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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) precatalysts in a 100% atom-efficient, intermolecular one-pot assembly from inexpensive alkyne and cumulene reagents.

Heterocyclic molecules play a crucial role in biological processes and are a constituent in two-thirds of the top-selling small molecule pharmaceuticals in the USA. 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. Whilst many complex and challenging heterocyclic syntheses may be achieved with catalytic methods, 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. Since our initial report of the calcium-catalysed intramolecular hydroamination of aminoalkenes, 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. Of direct relevance to the current work are the group 2 catalysed hydroacetylenation of carbodiimides (Scheme 1B) and the recently reported magnesium-mediated but stoichiometric synthesis of complex bis(hydantoins) (I, inset Scheme 1) from phenylacetylene and isocyanates. 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)$_2$]$_2$ (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 precedent catalytic reaction of a carbodiimide and terminal acetylene to provide a propargylamidine (II, Scheme 1B). 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).
the imidazolidin-2-one (2) within the first point of analysis at rt (Scheme 2, Table 1, entry 3). Analysis by $^1$H NMR spectroscopy 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 18h at rt (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 amide (see Supporting Information).

Subsequent reactions were performed at rt 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 rt 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 20min at rt (Table 1, entry 5), while the larger, tert-butyl-, adamantyl and 2,6-di-iso-propylphenyl-isocyanates, required 18hours to achieve good conversions (Table 1, entries 4, 9 and 12).

With 5 mol% 1c, all reactions proceeded to completion within less than 5min at rt. The Z/E product isomer ratio was found to be governed by both 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 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 rt using 5 mol% catalyst (Table 2, entries 1-2), the larger di(tert-butyl) derivative required much longer reaction times (40h) to achieve high conversions (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-toly)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-benzylidenemimidazolidin-2,4-ylidene)di]amine products (Scheme 3, Table 2, entries 5, 6). In the case of the tetra(p-toly)-substituted N-heterocyclyclic (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 2**

**Scheme 3**

<table>
<thead>
<tr>
<th>Ent.</th>
<th>R, Compd. No.</th>
<th>cat (mol%)</th>
<th>Time (h)</th>
<th>NMR yield (%)</th>
<th>Z/E (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1Bu, 2</td>
<td>1a 5.0</td>
<td>4d</td>
<td>53</td>
<td>33:67</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1b 5.0</td>
<td>2</td>
<td>37</td>
<td>20:80</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1c 5.0</td>
<td>0.1</td>
<td>&gt;99</td>
<td>22:78</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1e 0.5</td>
<td>18</td>
<td>87</td>
<td>23:77</td>
</tr>
<tr>
<td>5</td>
<td>Et, 3</td>
<td>1f 0.5</td>
<td>0.3</td>
<td>91</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>Pr, 4</td>
<td>1g 0.5</td>
<td>0.9</td>
<td>97</td>
<td>90:10</td>
</tr>
<tr>
<td>7</td>
<td>Pr, 5</td>
<td>1h 0.5</td>
<td>3</td>
<td>98</td>
<td>41:59</td>
</tr>
<tr>
<td>8</td>
<td>Cy, 6</td>
<td>1i 0.5</td>
<td>0.5</td>
<td>&gt;99</td>
<td>40:60</td>
</tr>
<tr>
<td>9</td>
<td>adamantyl, 7</td>
<td>1j 0.5</td>
<td>18</td>
<td>92</td>
<td>32:68</td>
</tr>
<tr>
<td>10</td>
<td>Ph, 8</td>
<td>1k 0.5</td>
<td>6</td>
<td>98</td>
<td>98:2</td>
</tr>
<tr>
<td>11</td>
<td>2,4,6-Me,Ph, 9</td>
<td>1l 0.5</td>
<td>14</td>
<td>78</td>
<td>90:10</td>
</tr>
<tr>
<td>12</td>
<td>2,6-Pr,C,Ph, 10</td>
<td>1m 0.5</td>
<td>18</td>
<td>78</td>
<td>90:10</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ent.</th>
<th>R</th>
<th>R', Compd. No.</th>
<th>cat (mol%)</th>
<th>Time (h)</th>
<th>NMR yield (%)</th>
<th>Z/E (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pr</td>
<td>Pr, 5</td>
<td>5.0</td>
<td>0.1</td>
<td>98</td>
<td>41:59</td>
</tr>
<tr>
<td>2</td>
<td>Cy</td>
<td>Cy, 11</td>
<td>5.0</td>
<td>0.1</td>
<td>97</td>
<td>25:75</td>
</tr>
<tr>
<td>3</td>
<td>Bu</td>
<td>Bu, 12</td>
<td>5.0</td>
<td>0.1</td>
<td>97</td>
<td>25:75</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>Bu, 13</td>
<td>5.0</td>
<td>0.1</td>
<td>99</td>
<td>34:66</td>
</tr>
<tr>
<td>5</td>
<td>p-tol</td>
<td>p-tol, 14</td>
<td>5.0</td>
<td>4⁺</td>
<td>97</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>(CH₃)₂NMe₂, 15</td>
<td>5.0</td>
<td>4⁺</td>
<td>89</td>
<td>2⁺</td>
</tr>
</tbody>
</table>

(a) 2 eq. RN=CaNR; 80 °C; b) mixture of all 4 regioisomers.

**Scheme 4**

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-

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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 (Figure 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)phenylnaphtalamidine and 2 eq. 2,6-di-isopropylphenylisocyanate 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(SiMe3)2] liberated upon amide protonolysis of 1a. A similar concerted mechanism has previously been proposed for the intramolecular cyclisation of aminoalkenes (Scheme 1A).11,12

Use of [Mg(CH2Ph)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 be a distorted square pyramidal bis(N-(2-phenylpropargylimidoyl)-carbamidate) 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 aminate moieties, forming two 6-membered [MgNCNCO] metallacycles (Figure 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 1H 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 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.

Conclusions
In conclusion we have demonstrated the applicability of readily available and inexpensive alkaline earth bis(amide) precatalyst 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.

Notes and references

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Details of the synthesis, characterization data and the crystallographic protocols employed in this study are given in the Supporting Information. See DOI: 10.1039/c000000x. CCDC 1008314 - 1008316 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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