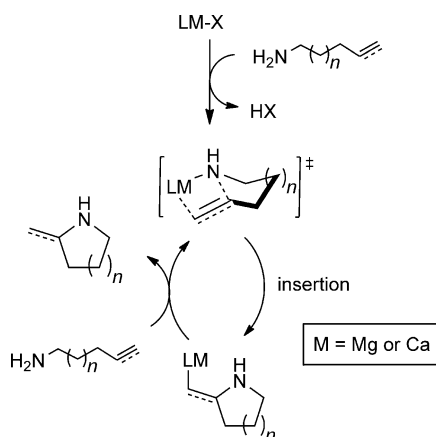


A Magnesium-Mediated Cascade Assembly for the Atom-Economical Synthesis of Bis(imidazolidine-2,4-dione)s**

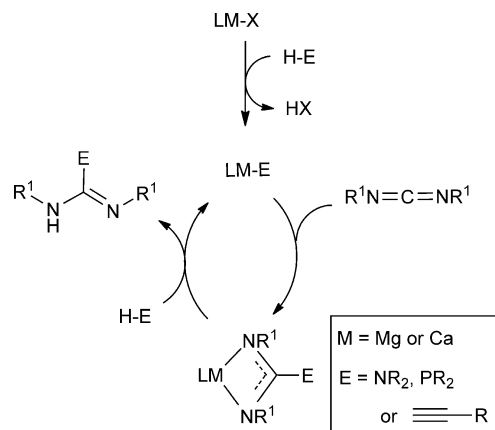
Michael S. Hill,* David J. Liptrot, and Mary F. Mahon

The ubiquity of N-heterocycles, particularly as components of drug and natural product structures, has stimulated enormous interest in the development of new methods for their preparation.^[1] Driven by considerations of atom-efficiency and energy use, the catalytic intramolecular hydroamination of aminoalkenes and aminoalkynes, for example, has garnered particularly intense attention.^[2] Our own work has concentrated upon the utility of heavier alkaline earth (Mg, Ca, Sr, Ba) complexes for the catalysis of just these C–N bond forming processes in which the activation barriers toward rate determining C=C insertion have been found to be profoundly influenced by the identity of the Group 2 metal cation (Scheme 1).^[3] Application of the same suite of pre-catalysts to



Scheme 1.

the intermolecular heterofunctionalization of carbodiimides with protic amine, phosphine, or terminal alkyne reagents has also provided access to the respective C–N, C–P and C–C coupled products and a plethora of guanidine,^[4] phosphaguanidine,^[5] and propargylamide^[6] molecules (Scheme 2). Although the formation of substituted ureas by the hydroamination of organic isocyanates has also been shown to proceed with considerable efficacy,^[7] previously reported



Scheme 2.

reactivity of these heterocumulenes with Group 2 and other electrophilic metal centers has been dominated by polymerization or oligomerization to form poly- or oligo-isocyanurates.^[8] This latter C–N coupling reactivity has been rationalized to proceed by multiple isocyanate insertion, the viability of which has been most relevantly demonstrated by Harder and co-workers through their isolation of a double insertion product from the reaction of cyclohexyl isocyanate with a calcium bis(iminophosphorano)diide.^[9] Mindful of this possibility and other recent examples of magnesium-mediated cascade reactivity,^[10] we here demonstrate that similar isocyanate oligomerization may be combined with an intramolecular alkyne insertion step reminiscent of that depicted in Scheme 1. The resultant cascade process allows the synthesis of unprecedented and structurally complex bis(imidazolidine-2,4-dione) molecules from these simple building blocks and with complete atom efficiency.

An initial NMR scale reaction was performed by addition of an excess (10 molar equivalents) of *n*-propyl isocyanate to a 2:1 mole ratio of phenylacetylene and commercial dibutylmagnesium in tetrahydrofuran (THF). This process provided evidence for consumption of the isocyanate reagent through the appearance of a number of non-equivalent and broadened resonances in the aliphatic region of the resultant ¹H NMR spectrum. Encouraged by this observation, the reaction was repeated on a preparative scale, whereupon work-up under moist aerobic conditions and crystallization at –18 °C from toluene solution provided single crystals of compound **1** suitable for single-crystal X-ray diffraction analysis.^[11] The results of this analysis, shown in Figure 1 a, revealed that compound **1** is a structurally complex bis(imidazolidine-2,4-dione), which may be considered to be a product

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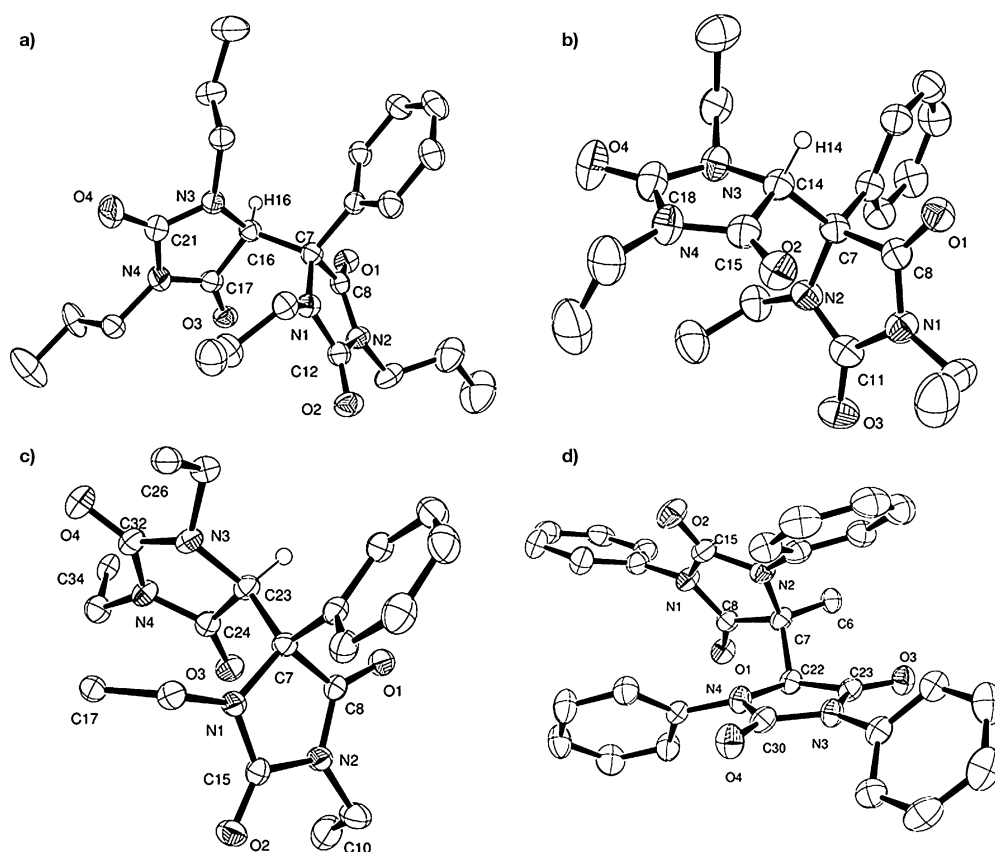
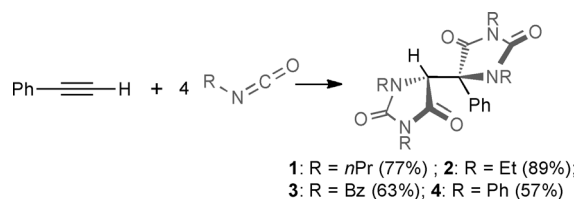


Figure 1. ORTEP representations of compounds **1** (a), **2** (b), **3** (c), and **4** (d). Thermal ellipsoids are depicted at 50% probability. Hydrogen atoms except those attached to C(16) (**1**), C(14) (**2**), and C(23) (**3**) and the phenyl rings of the benzyl groups of compound **3** attached through C(10), C(17), C(26) and C(34) are omitted for clarity.

from the combination of a single equivalent of phenylacetylene and four equivalents of *n*-propyl isocyanate (Scheme 3).

The potential generality of this reaction was demonstrated by extension of the reaction protocol to the synthesis of the analogous bis(imidazolidine-2,4-dione) compounds **2–4**, through use of the alternative ethyl (**2**), benzyl (**3**), and phenyl (**4**) isocyanate substrates, respectively. In each case identical reaction and work-up procedures yielded the crystalline bis(imidazolidine-2,4-dione) products in high yield (Figure 1b–d).

The crystallographic analyses and yields greater than 50 % confirmed that the formation of products **1–4** had, in each case, occurred diastereoselectively to provide either the *R,S*/*S,R* (**1–3**) or the *R,R*/*S,S* (**4**) pair of diastereomers.^[11] Although the imidazolidine-2,4-diones (hydantoin)s consti-

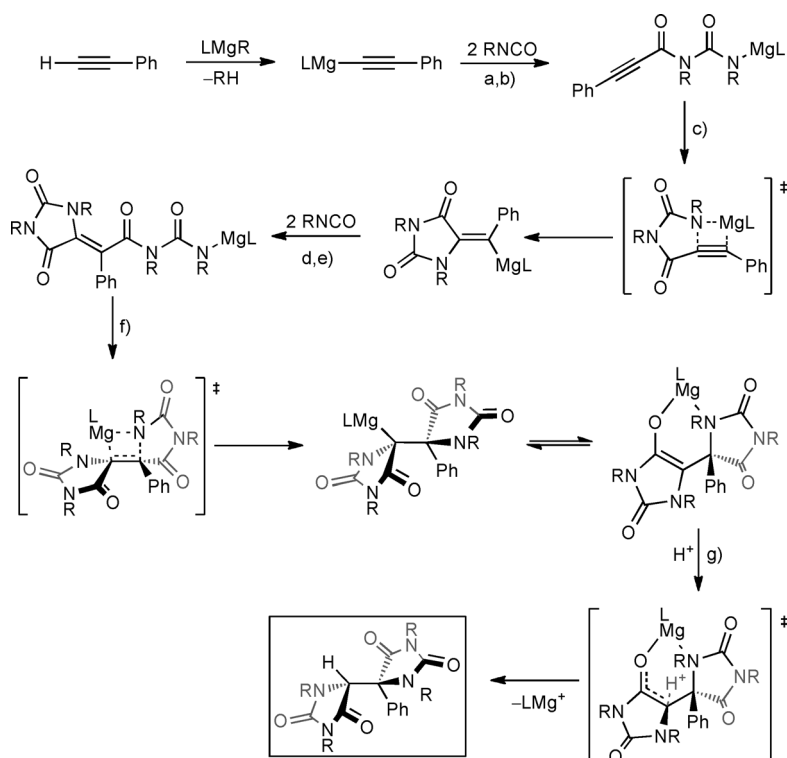


Scheme 3.

tute a very well established class of cyclic ureides,^[12] used as anticonvulsant drugs (e.g. phenytoin and its derivatives)^[13] and are components of a plethora of other commercial pharmaceutical products such as small-molecule inhibitors of cell division and non-steroidal androgen receptor antagonists or agonists,^[14] structures of the type exemplified by compounds **1–4** have not been hitherto reported in the literature possibly owing to the complexity of their formation by conventional methods. We propose that both the course and the diastereoselectivity of these reactions may be readily accounted for by consideration of well predated Group 2-based reactivity summarized in Schemes 1 and 2. A mechanism for the formation of compounds **1–4**, which accounts for the diastereoselectivity, is, thus, illustrated in Scheme 4.

A series of insertion steps underpin this reaction as follows; steps (a), (b), (d), and (e) are isocyanate insertions into metal–acetylide and metal–amidate bonds similar to those observed by both the groups of Hill and Harder for the heavier Group 2 congeners.^[7,9] Steps (c) and (f) are hydroaminations of an alkyne and alkene, respectively. These reactions are known to be catalyzed by magnesium albeit with lower reactivity than its heavier congeners and step (g) to yield the bis(imidazolidine-2,4-dione) products requires protonolysis of the as-formed metal alkyl. The geometry of the intermediate alkene formed may be predicted by consideration of the *syn*-addition which typically defines Group 2-catalyzed hydroamination.^[3] The observed diastereoselectivity is thus predicated upon a keto–enol tautomerization whereby the formation of a metal chelate directs protonation to the least hindered face of the *sp*² β -carbon (step (g), Scheme 4). The absence of larger rings can be attributed to the rapidity of alkyne hydroamination yielding five-membered rings in preference to larger rings and the likely irreversibility of this step. Finally, the lack of intermolecular hydroamination can be attributed to the relatively large entropic penalty this reaction would incur, making it disfavored with regards to the proposed intramolecular hydroamination.

A study of these reactions by electrospray ionization mass spectrometry (ESI-MS) performed on aliquots removed from



Scheme 4. Proposed stepwise mechanism yielding bis(imidazolidine-2,4-dione)s through metallocarboration and metalloamination steps.

THF solutions of reaction mixtures containing each of the isocyanates, phenylacetylene, and di-butylmagnesium in an 8:2:1 ratio and diluted in methanol provided strong evidence for the course of reaction illustrated in Scheme 4. The results of this study, shown in Table 1, revealed the presence of both the product of initial isocyanate insertion into the magnesium acetylide Mg–C bond, the propargyl amide, **A**, and the result of intramolecular alkyne Mg–N insertion, the alkene, **B**. Although alkene, **B**, could not be observed directly during the formation of compound **3**, we propose that this is likely to be a consequence of the propensity of the isocyanate to insert into the intermediate vinylmagnesium species. Identical ESI-MS studies of analogous reactions quenched with MeOD also provided ions assignable to the analogous deuterated versions of **1–4**.

Table 1: Details of the mass spectrometric analysis of the magnesium-mediated bicycle formation giving insight into the mechanism of the reaction.

Product	R	[A+H] ⁺		[B+Na] ⁺		[C+Na] ⁺	
		Expected	Observed	Expected	Observed	Expected	Observed
1	Pr	188.1075	188.1071	295.1422	295.1438	465.2478	465.2480
2	Et	174.0919	174.0915	267.1109	267.1107	409.1852	409.1879
3	Ph	222.0919	222.0925	363.1109		601.1852	601.1860
4	Bz	236.1075		391.1422	391.1417	657.2478	657.2469

In summary, we have reported the diastereoselective synthesis of a series of structurally complicated and unprecedented bis(imidazolidine-2,4-dione). Initial mechanistic evidence suggests a cascade of well preceded steps mediated by a Group 2 center that is viable for a range of alkyl and aryl isocyanates. Work is continuing to examine the broader scope of this reactivity through the inclusion of other heterocumulenes, alongside the viability of extending this process to a catalytic regime.

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- [11] X-ray diffraction data for **1**: C₂₄H₃₄N₄O₄, *M* = 442.55, monoclinic, *C*2/c, *a* = 20.8696(3), *b* =

13.0729(3), $c = 18.5290(4)$ Å, $\beta = 106.566(1)^\circ$, $V = 4845.36(17)$ Å³, $Z = 8$, $\rho = 1.213$ g cm⁻³, $T = 150(2)$ K, $R_1 [I > 2\sigma(I)] = 0.0596$, $wR_2 [I > 2\sigma(I)] = 0.1108$, R_1 [all data] = 0.1104, wR_2 [all data] = 0.1265, measured reflections = 44 500, unique reflections = 5469, $R_{\text{int}} = 0.1110$. **2**: C₂₇H₄₀N₄O_{5.75}, $M = 512.63$, monoclinic, $P2_1/a$, $a = 9.6689(2)$, $b = 23.2345(8)$, $c = 12.8044(4)$ Å, $\beta = 97.154(2)^\circ$, $V = 2854.14(15)$ Å³, $Z = 4$, $\rho = 1.193$ g cm⁻³, $T = 150(2)$ K, $R_1 [I > 2\sigma(I)] = 0.0795$, $wR_2 [I > 2\sigma(I)] = 0.1964$, R_1 [all data] = 0.1471, wR_2 [all data] = 0.2316, measured reflections = 41 517, unique reflections = 6480, $R_{\text{int}} = 0.0862$. **3**: C₄₀H₃₄N₄O₄, $M = 634.71$, monoclinic, $P2_1/n$, $a = 11.9110(3)$, $b = 20.4610(5)$, $c = 13.1590(4)$ Å, $\beta = 101.447(2)^\circ$, $V = 3143.20(15)$ Å³, $Z = 4$, $\rho = 1.341$ g cm⁻³, $T = 150(2)$ K, $R_1 [I > 2\sigma(I)] = 0.0563$, $wR_2 [I > 2\sigma(I)] = 0.1278$, R_1 [all data] = 0.1179, wR_2 [all data] = 0.1557, measured reflections = 52 000, unique reflections = 7205, $R_{\text{int}} = 0.1176$. **4**: C₄₃H₃₄N₄O₄, $M = 670.74$, monoclinic, $P2_1/n$, $a = 16.8320(8)$, $b = 9.5660(7)$, $c = 22.1100(4)$ Å, $\beta = 108.493(4)^\circ$, $V = 3376.2(4)$ Å³, $Z = 4$, $\rho = 1.320$ g cm⁻³, $T = 150(2)$ K, $R_1 [I > 2\sigma(I)] = 0.0967$, $wR_2 [I >$

$2\sigma(I)] = 0.1579$, R_1 [all data] = 0.1677, wR_2 [all data] = 0.1780, measured reflections = 12 194, unique reflections = 6811, $R_{\text{int}} = 0.0668$. CCDC 925518–925521 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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