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Alkaline earth catalysis for the 100% atom-efficient three component assembly of imidazolidin-2-ones†

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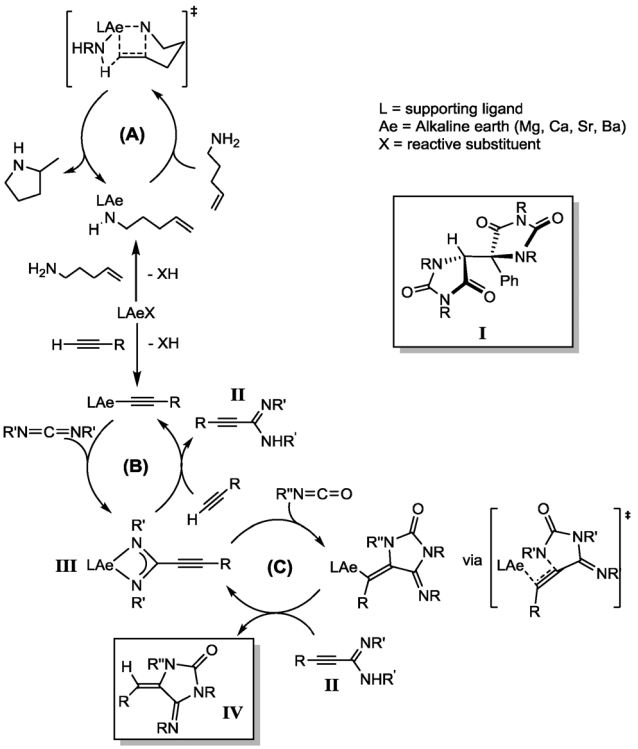
A variety of functionalised imidazolidin-2-ones may be synthesised under very mild reaction conditions using non-toxic and cost-effective alkaline earth bis(amide) pre-catalysts in a 100% atom-efficient, intermolecular one-pot assembly from inexpensive alkyne and cumulene reagents.

Heterocyclic molecules play a crucial role in biological processes[1] and are a constituent in two-thirds of the top-selling small molecule pharmaceuticals in the USA.[2] Azole derivatives are a particularly widespread motif in natural products and are among the 30 most frequently-used heterocycles in anticancer, anti-HIV and antibacterial drug molecules.[3,4] Whilst many complex and challenging heterocyclic syntheses may be achieved with catalytic methods,[5] a vast majority of these processes require either the preparation of specialised substrates and pre-catalysts derived from low abundance transition metals or are atom-inefficient from production of halide by-products.[6] Since our initial report of the calcium-catalysed intramolecular hydroamination of aminoalkenes (Scheme 1A),[7] we and others have applied pre-catalysts derived from the biologically compatible, inexpensive and environmentally benign alkaline earth (Ae) elements to an ever-growing array of multiple bond heterofunctionalisation and dehydrocoupling reactions.[8] Of direct relevance to the current work are the group 2 catalysed hydroacetylenation of carbodiimides (Scheme 1B)[9] and the recently reported magnesium-mediated but stoichiometric synthesis of complex bis(hydantoins) (**I**, inset Scheme 1) from phenylacetylene and isocyanates.[10] This latter process was rationalised as a cascade of hydroacetylenation, isocyanate insertion, intramolecular hydroamination and protonolysis steps akin to those depicted in Scheme 1. In this contribution we demonstrate that the readily available homoleptic amides, $[Ae\{N(SiMe_3)_2\}_2(THF)_2]$ (**1a**, Ae = Mg; **1b**, Ae = Ca; **1c**, Ae = Sr), may be employed for the ready elaboration of this chemistry to a generalised one pot catalytic regime. This is achieved through an initial and precedented catalytic reaction of a carbodiimide and terminal acetylene to provide a propargylamidine (**II**, Scheme 1B).[9] We speculated that, upon completion of this catalysis, addition of an isocyanate would instigate the formation of imidazolidin-2-ones (**IV**) through further insertion and protolytic reactivity (Scheme 1C).



Scheme 1

An initial reaction of *tert*-butylisocyanate with (*N*,*N*′-di-isopropyl)-phenylpropargylamidine, synthesised *in situ* using 5 mol% $[Sr\{N(SiMe_3)_2\}_2(THF)_2]$, **1c**, resulted in quantitative formation of the imidazolidin-2-one (**2**) within the first point of analysis at r.t. (Scheme 2, Table 1, entry 3). Analysis by ^{1}H NMR spectroscopy

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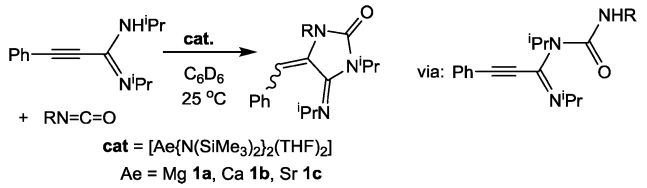
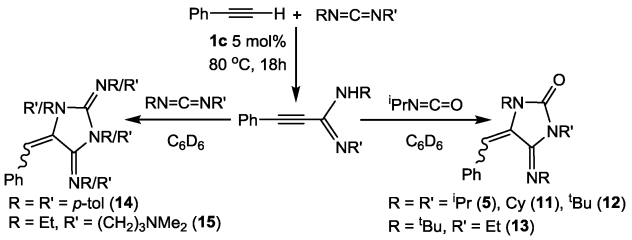
† Electronic supplementary information (ESI) available: Details of the synthesis, characterization data and the crystallographic protocols employed in this study are given. CCDC 1008314–1008316. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc05223d.



Scheme 2



Scheme 3

Table 1 Isocyanate scope for catalytic cyclisation with (*N*,*N*′-di-isopropyl)-phenylpropargylamidine

Ent.	R, compd no.	Cat (mol%)	Time (h)	NMR yield (%)	*Z*/*E* (%)
1	^{t}Bu, **2**	**1a** 5.0	4 d	53	33 : 67
2	^{t}Bu, **2**	**1b** 5.0	2	87	30 : 70
3	^{t}Bu, **2**	**1c** 5.0	0.1	>99	22 : 78
4	^{t}Bu, **2**	**1c** 0.5	18	87	23 : 77
5	Et, **3**	**1c** 0.5	0.3	91	83 : 17
6	Pr, **4**	**1c** 0.5	0.5	97	90 : 10
7	^{i}Pr, **5**	**1c** 0.5	3	98	41 : 59
8	Cy, **6**	**1c** 0.5	3	>99	40 : 60
9	Adamantyl, **7**	**1c** 0.5	18	92	32 : 68
10	Ph, **8**	**1c** 0.5	0.5	>99	85 : 15
11	2,4,6-Me$_3$Ph, **9**	**1c** 0.5	6	98	98 : 2
12	2,6-^{i}Pr$_2$C$_6$Ph, **10**	**1c** 0.5	18	78	90 : 10

revealed a 22 : 78 mixture of the *Z* and *E* isomers displaying characteristic benzylidene singlet resonances at 6.50 and 5.95 ppm, respectively. Lowering the catalyst loading to 0.5 mol% afforded the same isomer mixture in 87% yield after 18 h at r.t. (Table 1, entry 4). Performance of an identical reaction with 5 mol% of the analogous magnesium and calcium pre-catalysts, **1a** and **1b**, revealed the intermediacy of a highly moisture-sensitive urea derivative (Scheme 2), identified by comparison with isolated compounds synthesised by direct reaction between the isocyanate and the amidine (see ESI†).

Subsequent reactions were performed at r.t. with 0.5 mol% **1c**, using (*N*,*N*′-di-isopropyl)phenylpropargylamidine and the range of isocyanates shown in Table 1. In all cases isocyanate insertion was virtually instantaneous at r.t. whereas the rate of cyclisation to the corresponding imidazolidin-2-one was found to be dependent on the steric pressure exerted by the isocyanate substituent: ethylisocyanate afforded a 91% NMR yield within 20 min at r.t. (Table 1, entry 5), while the larger, *tert*-butyl-, adamantyl and 2,6-di-isopropylphenyl-isocyanates, required 18 hours to achieve good conversions (Table 1, entries 4, 9 and 12).

With 5 mol% **1c**, all reactions proceeded to completion within less than 5 min at r.t. The *Z*/*E* product isomer ratio was found to be governed both by steric and electronic factors. Arylisocyanates predominantly yielded the *Z* isomer, independent of substituent steric demands (Table 1, entries 10–12). For alkylisocyanates, however, selectivity was observed to shift from predominantly *Z* for substituents of lower steric demands (Table 1, entries 5, 6) to predominantly *E* for those exerting greater steric pressure (Table 1, entries 1–4, 7–9). To evaluate the scope of amidine *N*-substitution a variety of phenylpropargylamidines were synthesised *in situ* from phenylacetylene and commercially available carbodiimides using **1c** as a pre-catalyst. Upon full conversion to the amidine 1 eq. isopropylisocyanate was added. Formation of the heterocyclic products proved

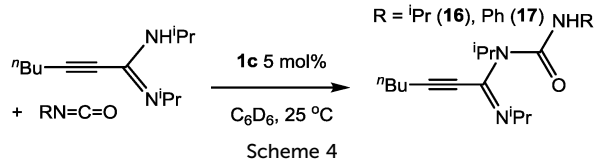
Table 2 Propargylamidine scope for the synthesis of 1-isopropyl-(5-benzylidene-4-imino)imidazolidin-2-ones

Ent.	R	R′, compd no.	Cat (mol%)	Time (h)	NMR yield (%)	*Z*/*E* (%)
1	^{i}Pr	^{i}Pr, **5**	5.0	0.1	98	41 : 59
2	Cy	Cy, **11**	5.0	0.1	97	25 : 75
3	^{t}Bu	^{t}Bu, **12**	5.0	40	75	25 : 75
4	Et	^{t}Bu, **13**	5.0	0.1	99	34 : 66
5	*p*-tol	*p*-tol, **14**	5.0	4[a]	97	75 : 25
6	Et	(CH$_2$)$_3$NMe$_2$, **15**	5.0	4[a]	89	—[b]

[a] 2 eq. RN=C=NR′, 80 °C. [b] Mixture of all 4 regioisomers.

highly dependent on the steric demands of the amidine *N*-substituents (Scheme 3). While the di(isopropyl) and dicyclohexyl derivatives provided essentially instantaneous and quantitative conversion at r.t. using 5 mol% catalyst (Table 2, entries 1–2), the larger di(*tert*-butyl) derivative required much longer reaction times (40 h) to achieve high conversion (Table 2, entry 3). The unsymmetrical 1-ethyl-3-(*tert*-butyl)amidine substrate provided evidence for kinetic discrimination in these reactions through exclusive isocyanate insertion at the *N*-ethyl nitrogen atom, with a product isomer ratio intermediate between that of the di(isopropyl) and di(*tert*-butyl) derivatives (entry 4). Substrates with smaller functionalities, such as di(*p*-tolyl)carbodiimide and [1-(*N*,*N*′-dimethylaminopropyl)-3-(*tert*-butyl)carbodiimide] did not provide access to the desired propargylamidines but underwent double carbodiimide insertion/cyclization to yield *N*,*N*′-[(5-benzylidene-imidazolidin-2,4-ylidene)diamine] products (Scheme 3, Table 2, entries 5, 6). In the case of the tetra(*p*-tolyl)-substituted N-heterocycle (**14**), a 75% selectivity for the *Z*-isomer was observed (entry 5), in line with observations for products derived from arylisocyanates (Table 1, entries 10–12). Analysis of the product distribution from the reaction of the 1-(*N*,*N*′-dimethylaminopropyl)-3-*tert*-butyl derivative was marred by the presence in solution of all 4 possible insertion regioisomers as well as *E*/*Z*-isomerism (Table 2, entry 6).

In contrast, the strontium-catalysed reaction of isocyanates with (*N*,*N*′-di-isopropyl)-*n*-butylpropargylamidine did not afford the desired imidazolidin-2-ones but only the urea insertion products (**16**, **17**) (Scheme 4). The latter species did not undergo cyclisation even after prolonged heating at 100 °C. Similarly, group 2-mediated intramolecular hydroamination of aminoalkenes has been observed to be hindered by the presence of terminal alkyl substituents on the alkene moiety, whereas terminal aryl substitution promotes cyclisation due to an activating electronic effect.[11]



Scheme 4

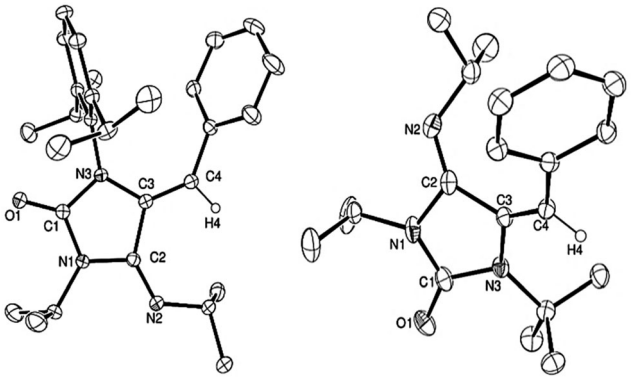
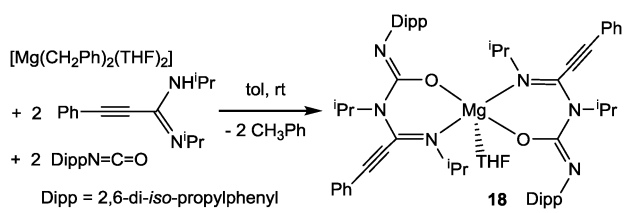


Fig. 1 ORTEP representations of compounds (*Z*)-**10** (left) and (*E*)-**2** (right). Ellipsoids at 30% probability. Hydrogen atoms omitted for clarity except H4.

Single crystal X-ray diffraction experiments performed on the products resulting from the reactions of (*N*,*N*′-di-isopropyl)-phenylpropargylamidine with 2,6-di-isopropyl-phenyl- and *tert*-butylisocyanate, respectively, revealed the structures of compounds (*Z*)-**10** and (*E*)-**2**, which corresponded to the major isomers formed in the reactions as observed by solution NMR analysis (Fig. 1). In both cases bond lengths and angles are within the range expected for these (5-benzylidene-4-imino)-imidazolidin-2-ones.

To investigate the nature of the alkaline earth species at work in this catalysis, a stoichiometric reaction between **1a**, 2 eq. (*N*,*N*′-di-isopropyl)phenylpropargylamidine and 2 eq. 2,6-di-isopropyl-phenylisocyanate was performed. This did not yield the expected magnesium insertion complex but was observed by NMR analysis to provide complete conversion of substrates to the corresponding N-heterocyclic product **10** with reformation of **1a**. This result suggests that cyclisation is assisted by the presence of protic $[HN(SiMe_3)_2]$ liberated upon amidine protonolysis of **1a**. A similar concerted mechanism has previously been proposed for the intramolecular cyclisation of aminoalkenes (Scheme 1A).[11,12]

Use of $[Mg(CH_2Ph)_2(THF)_2]$ in place of **1a** yielded the desired homoleptic insertion complex, compound **18**, in quantitative yield (Scheme 5). An X-ray diffraction experiment revealed **18** to



Scheme 5

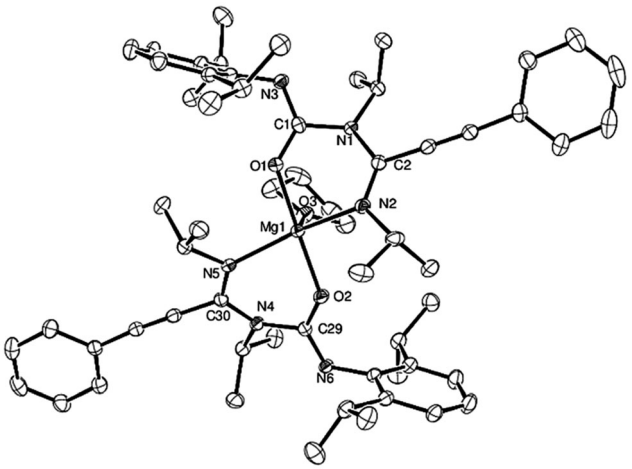
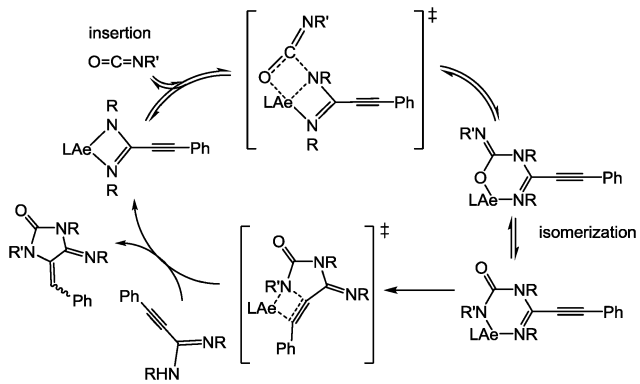


Fig. 2 ORTEP representation of compound **18**. Ellipsoids at 30% probability. Hydrogen atoms omitted for clarity.

be a distorted square pyramidal bis(*N*-(2-phenylpropargylimidoyl)-carbamimidate) magnesium complex, with a THF molecule in the axial position. Coordination in the basal plane is provided by the oxygen atoms of the inserted isocyanates and the imino-nitrogen of the amidinate moieties, forming two 6-membered [MgNCNCO] metallacycles (Fig. 2). The rather short C–O bond lengths [1.275(4), 1.274(4) Å], elongated C1–N1 [1.451(4) Å] and C29–N4 bonds [1.452(4) Å] and the planarity of the N1 and N4 nitrogen atoms suggest some degree of delocalisation over the chelate rings. The short C1–N3 [1.289(4) Å] and C29–N6 [1.291(4) Å] bond lengths are clearly indicative of pendant imine functionalities.

Complex **18** provided similar catalytic activity to **1a** for the formation of **2**, suggesting that molecules of this type are formed as intermediates during the catalysis. Variable temperature ^{1}H NMR experiments performed on compound **18** also indicated the potential for isocyanate de-insertion at higher temperatures. A van't Hoff analysis of this equilibrium provided ΔH° = +88 kJ mol^{-1} and ΔS° = 208 J K^{-1} mol^{-1} allowing ΔG°(298 K) to be estimated as +26 kJ mol^{-1} for the dissociative process. Interpretation of this latter value remains difficult as it requires deconvolution of both the de-insertion and the potential for dimerization of the resultant propargylamidinate species.[9a] The positive but low



Scheme 6

free energy change at 298 K, however, indicates that this potential reversibility is likely to be significant during the course of the catalysis at ambient or slightly elevated temperatures. This observation and the notable regioselectivity of the catalysis toward imidazolidine formation, thus, lead us to suggest the refined mechanistic hypothesis depicted in Scheme 6.

In conclusion we have demonstrated the applicability of readily available and inexpensive alkaline earth bis(amide) precatalysts to the facile one-pot, 100% atom-efficient, stepwise synthesis of a wide variety of highly functionalized imidazolidin-2-ones from simple commercially available building blocks. We are currently seeking to develop extensions to this catalytic heterocycle synthesis through the incorporation of alternative heterocumulenes into catalytic manifolds analogous to those shown in Schemes 1B/C and 6 and to exploit the additional functionality inherent in molecules such as (*Z*)-**10** and (*E*)-**2** in subsequent, sequential atom-efficient transformations.

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