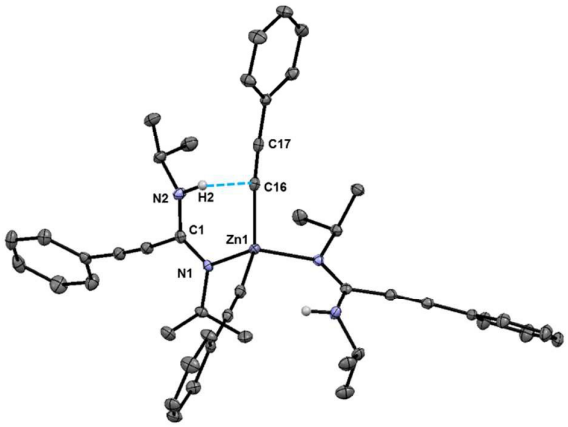
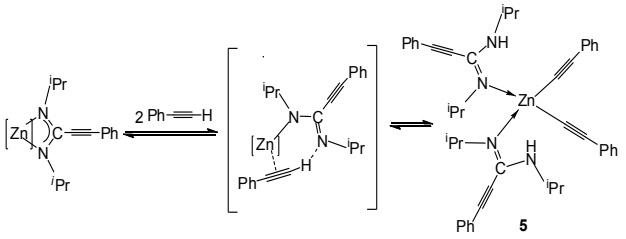


Figure 3. Molecular structure of compound **5**: H atoms, excepting H2, are omitted for clarity and ORTEP ellipsoids are plotted at 50% probability level.



Scheme 5. Proposed mechanism for the formation of **5**.

An intramolecular NH---C hydrogen bond (2.125 Å) was observed between a nitrogen atom of the neutral guanidine (N2) and the Cα atom of the alkynyl ligand, well below the sum of Van der Waals radii for these atoms (1.20 Å for H, 1.70 Å for C).[31] That could cause the observed downfield shift of the NH proton in NMR spectra and the broadening of this and other peaks, by a probable fast exchange of the labile proton atom between the nitrogen and carbon atoms. When crystals of compound **5** were dissolved in C_6D_6, their ^{1}H NMR spectra were identical to those obtained from the reaction between **4** and two equivalents of alkyne. A variable temperature ^{1}H NMR experiment in toluene–d^8 reveals a complex equilibrium between different species showing simultaneously dynamic processes. We observed that the relative intensity of the peak

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assigned to the CH proton of free alkyne decreases as temperature was lowered. Alongside, the broad peak near δ 9 ppm starts to decrease in intensity and a new broad signal near δ 9.8 ppm began to emerge already at -10 °C, being a clear doublet at -90 °C. The latter peak was coupled with a multiplet near δ 4 ppm, which were assigned to NH and CH(^{i}Pr) groups, respectively, in a coordinated amidine, probably affected by the NH---C weak interaction commented above. Another doublet at near δ 3.7 ppm assigned to an unaffected NH(^{i}Pr) group can be also observed at this temperature. In addition, two pairs of broad doublets were tentatively assigned to methyl groups in two types of coordinated amidines (see Figure S6).

We believe that a complex similar to **5** participates in the catalytic cycle as the resting state of the catalyst, as the characteristic peak at δ 9 ppm was observed in the NMR spectra at the end of most of the described catalytic studies. Thus, coordinated amidines could be easily removed by two carbodiimide molecules, followed by carbodiimide insertion to restart the cycle. For the first time, this kind of necessary intermediate in hydroalkynylation processes has been detected, isolated and structurally characterized. In addition, it should also be pointed out that, as commented before,[6g] the alkynyl zinc derivatives show interesting applications in organic synthesis, so such straightforward activation of terminal alkynes by means of the complex **4** opens interesting reactivity avenues for this complex beyond the hydroalkynylation process, potentially including the activation of other σ–bonds, *via* FLP chemistry.

To gain further insight into the formation of propiolamidines, quantitative kinetic data of the catalytic hydroalkynylation of *N,N'*–diisopropylcarbodiimide with PhC≡CH in the presence of $ZnEt_2$ **1** as catalyst were carried out in toluene–d_8. The reaction rates of the hydroalkynylation reaction at 70 °C were monitored over a period of three half–lives by ^{1}H NMR spectroscopy, using tetrakis(trimethylsilyl)silane as internal standard. Initially the order of the reaction with respect to DIC concentration ($[DIC]_0$ = 230 mM) was determined keeping the concentration of alkyne virtually unaltered. The study started by using 3 mol% of catalyst **1** ([**1**] = 7 mM), and the carbodiimide to alkyne molar ratio was stablished at 1:10 to keep approximately zero–order conditions for the alkyne. A plot of ln[DIC] against time did not provide a linear relationship, and the data fit better with a second–order kinetic behavior (Figure 4, left). The observed second order behavior with respect to [DIC] could implicate the formation of a compound similar to **5** with two coordinated molecules of carbodiimide and the consequent insertion of these carbodiimides in the Zn–C bond, as the rate–determining step.

Next, we determined the order of the reaction with respect to the concentration of PhC≡CH. During this study we stablished a relative PhC≡CH to DIC ratio of 1:10. Variation of the alkyne concentration provided evidence of a zero–order dependence of the reaction rate on alkyne concentration (Figure 4, right). Global pseudo–second order with respect to DIC concentration was confirmed when the reaction was monitored using equimolar concentrations of both reagents (Figure 5, left). In this case, the apparent constant rate was observed to be reduced by one order of magnitude due to the reduction of the initial alkyne concentration by also one order, suggesting a dependence on this initial concentration. Kinetic analysis of the reaction using PhC≡CD in the same conditions yielded a negligible kinetic isotopic effect (KIE) of k_H/k_D = 0.88, thus the protonolysis of $ZnEt_2$, or that of an intermediate amidinate complex, by the alkyne are unlikely to be rate–determining (Figure 5, left). Furthermore, initial addition of the amidine ($[amidine]_0$ = 120 mM) does not result in any substantial variation of the reaction rate (Figure S7), in contrast with the product inhibition observed with a strontium amido complex.[16c]

The first order rate of reaction with respect to catalyst concentration was confirmed conducting experiments at different catalyst precursor concentrations and fixing the carbodiimide to alkyne molar ratio at 1:10 (Figure 5, right).

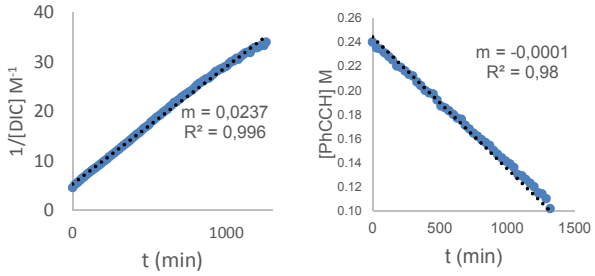

Figure 4. Left: second order kinetic analysis of the NMR scale reaction of N,N'–diisopropylcarbodiimide (0.23 M) with PhC≡CH (2.3 M) in toluene–d_8 (total volume 0.8 ml) with 3 mol% of **1** at 70 °C. Right: zero order kinetic analysis of the NMR scale reaction of N,N'–diisopropylcarbodiimide (2.3 M) with PhC≡CH (0.23 M) in toluene–d^8 (total volume 0.8 ml) with 3 mol% of 1 at 70 °C.

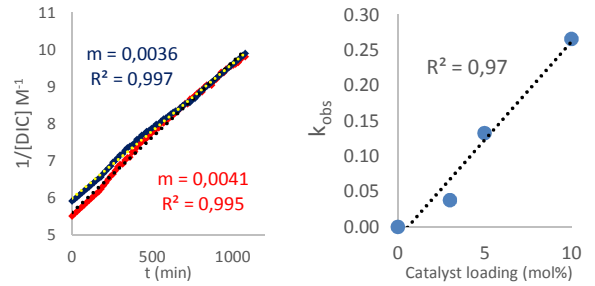

Figure 5. Left: second order kinetic analysis of the NMR scale reaction of *N,N'*–diisopropylcarbodiimide (0.23 M) with PhC≡CH (blue) or PhC≡CD (red) (0.23 M) in toluene–d_8 (total volume 0.8 ml) with 3 mol% of **1** at 70 °C. Right: linear correlation between the observed rate constant k and catalyst loading (mol%).

On the basis of these analyses, we propose the formulation of a rate law for the hydroalkynylation of N,N'–diisopropylcarbodiimide with phenylacetylene catalysed by 1 of the form shown in Equation (1).

$$\frac{-d[DIC]}{dt} = k.[\mathbf{1}][PhCCH]_0.[DIC]^2 \qquad (1)$$

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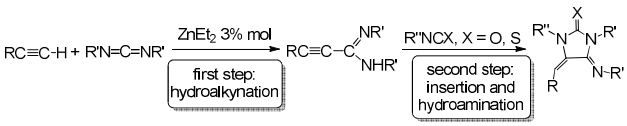
Catalytic intramolecular hydroamination studies

Considering the effectiveness of compound **1** as catalyst for hydroalkynylation under mild conditions, we decided to study the possibility of coupling this reaction with the addition of isocyanates, analogously to the reported catalytic activity proved by group 2 metal amido species.[17] The proposed pathway implied isocyanate insertion in an amidinate intermediate to obtain a κ^2–*N,O*–chelate which isomerises to the κ^2–*N,N* form necessary for an intramolecular hydroamination process, followed by protonolysis by an amidine molecule, to obtain the corresponding imidazolidin–2–ones (see Scheme 2).

On the other hand, $ZnEt_2$, activated by $[PhNMe_2H][B(C_6F_5)_4]$, has been recently described to show high reaction rates for the addition of aniline derivatives to primary alkynes in an intermolecular hydroamination process.[32] Likewise, the cyclization of alkynyl amides to form the corresponding nitrogen–containing heterocycles mediated by $ZnEt_2$ has also been reported.[5d]

Table 3. Alkyne, carbodiimide and heterocumulene scope for the catalytic synthesis of imidazolidin–2–ones (or thione).



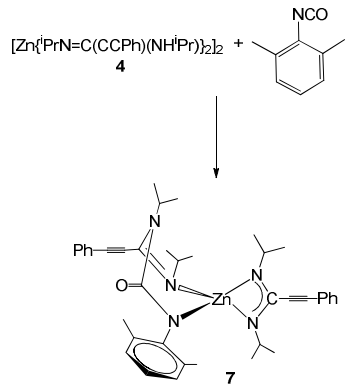
Entry	Alkyne	Carbodiimide	RNCX	Yield (%)[a]
1	PhC≡CH	DIC	PhNCO	**6a**/95
2	PhC≡CH	DCC	PhNCO	**6b**/88
3	PhC≡CH	EtNCN^{t}Bu	PhNCO	**6c**/83
4	PhC≡CH	DIC	PhNCS	**6d**/91
5	PhC≡CH	DIC	*p*MeC$_6$H$_4$SO$_2$NCO	**6e**/90[b]
6	PhC≡CH	DIC	2,6-Me$_2$C$_6$H$_4$NCO	**6f**/95
7	PhC≡CH	DIC	*t*BuNCO	**6g**/0[c]
8	*p*F-PhC≡CH	DIC	PhNCO	**6h**/91
9	*p*CF$_3$PhC≡CH	DIC	PhNCO	**6i**/94
10	*p*CF$_3$OPhC≡CH	DIC	PhNCO	**6j**/90
11	*p*MeOPhC≡CH	DIC	PhNCO	**6k**/90

[a] Yields obtained *via* spectroscopic ^{1}H NMR with respect to the urea. Reactions carried out using 0.5 mL of solvent, 0.5 mmol of alkyne, 0.5 mmol of carbodiimide, and 0.015 mmol of catalyst (3 mol%), at 70 °C, for 24 h, and then 0.5 mmol of isocyanate (or isothiocyanate), at 70 °C, for 24h. [b] Obtained after 7h of reaction. [c] The reaction yields the urea without cyclization.

Keeping this in mind, the catalytic activity of $ZnEt_2$ with different alkynes, carbodiimides and isocyanates (and one isothiocyanate) was checked in order to test the versatility of the simple zinc compound **1** (Table 3). As one can draw from Scheme 2, the reaction is favoured with electron–withdrawing substituents in the C≡C triple bond, increasing the electron–deficiency and assisting the nucleophilic attack. Following the catalytic cycle, in a first step, the amidines were obtained as described previously, followed by the addition of the heterocumulene molecule. The first observation was, regardless of the isocyanate used, the almost quantitative formation of *open* ureas of the type RC≡C(NR')(NR'(CO)NHR") in few minutes at room temperature, displaying a characteristic downfield shifted peak, assigned to the NH moiety in the NMR spectra. These would be the true starting reagents to be transformed into the corresponding heterocycles. In fact, after warming for 24 h at 70 °C, the corresponding cyclic ureas were obtained in good yields (Table 3). The *open* urea obtained from ^{t}BuNCO did not undergo the intramolecular cyclization probably due to the bulkyness of the isocyanate substituent (entry 7, Table 3).

Single crystals adequate for X–ray diffraction studies were obtained from the NMR scale reaction for (4Z,5E)–4–benzylidene–3–(2,6–dimethylphenyl)–1–isopropyl–5–(isopropylimino)imidazolidin–2–one **6f** (entry 6, Table 3). The molecular structure is displayed in Figure S8. The bond lengths and angles are within the range expected for these imidazolidin–2–ones.[17]

We propose that the reaction could take place through an insertion reaction of the isocyanate into a zinc amidinate, as occurs for group 2 catalysts. To gain insights into these hydroamination reactions, we carried out the reaction of complex **4** with 2,6–$Me_2C_6H_4NCO$. Regardless of the stoichiometry, only one equivalent of isocyanate reacts with the zinc complex, to obtain the heteroleptic imidamidate complex **7**, in quantitative yield in few minutes (Scheme 6).



Scheme 6. Synthesis of complex **7**.

The ^{1}H NMR spectra of **7** in C_6D_6 show, in addition to aromatic peaks, four doublets between δ 1 and 1.9 ppm, coupled in pairs with two multiplets at near δ 4.15 and 4.5 ppm, and assigned to isopropyl groups. One singlet in the δ 2.5 ppm region indicates that the rotation of the 2,6–dimethylphenyl group is not hindered in this molecule at room temperature (See Figure S9).

Crystals of compound **7** suitable for an X–ray diffraction study were grown from a concentrated toluene/hexane solution and the molecular structure is represented in Figure 6.

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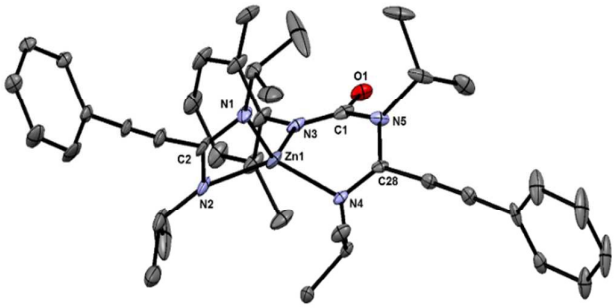

Figure 6. Molecular structure of compound **7**: H atoms are omitted for clarity and ORTEP ellipsoids are plotted at 20% probability level.

This study revealed complex **7** to be a pseudotetrahedral zinc complex with an amidinate and an imidamidate *N,N'*–chelate ligands, the latter forming a 6–membered [ZnNCNCN] boat–like metallacycle. This contrasts with the structure obtained for a similar bis(imidamidate) magnesium complex, where the ligands adopt a *N,O*–chelate ligand coordination, which would require an isomerization prior to the intramolecular hydroamination (See Scheme 2), no longer necessary for the zinc complex.[17] Although complex **7** appears to be chiral in the solid state, a rapid dynamic boat–to–boat inversion of the metallacycle in solution results in the equivalence of both isopropyl groups of the amidinate ligand. However, the methyl groups within these isopropyl groups are diastereotopic. This would explain the presence of four similar doublets in the ^{1}H NMR spectra, two of them assigned to the isopropyl moieties in the metallacycle and the other two corresponding to each pair of equivalent diastereotopic methyls. This was confirmed by the presence of only three peaks assigned to the methine carbon atoms by means of *g*HSQC experiments (See Figure S10).

Also, unlike the aforementioned magnesium derivative, compound **7** was stable in solution for days, under inert atmosphere, with no proof of isocyanate de–insertion. Participation of imidamidate species, similar to **7**, in the catalytic process of intramolecular hydroamination was confirmed, using **7** as catalyst in the coupling and cyclization of **2a** and 2,6–$Me_2C_6H_4NCO$. As commented above, instantaneous reaction between amidine and isocyanate gives rise to the corresponding *open* urea. After warming for 24 h at 70 °C, full conversion of this urea to the cyclic form was obtained.

Taking into account the different studies presented here, the coupled catalytic cycles for both hydroalkynylation and intramolecular hydroamination are proposed in Figure 7.

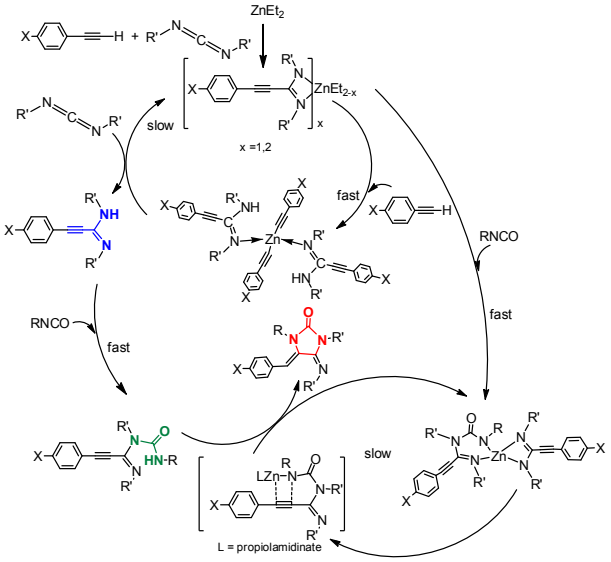

Figure 7. Proposed coupled catalytic cycles.

In a first step, alkyne and carbodiimide were catalytically transformed in propiolamidine (top cycle in Figure 7), through amidinate and alkynyl zinc intermediate complexes, followed by a rapid reaction of this amidine with isocyanate to obtain the *open* urea. This urea undergoes a catalysed intramolecular cyclization to produce the final imidazolidinone, through an imidamidate intermediate complex (bottom cycle in Figure 7).

Conclusions

In summary, the hydroalkynylation of carbodiimides has been achieved for the first time using a simple and low–cost zinc compound, $ZnEt_2$, as precatalyst, which offers a straightforward, atom–economic route to *N,N'*–disubstituted propiolamidines. Stoichiometric studies have allowed the isolation and full characterization of two zinc amidinates which have been proposed as plausible intermediates in this catalytic transformation, as well as a bisalkynyl–bisamidine complex, as the possible resting state of the catalyst. The rate law for the hydroalkynylation was deduced to be second order dependent on the carbodiimide concentration but to be zero order with respect to the alkyne, with a negligible kinetic isotopic effect, thus indicating that the C–H activation of the alkyne was favoured and the insertion of the carbodiimide in an alkynyl intermediate is the rate determining step of this reaction. Coupling this catalytic reaction with the addition of isocyanates (or isothiocyanates) allows to obtain ureas that were transformed into the corresponding imidazolidinones or –thione in a one–pot high atom–efficient process. This last process seems to occur through imidamidate intermediates, one of them was isolated and fully characterized, *via* an intramolecular hydroamination reaction catalysed by a zinc compound. Further stoichiometric and catalytic transformations involving the use of these Zn–based compounds are currently under study in our group.

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Experimental Section

General Considerations.

All reactions were performed using standard Schlenk and glove−box techniques under an atmosphere of dry nitrogen. Solvents were purified by passage through a column of activated alumina (Innovative Tech.), degassed under nitrogen and stored over molecular sieves in the glove−box prior to use. Microanalyses were carried out with a Perkin−Elmer 2400 CHN analyzer. NMR spectra were recorded on a Varian FT−400 spectrometer using standard VARIAN−FT software. Mass spectroscopic analyses were performed on an Advion expression CMS instrument (electron impact). $ZnEt_2$ (1 M in hexane), $ZnEt_2$ (1.1 M in toluene), $ZnMe_2$ (2 M in toluene), alkynes, carbodiimides and isocyanates were purchased from Aldrich and used as received.

Procedure for hydroalkynylation reactions at NMR tube scale

Catalytic reactions were performed on a small scale in an NMR tube fitted with a concentric Teflon valve with 0.5 mmol of alkyne, 0.5 mmol of carbodiimide and the adequate amount of catalyst in the adequate solvent (toluene−d_8 preferentially) under nitrogen. Conversion of the starting material to product was determined by integration of the product resonances relative to the substrate peaks in the ^{1}H NMR spectrum. Compounds **2a–g** were identified by comparing their NMR spectra with the literature data.[10,11,12b,14,16a,17]

Preparative Scale Reaction for 2a.

In the glovebox, phenylacetylene (3 mL, 27 mmol) and *N,N'*−diisopropylcarbodiimide (4.2 mL, 27 mmol) in toluene (10 mL) were added in a Schlenk tube. $ZnEt_2$ (0.8 mmol) was then added to the above reaction mixture. The Schlenk tube was taken outside the glovebox and the reaction was stirred at 70 °C for the 24 h. Then, the solution was concentrated under reduced pressure, hexane was added and the mixture was placed in a refrigerator at −20 °C for 16 h. After filtration the product was obtained as yellowish microcrystalline solid. The mother liquor was reconcentrated *in vacuo* and placed in a refrigerator at −20 °C for 16 h to obtain a second crop of crystals. Total isolated yield 85%.

Synthesis of $[ZnEt\{C(C{\equiv}CPh)(N^iPr)_2\}]_2$ 3.

To a $ZnEt_2$ (1 mmol) solution in toluene (5 mL), amidine **2a** (0.23 g, 1 mmol) was added. After stirring for 15 min at room temperature, the solvent was eliminated under reduced pressure and 3 mL of pentane were added. The solution was stored at −20 °C overnight affording colorless crystals of complex **3** (0.29 g, 90 %). ^{1}H NMR (400 MHz, 298 K, C_6D_6) δ (ppm) = 7.33 (m, 2H, C_6H_5), 6.96 (m, 3H, C_6H_5), 4.25 (sept, 2H, J = 6.3 Hz, CH), 1.67 (t, 3H, J = 8.2 Hz, $ZnCH_2CH_3$), 1.37 (d, 12H, J = 6.3 Hz, Me), 0.82 (2H, q, J = 8.2 Hz, $ZnCH_2CH_3$). $^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6) δ (ppm) = 154.51 (CN_2), 131.87, 129.13, 128.29, 121.58 (C_6H_5), 96.10 (Ph*C*≡C), 80.55 (PhC≡*C*), 50.80 (CH), 25.31 (CH_3), 12.87 ($ZnCH_2CH_3$), 4.16 ($ZnCH_2CH_3$). Anal. Calcd. for $C_{17}H_{24}N_2Zn$: C, 63.46; H, 7.52; N, 8.71. Found, C, 63.39; H, 7.45; N, 8,60.

Synthesis of $[Zn\{C(C{\equiv}CPh)(N^iPr)_2\}_2]_2$ 4.

To a $ZnEt_2$ (1 mmol) solution in toluene (5 mL), amidine **2a** (0.43 g, 2 mmol) was added. After 2 h stirring at room temperature, the solvent was eliminated under reduced pressure and 5 mL of pentane were added. The solution was stored at −20 °C overnight affording light yellow crystals of complex **4** (0.49 g, 94 %). ^{1}H NMR (400 MHz, 298 K, C_6D_6) As a mixture of dimer and monomer δ (ppm) = 7.49, 7.39, 6.94 (m, C_6H_5, dimer and monomer), 4.45 (m, 4H, CH, dimer), 4.31 (sept, 2H, CH, monomer, J = 6.3 Hz), 1.68 (broad d, 12H, CH_3, dimer), 1.56 (broad d, 12H, CH_3, dimer), 1.36 (broad d, 12H, CH_3, monomer). $^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6) δ (ppm) = 158.29, 155.18, 132.30, 132.27, 132.26, 129.38, 129.31, 129.00, 128.72, 128.62, 122.92, 122.50, 122.26, 96.82, 96.10, 82.37, 81.37, 79.76, 52.62, 49.07, 48.35, 26.34, 25.70, 25.21. Anal Calcd for $C_{30}H_{38}N_4Zn$: C, 69.29; H, 7.37; N, 10.77. Found, C, 70.01; H, 7.41; N, 10.82.

Synthesis of $[Zn\{C(C{\equiv}CPh)(N^iPr)(NH^iPr)\}_2(C{\equiv}CPh)_2\}]$ 5. Phenylacetylene (62 µl, 0.60 mmol) was added to a toluene solution (5 mL) of compound **4** (0.150 g, 0.29 mmol). After stirring for 15 min at room temperature, the solution was concentrated under reduced pressure and 3 mL of pentane were added and the reaction mixture was kept at −20 °C for 16 h, affording colorless crystals of complex **5** (0.085 g, 40 %). Partial spectroscopic data from **5** solutions (see the text): ^{1}H NMR (400 MHz, 298 K, C_6D_6) δ (ppm) = 9.05 (bs, NH), 7.9−6.9 (m, C_6H_5), 4.45 (sept, CH, J = 6.5 Hz), 4.24 (m, CH), 2.00−1.35 (bs, CH_3), 1.45 (d, CH_3, J = 6.5 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, 298 K, C_6D_6) δ (ppm) = 155.25, 151.85, 131.72, 129.48, 128.29, 125.74, 121.74, 121.00, 113.38, 110.53, 108.21, 107.77, 97.14, 96.19, 81.39, 78.20, 53.54, 49.22, 43.94, 24.63, 22.71. Anal Calcd for $C_{46}H_{50}N_4Zn$: C, 76.28; H, 6.96; N, 7.74 Found, C, 75.99; H, 6.90; N, 7.68.

General procedure for kinetic experiments.

Kinetic experiments were performed using a Varian FT−400 MHz spectrometer. A standard solution 0.11 M of catalyst **1** was made, obtained from a 1.1 M solution in toluene and diluted in deuterated toluene. The described kinetic experiments were carried out on the *N,N'*−disopropylcarbodiimide and phenylacetylene (or deuterated phenylacetylene) to form the corresponding propiolamidine **2a**.

The reactions were carried out in J−Young NMR tubes and the reaction rates were measured by monitoring the disappearance of carbodiimide (or alkyne) relative to the internal standard tetrakis(trimethylsilyl)silane (6 mg) by ^{1}H NMR spectroscopy at the described intervals over more than three half−lives. All data were processed using Varian integral analysis software. Reaction rates were derived by fitting data to zero, first or second order equations by using linear trend lines generated by Microsoft Excel software.

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Procedure for isocyanate insertion and hydroamination reactions at NMR tube scale.

Catalytic reactions were performed on a small scale in an NMR tube fitted with a concentric Teflon valve with 0.5 mmol of alkyne, 0.5 mmol of carbodiimide and $ZnEt_2$ (3 mol%) in toluene−d_8 under nitrogen, at 70 °C for 24 h. Then 0.5 mmol of the corresponding isocyanate or isothiocyanate were added to the NMR tube inside the glovebox, and the mixture was further heated at 70 °C for 24 h. Compounds **6a, d, g** were identified by comparing their NMR spectra with the literature data.[17]

Synthesis of [Zn{C(C≡CPh)(N^{i}Pr)$_2$}{(N(2,6−Me$_2$C$_6$H$_3$))(CO)(N^{i}Pr)C(C≡CPh)(N^{i}Pr)}] 7.

2,6−$Me_2C_6H_3NCO$ (54 μl, 0.38 mmol) was added to a toluene solution (5 mL) of compound **4** (0.20 g, 0.38 mmol) . After stirring for 15 min at room temperature, the solution was concentrated under reduced pressure and 5 mL of hexane were added and the mixture was placed in a refrigerator at −20 °C for 16 h, affording colorless microcrystals of complex **7** (0.24 g, 95%). ^{1}H NMR (400 MHz, 298 K, C_6D_6) δ (ppm) = 7.33−6.87 (m, 13H, C_6H_5, C_6H_3), 4.42 (m, 2H, CH), 4.13 (m, 2H, CH), 2.55 (s, 6H, $Me_2C_6H_3$), 1.89 (d, 6H, CH_3, J = 6.5 Hz), 1.39 (d, 6H, CH_3, J = 6.6 Hz), 1.19 (d, 6H, CH_3, J = 6.6 Hz), 0.98 (d, 6H, CH_3, J = 6.3 Hz). ^{13}C{^{1}H} NMR (100 MHz, 298 K, C_6D_6) δ (ppm) = 156.03, 155.13, 148.83, 146.09, 133.77, 132.36, 132.23, 130.62, 129.37, 128.91, 128.60, 128.51, 128.13, 127.88, 124.05, 122.03, 120.50, 100.20, 97.15, 54.87, 54.57, 47.62, 26.13, 25.59, 24.21, 22.20, 19.42. Anal Calcd for $C_{39}H_{47}N_5OZn$: C, 70.21; H, 7.10; N, 10.50 Found, C, 70.25; H, 7.16; N, 10.58.

X−ray diffraction studies

X−ray data collection of suitable single crystals of compounds **3**, **4**, **5** and **7** were done at 100(2) K on a Bruker VENTURE area detector, while compound **6f** was measured on APEX area detector, both equipped with graphite monochromated Mo−Kα radiation (λ = 0.71073 Å) by applying the ω−scan method. The data reduction was performed with the APEX2 software and corrected for absorption using SADABS.[33,34] Crystal structures were solved by direct methods using the SIR97 program and refined by full−matrix least−squares on F2 including all reflections using anisotropic displacement parameters by means of the WINGX crystallographic package.[35,36] All hydrogen atoms were included as fixed contributions riding on attached atoms with isotropic thermal displacement parameters 1.2 times or 1.5 times those of their parent atoms for the organic ligands. In compound **5**, H2 atoms were located with the aim to study the intramolecular NH---C hydrogen bond. Details of the structure determination and refinement of compounds are summarized in Table S1. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC 1554604−1554608. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (Fax: +44−1223−335033; e−mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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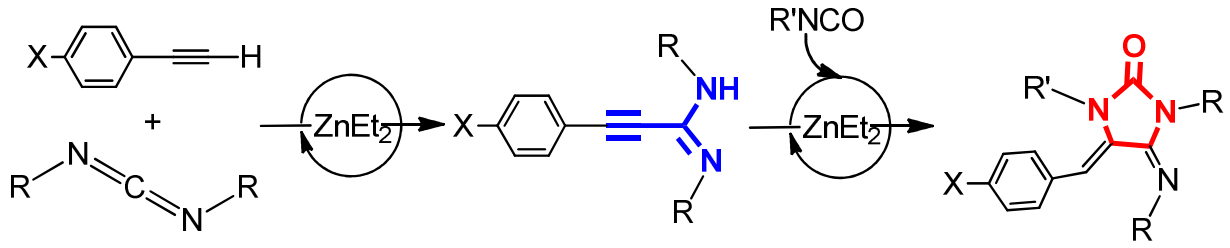

The well-known simple $ZnEt_2$ is an efficient catalyst for the addition of terminal alkynes to carbodiimides through the formation of amidinate intermediate complexes and straightforward C-H bond activation of alkynes. Consecutive isocyanate addition allows to obtain imidazolidinones via intramolecular catalytic hydroamination.