DOI: 10.1002/chem.201501328

Synthetic Methods

Group 2 Catalysis for the Atom-Efficient Synthesis of Imidazolidine and Thiazolidine Derivatives

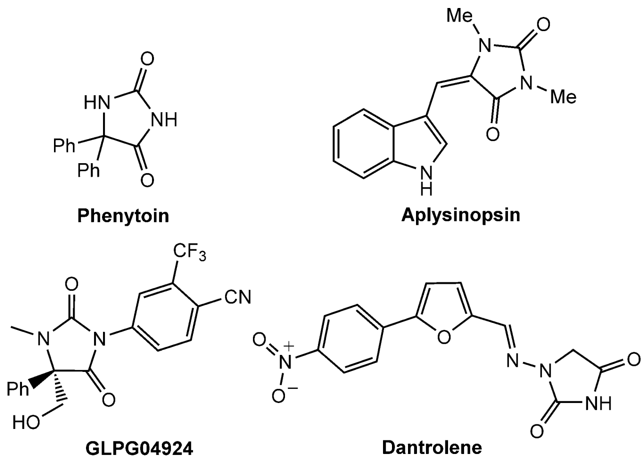
Merle Arrowsmith, Michael S. Hill,* and Gabriele Kociok-Köhn[a]

Abstract: A wide variety of functionalised imidazolidine-2-ones and -thiones, 2-imino-imidazolidines and thiazolidine-2-thiones have been synthesised under very mild reaction conditions by using simple and cost-effective alkaline earth bis(amide) precatalysts, $[Ae\{N(SiMe_3)_2\}_2(THF)_2]$ (Ae = Mg, Ca, Sr). The reactions ensue with 100% atom efficiency as one-pot cascades from simple, commercially available terminal alkyne and heterocumulene reagents. The reactions take place through the initial assembly of propargylamidines, which are utilised in subsequent cyclisation reactions through addition of the isocyanate, isothiocyanate and, in one case, carbon disulfide reagents. This reactivity is deduced to take place through a well-defined sequence of heterocumulene hydroacetylenation and alkyne hydroamidation steps, which are all mediated at the alkaline earth centre. The rate and regioselectivity of the cyclisation reactions are, thus, found to be heavily dependent upon the identity of the catalytic alkaline earth centre employed. Similarly, the selectivity of the reactions was observed to be profoundly affected by stereoelectronic variations in the individual substrates, albeit by a similar Group 2-centred reaction mechanism in all cases studied.

Introduction

Heterocyclic moieties are constituents of two-thirds of the top-selling small-molecule pharmaceuticals in the USA.[1] The imidazolidine-2,4-dione (hydantoin) moiety is a particularly notable constituent of many biologically active compounds and numerous hydantoin derivatives have been identified as anticonvulsant, antiulcer, antiarrhythmic, antimuscarinic, antiviral and antidiabetic agents.[2] For example, phenytoin is commonly used in the treatment of epilepsy[3] and aplysinopsin, isolated from the sponge *Aplysinopsis reticulate*, has been shown to exhibit cytotoxicity against cancer cells.[4] The agonist of the human-androgen receptor, GLPG04924,[5] and the hydantoin muscle relaxant, dantrolene,[6] have been widely employed in a medical context. Many herbicides also contain hydantoin skeleta as an integral part of their structure, and they are also applied as intermediates for the synthesis of enantiomerically pure amino acids by dynamic kinetic resolution.[7,8]

The development of efficient and preferentially catalytic methods for the rapid construction of molecularly diverse



hydantoin molecules from simple and inexpensive starting materials is clearly very desirable. In this regard, several transition-metal-catalysed methods have been reported. A copper-based amination reaction of esters with di-*tert*-butyldiaziridinone has been shown to afford 1,3,5-trisubstituted hydantoins,[9] whereas a palladium-catalysed carbonylation reaction of aldehydes with ureas and carbon monoxide furnishes 5-, 3,5-, and 1,3,5-substituted hydantoins[10] and a nickel-catalysed protocol starting from acrylates and isocyanates has recently been described.[11] Of most relevance to the current work, several processes have been described, in which the hydantoin core is assembled from one molecule of phenylacetylene and two molecules of isocyanate through iron,[12] ruthenium[13] or manganese catalysis.[14] Although described in some cases as proceeding as a [2+2+1]cycloaddition, these processes are otherwise mechanistically uncertain.

[a] Dr. M. Arrowsmith, Prof. M. S. Hill, Dr. G. Kociok-Köhn
Department of Chemistry, University of Bath
Claverton down, Bath, BA2 7AY (UK)
E-mail: msh27@bath.ac.uk

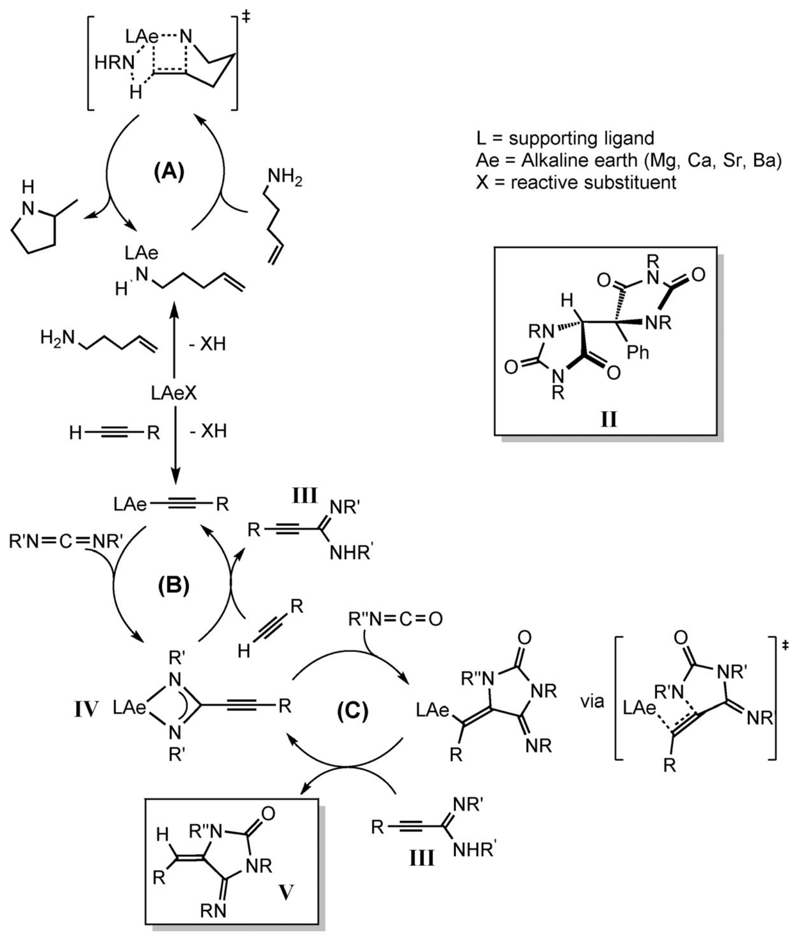
*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501328. It contains experimental procedures, full characterisation data, and details of the X-ray analyses of compounds Z-**3**, E-**12**, E-**25**, Z-**32**, **II** and **V**. CCDC1008314, 1008315, 1008316, 1051077, 1051078, and 1051079 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.*

The alkaline earth elements (Mg, Ca, Sr and Ba) comprise an alternative suite of underexploited but inexpensive and potentially more sustainable and environmentally benign catalytic elements in their effectively invariant 2+ oxidation state. For some time, we have been engaged in a programme of research to develop a defined catalytic and reaction chemistry, derived largely from sequences of metal-centred σ-bond metathesis and polarised insertion reactions.[15] Since our initial report of the calcium-catalysed intramolecular hydroamination of aminoalkenes (Scheme 1 A),[16,17] we and others have applied alkaline earth pre-catalysts to an ever-growing array of molecular catalytic reactions.[18–33] Of most relevance to the current work, we have previously reported that complex bis(hydantoins) (**II**, inset Scheme 1) may be synthesised, albeit in a stoichiometric sense, through a magnesium-based cascade reaction between phenylacetylene and an organic isocyanate.[33] Subsequent to this discovery, which was rationalised to take place through a sequence of intramolecular isocyanate hydroacetylenation and intermolecular C≡C and C=C hydroamidation steps, we have described in preliminary form an extension of this chemistry to a one-pot catalytic regime.[34] In this latter case, reactions catalysed by the readily available bis-hexamethyldisilazides [Ae{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (**I a**, Ae = Mg; **I b**, Ae = Ca; **I c**, Ae = Sr) allowed the facile synthesis of a variety of highly functionalised imidazolidin-2-ones with 100% atom efficiency (Scheme 1 B and C). These reactions take place via the initial catalytic formation of a propargylamidine (**III** in Scheme 1 B),[35] whereupon addition of an organic isocyanate initiates a further cascade of reactions involving isocyanate insertion into the catalytically active Group 2 amidinate (**IV** in Scheme 1 B and C), intramolecular Ae–N insertion of the alkynyl residue and protonolysis of the cyclised alkaline earth vinyl intermediate by the remaining propargylamidine (**III**) to regenerate **IV** and provide the imidazolidin-2-one derivative (**V**, Scheme 1 C). Herein, we provide a full description of the scope of this reactivity and reveal that this approach is easily extended to alternative sulfur-based heterocumulenes for the synthesis of imidazolidin-2-thiones and thiazole derivatives.

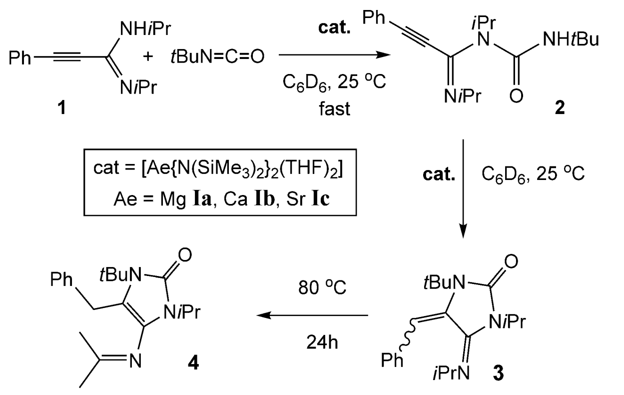
Results and Discussion

We have recently reported the use of the alkaline earth bis(amido) complexes, [Ae{N(SiMe$_3$)$_2$}$_2$(THF)$_2$] (Ae = Mg **Ia**, Ca **Ib**, Sr **Ic**) for the synthesis of propargylamidines by hydroacetylenation of carbodiimides.[35] Following this procedure (*N*,*N*′-diisopropyl)-phenylpropargylamidine (**1**) was synthesised in situ by using 5 mol% of **I c**. Subsequent addition of one molar equivalent of *tert*-butylisocyanate resulted in quantitative formation of the corresponding imidazolidin-2-one (**3**) within the first point of analysis at room temperature (Scheme 2; Table 1, entry 3). The resultant ^{1}H NMR spectrum displayed two new characteristic benzylidene singlets present in a 22:78 ratio at $\delta = 6.50$ and 5.95 ppm, respectively, coupling in the ^{13}C{^{1}H} NMR spectrum to signals at $\delta = 112.4$ and 120.9 ppm, respectively. These were assigned by a NOESY NMR experiment to the *Z* and *E* isomers of **3**, respectively (Figure 1).

The catalyst loading could be lowered to 0.5 mol%, affording (*Z*)-**3** and (*E*)-**3** in the same ratio with an 87% yield from an 18 hour reaction at room temperature (Table 1, entry 4). The reaction of **1** with *tert*-butylisocyanate by using 5 mol% of the analogous magnesium and calcium precatalysts, **I a** and **b**, revealed the intermediacy of a linear urea derivative (**2**) resulting from isocyanate insertion into the amidine within the first point of analysis and presenting a distinctive downfield N*H* singlet at $\delta_{1H} = 10.48$ ppm



Scheme 1. Alkaline earth-catalysed intramolecular hydroamination of aminoalkenes (**A**), hydroacetylation of carbodiimides (**B**) and catalytic synthesis of imidazolidin-2-ones (**C**).



Scheme 2.

Table 1. Isocyanate scope for the catalytic synthesis of (5-benzylidene-4-imino)imidazolidin-2-ones from **1** by using precatalysts **Ia**–**c** in C_6D_6 at room temperature.

Entry	R	Product	Cat. [mol %]	*t* [h]	NMR yield [%][a]	*Z*/*E* [%]
1	*t*Bu	**3**	**Ia** 5.0	4 d	53	33:67
2	*t*Bu	**3**	**Ib** 5.0	2	87	30:70
3	*t*Bu	**3**	**Ic** 5.0	0.1	>99	22:78
4[b]	*t*Bu	**3**	**Ic** 0.5	18	87	23:77
5[b]	Ad	**5**	**Ic** 0.5	18	92	32:68
6[b]	Cy	**6**	**Ic** 0.5	3	>99	40:60
7[b]	*i*Pr	**7**	**Ic** 0.5	3	98	41:59
8[b]	*n*Pr	**8**	**Ic** 0.5	0.5	97	90:10
9[b]	Et	**9**	**Ic** 0.5	0.3	91	83:17
10[b]	Ph	**10**	**Ic** 0.5	0.5	>99	85:15
11[b]	2,4,6-$Me_3C_6H_2$	**11**	**Ic** 0.5	6	98	98:2
12[b]	2,6-*i*$Pr_2C_6H_3$	**12**	**Ic** 0.5	18	78	90:10

[a] Determined by integration of benzylidene protons against an internal $HN(SiMe_3)_2$ standard. [b] By using isolated compound **1**.

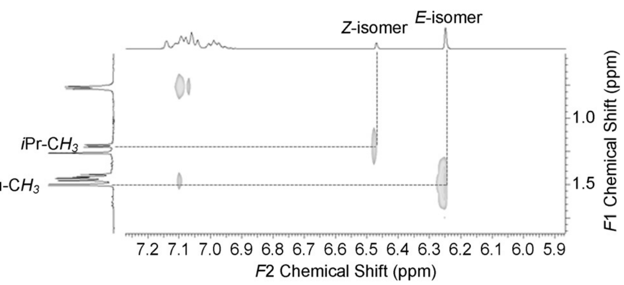
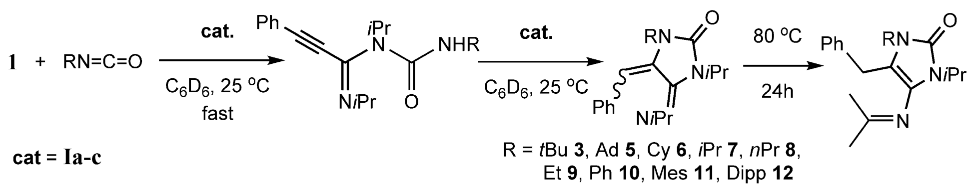


Figure 1. Identification of (*Z*)-3 and (*E*)-3 by NOESY NMR spectroscopy.

(Scheme 2). Although the magnesium-catalysed cyclisation to compound **2** took several days to reach completion at room temperature (Table 1, entry 1), **3** could not be isolated by methanol quenching of the catalyst because this also reversed the formation of **3**. The rate of cyclisation dramatically increased with increasing metal cation size, in the order of Sr > Ca ≫ Mg (Table 1, entries 1–3). A minor dependence on metal-cation identity was also observed for the *Z*/*E* isomer ratio of the product, varying from approximately 1:2 for magnesium to 1:4 for strontium (Table 1, entries 1–3). Once full conversion to **3** was reached, the isomer ratio did not change upon heating to 60 °C, suggesting no interconversion between the two isomers (see below for a rationale for the independent formation of each isomer). Heating to 80 °C, however, induced tautomerisation of the benzylidene and isopropylimino moieties to the corresponding 5-isopropylidenamino-4-benzyl-imidazole-2-one (**4**) via a [1,5] sigmatropic H shift. Compound **4** displayed a distinctive ^1H NMR benzyl singlet (2 H) resonance around 3.3 ppm, which correlated with a $^{13}C\{^1H\}$ resonance at $\delta = 103.2$ ppm, and two distinct isopropylidene methyl singlets (3H each) at 1.6 and 1.8 ppm, which were shown to be mutually coupled by a COSY NMR experiment.

Encouraged by these results, the scope of the isocyanate substrates that could be employed in this reaction was investigated by using propargylamidine **1**, with 0.5 mol % of **Ic** at room temperature (Scheme 3). Although isocyanate insertion to form the linear analogue of **2** proved virtually instantaneous and independent of isocyanate identity, the rate of subsequent cyclisation to the corresponding imidazolidin-2-one was strongly influenced by the nature of the isocyanate substituent. Although the least sterically demanding substrate, ethylisocyanate, gave a 91 % conversion, as was determined by ^1H NMR spectroscopy within 20 minutes at room temperature (Table 1, entry 9), the bulkiest substrates, *tert*-butyl, adamantyl and 2,6-diisopropylphenylisocyanate, required extended reaction times to reach good conversions (Table 1, entries 4, 5 and 12). When the catalyst loading was increased to 5 mol %, however, all reactions proceeded to completion within less than five minutes at room temperature. The *Z*/*E* isomer ratio of the products was found to be governed by both steric and electronic factors. Although the various arylisocyanates primarily gave the *Z* isomer (Table 1, entries 10–12), the selectivity of isomer formation for reactions with alkylisocyanates was found to be sensitive to the steric demands of the *N*-bound organic substituent. Although isocyanates bearing primary ethyl and *n*-propyl substituents provided predominant formation of the *Z* isomer (Table 1, entries 8–9), this shifted to a preference for *E*



Scheme 3.

isomer formation for secondary and tertiary alkyl substituents (Table 1, entries 1–7). The mesityl derivative **11**, however, was formed essentially as a single *Z*-isomer (Table 1, entries 11), whereas a maximum *E*-selectivity of 78% was achieved for the *tert*-butyl derivative **3** (Table 1, entries 3). It thus appears that, for the alkyl derivatives at least, the orientation of the benzylidene phenyl group depends on the relative steric pressure imposed by the imino-isopropyl and isocyanate alkyl substituents. We tentatively suggest that this notable preference toward *Z*-isomer formation for all aryl derivatives studied possibly reflects a stabilising π interaction between the benzylidene phenyl substituent and the *N*-aryl moieties during heterocycle assembly at the metal centre.

The reactions were easily translated to a preparative scale. The amidine **1** was prepared on a 10 mmol scale by using 2.5 mol% of **Ic** overnight in hexanes at 80 °C, and crystallised in 88% yield. The subsequent reaction of **1** with phenylisocyanate on a 0.88 mmol scale by using 2.5 mol% of **Ic** in 0.5 mL of *n*-hexane was highly exothermic, and crystallisation of the heterocyclic product **10** commenced almost instantaneously. After one hour at room temperature, the reaction mixture was filtered, and the colourless solid dried in vacuo to yield **10** in near quantitative yield (285 mg, 93%). Single-crystal X-ray diffraction experiments were performed on samples of compounds **3** and **12**, which were obtained from the NMR scale reactions after quenching with methanol, filtration and slow evaporation of the solvent at 4 °C. The results of these experiments, which have been reported previously in preliminary form,[34] are displayed in Figure 2 and show (*E*)-**3** (left) and (*Z*)-**12** (right), both of which correspond to the major isomer observed by ^{1}H NMR spectroscopy (Table 1, entries 3 and 12). In both cases, bond lengths and angles are within the range expected for these (5-benzylidene-4-imino)-imidazolidin-2-ones.[33]

The influence of amidine *N*-substitution on the reaction was evaluated through the synthesis of a number of phenylpropargylamidines from phenylacetylene and commercially available carbodiimides by using 5 mol% of **Ic** in C_6D_6 at 60 °C. Once full conversion to the amidine had been achieved, one molar equivalent of isopropylisocyanate was added, and the reaction

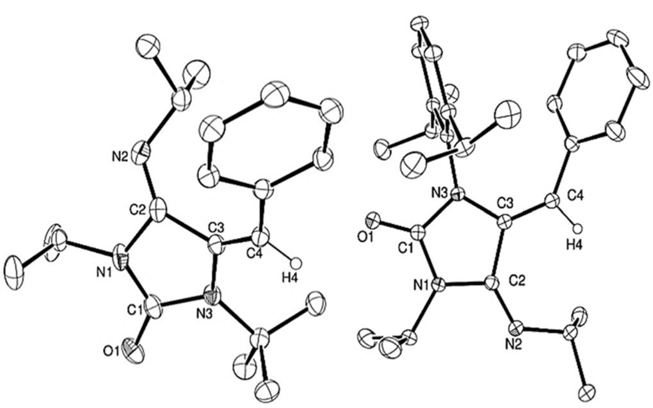
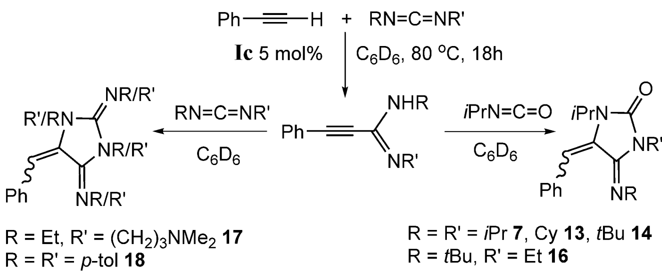


Figure 2. ORTEP representations of compounds (*Z*)-**3** (left) and (*E*)-**12** (right). Ellipsoids are drawn at 30% probability. Hydrogen atoms are omitted for clarity, except for the benzylidene proton H4.

was monitored by ^{1}H NMR spectroscopy. The rate of insertion and subsequent cyclisation was found to be highly dependent on the steric demands of the amidine *N*-substituents (Scheme 4). Although di(isopropyl)- and dicyclohexylcarbodi-



Scheme 4.

imide-derived phenylpropargylamidines provided instantaneous and quantitative conversion to the respective heterocyclic products **7** and **13** at room temperature (Table 2, entries 1 and 2), the much more sterically hindered di(*tert*-butyl) derivative required 40 h at room temperature to reach only 75% conversion to heterocycle **14** (Table 2, entry 3). Although all three symmetrical (*N*,*N*′-dialkyl)phenylpropargylamidines displayed a bias towards the *E*-isomer, this was significantly more pronounced for the dicyclohexyl and di(*tert*-butyl) substituted imidazolidin-2-ones, compounds **13** and **14** (Table 2, entries 1–3). Notably, the unsymmetrical [1-ethyl-3-(*tert*-butyl)]phenylpropargylamidine precursor **15** led to exclusive isocyanate insertion at the less hindered *N*-ethyl nitrogen atom, yielding a single heterocyclic product, compound **16**. The *Z*/*E* isomer ratio of this latter species was intermediate between that of the di(isopropyl) and di(*tert*-butyl) derivatives (Table 2, entry 4). Carbodiimides with less sterically demanding *N*-substituents, such as di(*p*-tolyl)carbodiimide and [1-(*N*,*N*′-dimethylaminopropyl)-3-*tert*-butyl)carbodiimide, proved unsuitable for simple hydroacetylenation in the first step of the reaction. Rather, they underwent twofold carbodiimide insertion followed by intra-

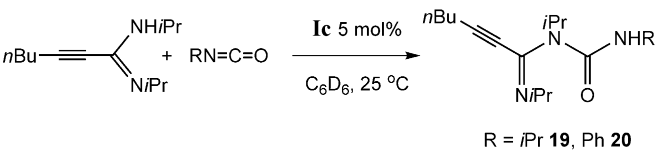
Table 2. Carbodiimide scope for the synthesis of (5-benzylidene-4-imino)imidazolidin-2-ones from phenylacetylene and isopropylisocyanate by using 5 mol% of **Ic** in C_6D_6 at room temperature.

Entry	R	R′	Product	*t* [h]	NMR yield [%][a]	*Z*/*E* [%]
1	*i*Pr	*i*Pr	**7**	0.1	98	41:59
2	Cy	Cy	**13**	0.1	97	25:75
3	*t*Bu	*t*Bu	**14**	40	75	25:75
4	Et	*t*Bu	**16**	0.1	99	34:66
5	Et	$(CH_2)_3NMe_2$	**17**[b]	4	89	–[c]
6	*p*-tol	*p*-tol	**18**[b]	4	97	75:25

[a] Determined by integration of benzylidene protons against an internal $HN(SiMe_3)_2$ standard. [b] RN=C=NR′ (2 equiv), 80 °C. Use of **Ia** instead of **Ic** did not afford better selectivity for the formation of the desired propargylamidine over the double carbodiimide insertion/cyclisation products **17** and **18**. [c] Mixture of all four possible regioisomers.

molecular hydroamidation/cyclisation to yield the *N*,*N*′-[(5-benzylidene-imidazoldin-2,4-ylidene)diamine products **17** and **18** (Scheme 4, Table 2, entries 5 and 6). Sufficiently selective access to the desired propargylamidines could also not be achieved through application of the less reactive magnesium precatalyst, **Ia**, although in this case, double carbodiimide insertion and the rate of subsequent intramolecular hydroamidation were significantly perturbed. *Z*-Selectivity of 75% was observed in the *N*,*N*′,*N*′′,*N*′′′-tetra-*p*-tolyl product (**18**) in line with the *Z*-selectivity observed for arylisocyanate insertion/cyclisation (Table 2, entry 6). Unfortunately, unlike the unsymmetrical carbodiimide-derived product **16**, no regioselectivity was observed when employing [1-(*N*,*N*′-dimethylaminopropyl)-3-ethyl] carbodiimide presumably due to the lack of steric discrimination between the two carbodiimide substituents. In this case, the formation of all four possible insertion regioisomers, as well as *E*/*Z*-isomerism for each of them, was observed (Scheme 4; Table 2, entry 5).

The influence of acetylenic substitution was also investigated. The strontium-catalysed reaction of isopropyl or phenylisocyanate with (*N*,*N*′-diisopropyl)-*n*-butylpropargylamidine did not provide the desired heterocycles. Rather, the reactions stalled after formation of the linear urea molecules, **19** and **20**, resulting from isocyanate insertion (Scheme 5). The latter species did not undergo intramolecular hydroamidation/



Scheme 5.

cyclisation even after prolonged heating at 100°C. Similar observations have been made in the intramolecular hydroamination of aminoalkenes, in which cyclisation is hindered by the presence of terminal alkyl substituents on the alkene moiety, whereas terminal aryl substitution promotes cyclisation due to an activating electronic effect.[16,17]

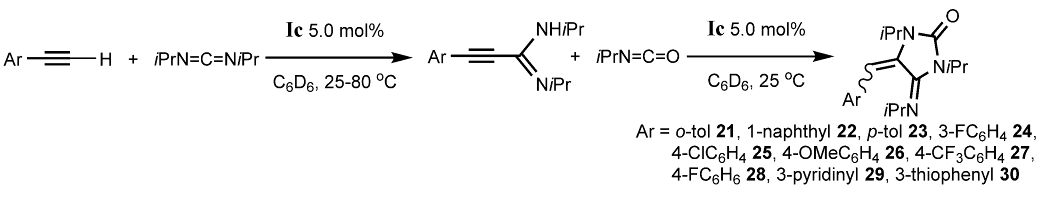
In contrast, aryl or heteroaryl substitution on the acetylenic fragment afforded clean and near-quantitative formation of the desired imidazolidin-2-ones in stepwise reactions with di(isopropyl)carbodiimide and isopropylisocyanate by using 5 mol% of **Ic** (Scheme 6). Although under these conditions, intermolecular hydroamidation of the isocyanate with the propargylamidine remained instantaneous and quantitative in all cases, the subsequent intramolecular cyclisation step proved to be highly dependent on the substitution pattern of the acetylenic aryl moiety. *Ortho*-substitution, with substrates, such as *o*-tolylacetylene and 1-naphthylacetylene, resulted in significantly reduced cyclisation rates compared to the parent phenylacetylene (Table 3, entries 2 and 3). However, *para*-methyl-

Table 3. Arylacetylene scope for the synthesis of (5-benzylidene-4-imino)imidazolidin-2-ones from di(isopropyl)carbodiimide and isopropylisocyanate by using 5 mol% of **Ic** in C_6D_6 at room temperature.

Entry	Ar	Product	*T* [°C]	*t* [h]	NMR yield [%][a]	*Z*/*E* [%]
1	Ph	**7**	25	0.1	98	41:59
2	*o*-tol	**21**	25	8	93	40:60
3	1-naphthyl	**22**	25	8	91	42:58
4	*p*-tol	**23**	25	0.1	>99	42:58
5	3-F-C_6H_4	**24**	25	1.5	98	32:68
6	4-Cl-C_6H_4	**25**	25	1	96	36:64
7	4-OMe-C_6H_4	**26**	25	5	90	55:45
8	4-CF_3-C_6H_4	**27**	25	24	89	20:80
9	4-CF_3-C_6H_4	**27**	60	2	>99	20:80
10	4-F-C_6H_4	**28**	25	24	90	40:60
11	3-pyridinyl[b]	**29**	25	0.1	>99	38:62
12	3-thiophenyl	**30**	25	0.1	>99	63:37

[a] Determined by integration of benzylidene protons against an internal $HN(SiMe_3)_2$ standard. [b] 3-Pyridinylpropargylamidine was synthesised by using 5 mol% of **Ia** at 40°C for one day, because **Ic** resulted in double insertion of the carbodiimide and formation of the imidazolidin-2,4-ylidene product analogous to **29**.

substitution had no effect on the efficacy of the intramolecular hydroamidation step (Table 3, entry 4). It is also notable that the *Z*/*E* isomer ratio was unaffected by alkyl or aryl substitution on the phenyl ring (Table 3, entries 1–4). For *para*-substituents, a clear trend of decreasing rate of cyclisation with increasing substituent electron-withdrawing effect was observed; from one hour to achieve 96% conversion to the *para*-chloro derivative, **25**, to 24 h to reach 90% conversion for the *para*-trifluoromethyl and *para*-fluoro derivatives, **27** and **28** (Table 3, entries 6–10). This trend contrasts with our previous observations, in which the rate of cyclisation during the intramolecular hydroalkoxylation of hydroxyalkynes bearing *para*-substituted terminal aryl groups was seen to increase with increasingly electron-withdrawing substitution in the *para* position.[16e] We tentatively ascribe the apparent reversal in reactivity in the present instance to a more remote effect of stronger electron-withdrawing *para*-substitution on the polarisation of the alka-



Scheme 6.

line earth amidinate nitrogen centres and consequent less facile isocyanate insertion. In mitigation of this hypothesis, monitoring of these reactions by ^{1}H NMR spectroscopy revealed that isocyanate insertion into the more electron-poor amidines is less rapid and provides lower conversion than with the more electron-rich amidines. In contrast, *meta*-fluoro-substitution resulted in only a small decrease in reactivity, yielding 98% of the heterocyclic product, **24**, in 1.5 h (Table 3, entry 5). The nature of the electron-withdrawing substituent also influences the *Z*/*E* selectivity, although no discernible pattern could be discriminated.

It is notable that these reactions were tolerant of chloro substitution on the phenyl ring, providing the potential for further catalytic functionalisation of the aryl moiety. After quenching and extraction with methanol, compound **25** crystallised in good yield (85%) upon solvent evaporation at room temperature. Figure 3 shows the results of a single-crystal X-ray diffraction experiment on the major (*E*)-isomer. Heteroaryl-substituted heterocycles could also be obtained in this manner. *N*,*N'*-Diisopropyl-3-pyridinylpropargylamidine was synthesised by using the magnesium precatalyst **Ia** in preference to the strontium precursor **Ic**, which was found to provide twofold carbodiimide insertion and cyclisation. Under these conditions, insertion of isopropylisocyanate and cyclisation were very rapid and effectively quantitative to give the pyridine-substituted heterocycle **29** in excellent yield (Table 3, entry 11). Attempts to synthesise the 2-pyridinyl analogue, however, were less discriminating, because even the use of **Ia** resulted in competitive carbodiimide insertion, with MS (ESI) analysis detecting molecular weights indicative of 1:1, 1:2, 2:1, 2:2 and even 3:2 acetylene/carbodiimide ratios. The strontium-catalysed reaction of 3-thiophenylacetylene with di(isopropyl)carbodiimide did provide the desired amidine, allowing subsequent isocyanate insertion and cyclisation. In this case, however, three different products were obtained: the expected *Z* and *E* isomers of heterocycle **30**, present in a 63:37 ratio, as well as a new compound, which was identified as the Diels–Alder adduct of two molecules of this heterocyclic product.

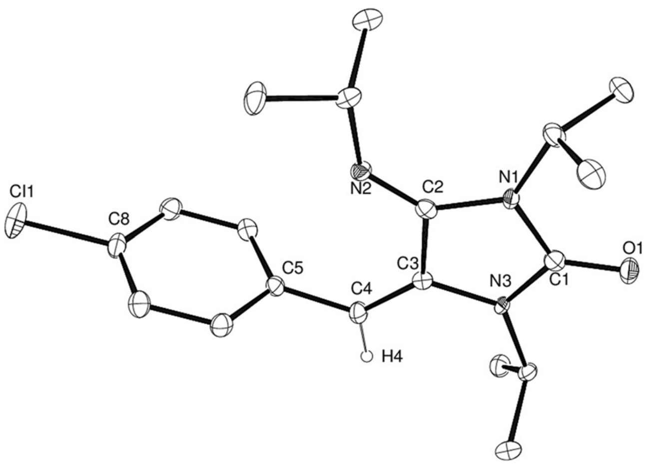
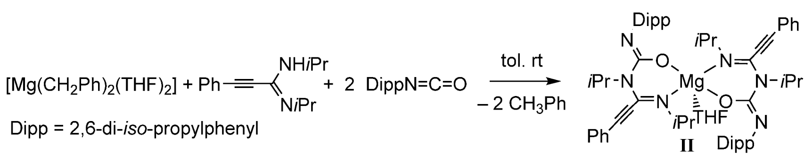


Figure 3. ORTEP representation of compound (*E*)-**25**. Ellipsoids at 30% probability. Hydrogen atoms omitted for clarity except for the benzylidene proton H4.

A stoichiometric reaction between **Ia**, two equivalents of (*N*,*N'*-diisopropyl)phenylpropargylamidine and two equivalents of 2,6-diisopropy phenylisocyanate did not yield the expected magnesium insertion complex. Analysis by NMR spectroscopy instead indicated complete consumption of the substrates to form the corresponding *N*-heterocyclic product **3** with reformation of **Ia**, suggesting that cyclisation requires the presence of $[HN(SiMe_3)_2]$ liberated upon protonolysis of **Ia** with the amidine.

In contrast, a further stoichiometric reaction utilising $[Mg(CH_2Ph)_2(THF)_2]$ in place of **Ia**, and with consequent liberation of the aprotic toluene conjugate acid, gave the desired homoleptic insertion complex **II** in quantitative yield (Scheme 7). An X-ray diffraction experiment, preliminary details of which were included in our previous communication,[34] revealed **II** to be a distorted square pyramidal magnesium 2-(propargylamidino)imidate complex, with a THF molecule coordinated in the apical position. Coordination in the basal plane is provided by the oxygen atoms arising from the inserted isocyanate substrates and the imino nitrogen of the amidinate moieties to form a quasi-planar 6-membered [MgNCNCO] metallacycle (Figure 4). The rather short C–O bond lengths [1.275(4), 1.274(4) Å], lengthened C1–N1 [1.451(4) Å] and C29–N4 bonds [1.452(4) Å] and planarity of the N1 and N4 nitrogen atoms within **II** suggest some degree of delocalisation over the chelate ring. The short C1–N3 [1.289(4) Å] and C29–N6 [1.291(4) Å] bond lengths are clearly indicative of pendant imine functionalities. Isolated samples of complex **II** also gave similar catalytic activity to **Ia** for the formation of **3**, suggesting it is a catalytic intermediate.

A variable-temperature ^{1}H NMR experiment performed on **II** in [D$_8$]toluene provided evidence for isocyanate de-insertion at higher temperatures (Scheme 8). A van't Hoff analysis of this equilibrium provided $\Delta H^{\ddagger} = +88\ \mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\ddagger} = 208\ \mathrm{J\,K^{-1}\,mol^{-1}}$, giving a $\Delta G^{\ddagger}$(298 K) value of $+26\ \mathrm{kJ\,mol^{-1}}$ for the de-insertion process. Although a definitive interpretation of this latter value would require deconvolution of both the de-insertion and potential dimerisation of the resultant bis(propargylamidinate) species, **III**, this positive but low free energy of activation at 298 K indicates that the potential for this reversibility is likely to be significant during the course of the catalysis at ambient or slightly elevated temperatures.



Scheme 7.

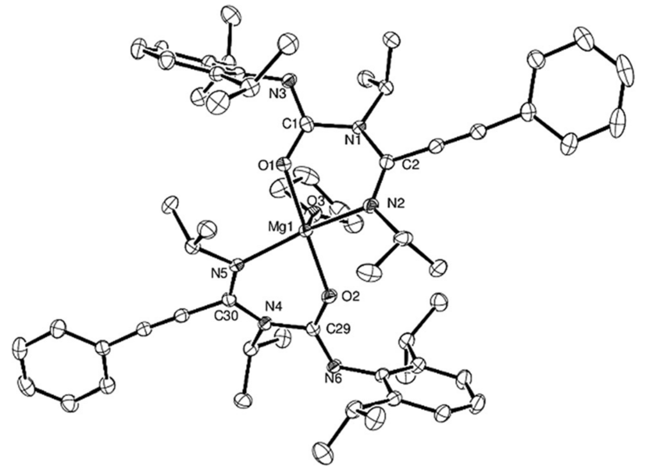


Figure 4. ORTEP representation of compound **II**. Ellipsoids are drawn at 30% probability. Hydrogen atoms are omitted for clarity.

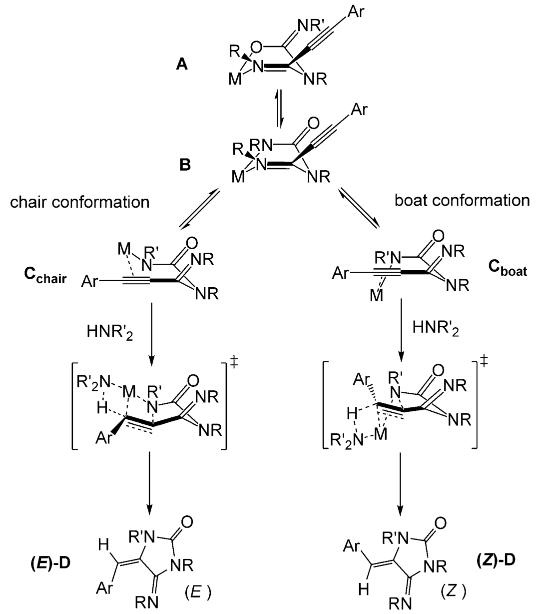


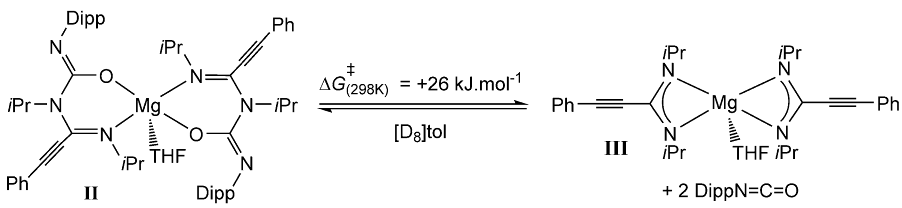
Figure 5. Proposed mechanism for the independent formation of *E*- and *Z*-heterocycles.

Based on the structure of **II** and the selectivity of the reactions toward the formation of the kinetic imidazolidin-2-one products rather than the thermodynamic 2-iminooxazolidines, we propose that the *N,O*-chelate **A** shown in Figure 5 first isomerises to the corresponding *N,N*-chelate **B** by decoordination of the oxygen atom and rotation of the imidate imino residue to coordinate to the metal centre. The metal-bound nitrogen atom of the amidino fragment must then necessarily decoordinate and rotate to allow the alkyne to interact with the metal centre. This may result in either a $\mathbf{C_{chair}}$ or a $\mathbf{C_{boat}}$ conformation, giving rise upon proton-assisted insertion/cyclisation to the heterocyclic products (*E*)-**D** and (*Z*)-**D**, respectively. Taking into account all these observations, the catalytic cycle presented in Figure 6 may be envisaged.

The insertion/cyclisation reactivity was further extended to a variety of isothiocyanates, yielding the corresponding imidazolidin-2-thiones, compounds **31**–**35** (Scheme 9). All such compounds presented a characteristic ^{13}C NMR thione resonance around 180 ppm, as well as two distinct ^{1}H NMR benzylidene singlets at approximately 6.5 and 5.9 ppm corresponding to the *Z* and *E* isomers, respectively. Reactions using 0.5 mol% of **Ia** were significantly slower than for the corresponding isocyanates. However, quantitative conversion to the imidazolidin-2-thiones products was achieved within 30 minutes at room temperature with 5 mol% of **Ic**.

Unlike the isocyanate-based reactions, the linear isothiocyanate insertion intermediates analogous to **2** were not distinguishable by ^{1}H NMR spectroscopy due to broadening of the resonances. The *Z*/*E* isomer distribution of the products, however, quantified by integration of the ^{1}H NMR singlets of the benzylidene protons, followed similar patterns to that of the imidazolidin-2-ones. Aryl substituents and the less sterically hindering ethyl functionality predominantly yielded the *Z* isomer (Table 4, entries 1–3), whereas the more sterically demanding isopropyl and cyclohexyl derivatives yielded the *E* isomer as the major product (Table 4, entries 4 and 5). The steric influence of the isothiocyanate alkyl substituent appeared more pronounced, however, than for the corresponding isocyanates, presumably due to the greater steric repulsion of the exocyclic sulfur versus oxygen atom. In contrast to the isocyanate-based reactions, no observable isothiocyanate insertion was evident even at high temperature for the larger *tert*-butyl and adamantyl derivatives (Table 4, entries 6 and 7). The isolated imidazolidin-2-thiones proved to be very moisture-sensitive and had to be isolated in a glovebox. An X-ray diffraction analysis experiment performed on single crystals of the 4-*tert*-butylphenyl derivative gave the structure of the predominant *Z*-isomer, (*Z*)-**32** (Figure 7) clearly revealing the maintenance of the thione functionality [C=S 1.654(2) Å].[34]

Insight into the possible course of reaction during the synthesis of compounds **31**–**35** was provided by a reaction between the homoleptic calcium (*N,N'*-diisopropyl)phenylpropargylamidinate dimer, **IV**,[35] and two molar equivalents of (*para*-*tert*-butyl)phenylisothiocyanate in toluene. This process provided clean access to the heteroleptic calcium compound **V** (Scheme 10), a single-crystal X-ray crystallographic analysis of



Scheme 8.

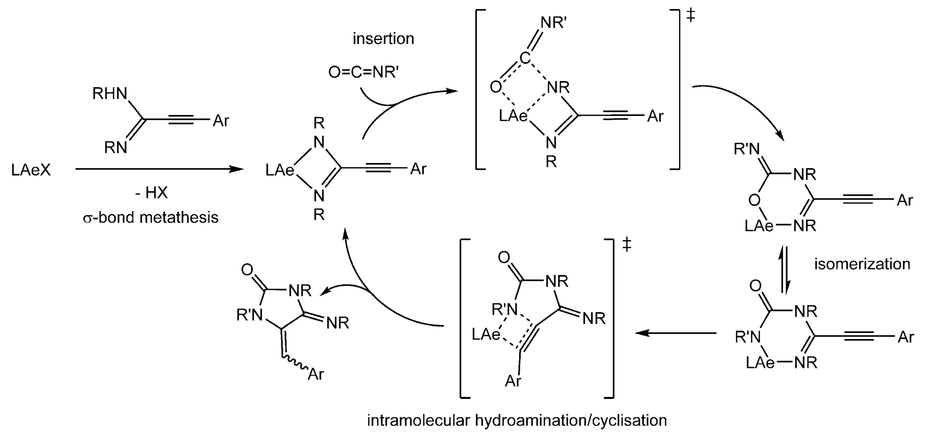
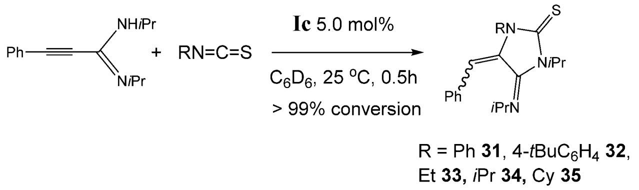


Figure 6. Mechanism for the alkaline earth-catalysed formation of imidazolidin-2-ones from arylpropargylamidines and isocyanates.

imidazolidine products bearing an exocyclic thione moiety are formed in kinetic preference to the more thermodynamically stable thiazole heterocycles.

Although no evidence for the formation of the alternative thiazolidine isomers was observed during the synthesis of compounds **31**–**35**, a further extension of this protocol demonstrated that the thiazolidine ring system was accessible through the strontium-catalysed reaction of carbon disulfide with (*N*,*N'*-diisopropyl)phenylpropargyl-



Scheme 9.

Table 4. Isothiocyanate scope for the catalytic synthesis of (5-benzylidene-4-imino)imidazolidin-2-thiones from **1** by using 5 mol% of **Ic** in C_6D_6.

Entry	R	Product	*T* [°C]	*Z/E* [%]
1	Ph	**31**	25	97:3
2	4-*t*Bu-C_6H_4	**32**	25	95:5
3	Et	**33**	25	88:12
4	*i*Pr	**34**	25	5:95
5	Cy	**35**	25	15:85
6	*t*Bu	–	80	–
7	Ad	–	80	–

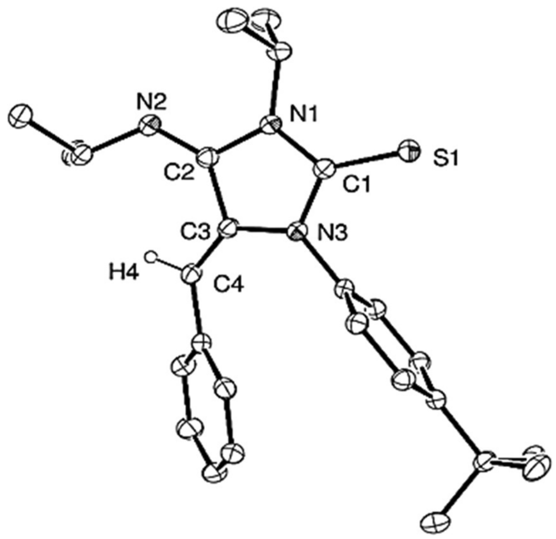
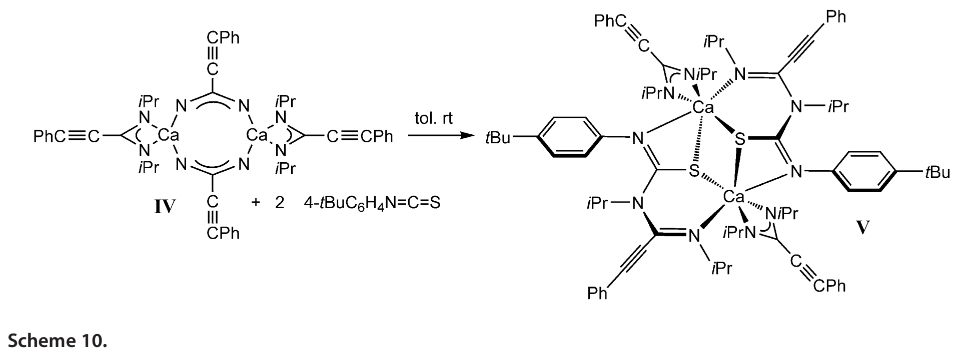


Figure 7. ORTEP representation of compound (*Z*)-**32**. Ellipsoids are drawn at 30% probability. Hydrogen atoms are omitted for clarity, except for that on the benzylidene moiety.

which revealed it to be a dimeric calcium species bearing terminal amidinate ligands and bridging (2-propargylamidino)imidothioate ligands (Figure 8). The latter units form a six-membered *N*,*S*-chelate, with the sulfur atom bridging between both calcium centres, and coordination to the second alkaline earth centre through the pendant *N*-(4-*tert*-butylphenyl)imino nitrogen. The sulfur-containing ligand is effectively analogous to the isocyanate-derived magnesium chelate within the homoleptic species, compound **II**. Thus, we suggest the formation of the catalytic production of the imidazolidin-2-thione derivatives also follows a similar mechanistic pathway, in which the

amidine. At 60 °C, CS_2 insertion followed by intramolecular hydrothiolation, proceeded smoothly to give the (4-benzylidene-5-imino)thiazolidin-2-thione product, **36**, which over a period of 48 h fully tautomerised to the corresponding 5-benzyl-1,3-thiazole-2-thione (**37**; Scheme 11).



Scheme 10.

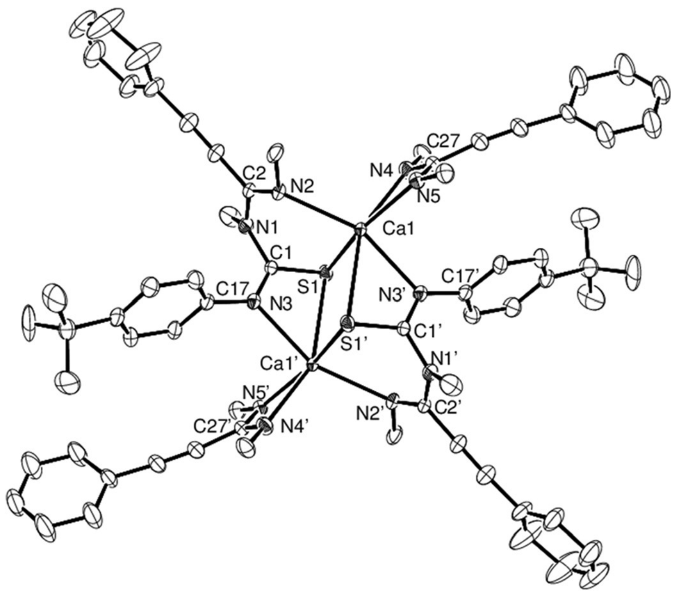
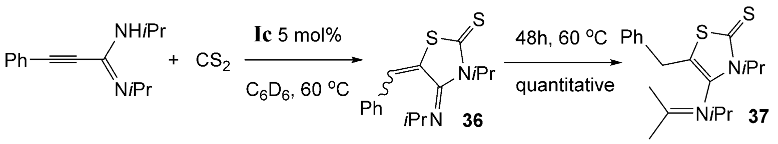


Figure 8. ORTEP representation of compound **V**. Ellipsoids are drawn at 30% probability. Hydrogen atoms and isopropyl methyl groups are omitted for clarity.



Scheme 11.

Conclusion

We have demonstrated the applicability of readily available and sustainable alkaline earth bis(amide) precatalysts to the facile one-pot, 100% atom-efficient, stepwise synthesis of a wide variety of highly functionalised imidazolidin-2-ones, imidazolidin-2-thiones, *N*,*N*′-[(5-benzylidene-imidazoldin-2,4-ylidene)diamines and 1,3-thiazolidin-2-thiones from the simplest commercially available building blocks. Although the current investigation is relatively broad in scope, we suggest that the formation of compound **37** indicates that even broader manifestations of this protocol may be achieved through the incorporation of further alternative heterocumulene substrates. Catalytic access to a variety of valuable heterocyclic derivatives may thus be readily achieved in a cost-efficient manner and with complete atom efficiency. We are continuing to explore these possibilities and will describe our investigations in future publications.

Acknowledgements

We thank the EPSRC (UK) for generous funding.

Keywords: alkaline earths metals · cascade reactions · cycloaddition · synthetic methods

[1] J. A. Joule, K. Mills, *Heterocycles in Medicine, in Heterocyclic Chemistry* 5th ed., Wiley-Blackwell, Hoboken, NJ, **2010**.
[2] M. Meusel, M. Gutschow, *Org. Prep. Proc. Int.* **2004**, *36*, 391 – 443.
[3] K. K. Borowicz, M. Banach, *Pharmacol. Rep.* **2014**, *66*, 545 – 551.
[4] J. M. Chezal, G. Delmas, S. Mavel, H. Elakmaoui, J. Metin, A. Diez, Y. Blache, A. Gueiffier, M. Rubiralta, J. C. Teulade, O. Chavignon, *J. Org. Chem.* **1997**, *62*, 4085 – 4087.
[5] F. Nique, S. Hebbe, N. Triballeau, C. Peixoto, J.-M. Lefrancois, H. Jary, L. Alvey, M. Manioc, C. Housseman, H. Klaassen, K. Van Beeck, D. Guedin, F. Namour, D. Minet, E. Van der Aar, J. Feyen, S. Fletcher, R. Blanque, C. Robin-Jagerschmidt, P. Deprez, *J. Med. Chem.* **2012**, *55*, 8236 – 8247.
[6] T. Krause, M. U. Gerbershagen, M. Fiege, R. Weisshorn, F. Wappler, *Anaesthesia* **2004**, *59*, 364 – 373.
[7] M. Shiozaki, *Carbohydr. Res.* **2002**, *337*, 2077 – 2088.
[8] S. G. Burton, R. A. Dorrington, *Tetrahedron: Asymmetry* **2004**, *15*, 2737 – 2741.
[9] B. Zhao, H. Du, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7220 – 7221.
[10] M. Beller, M. Eckert, W. A. Moradi, H. Neumann, *Angew. Chem. Int. Ed.* **1999**, *38*, 1454 – 1457; *Angew. Chem.* **1999**, *111*, 1562 – 1565.
[11] T. Miura, Y. Mikano, M. Murakami, *Org. Lett.* **2011**, *13*, 3560 – 3563.
[12] Y. Ohshiro, K. Kinugasa, T. Minami, T. Agawa, *J. Org. Chem.* **1970**, *35*, 2136 – 2140.
[13] G. Süss-Fink, G. F. Schmidt, G. Herrmann, *Chem. Ber.* **1987**, *120*, 1451 – 1453.
[14] Y. Kuninobu, K. Kikuchi, K. Takai, *Chem. Lett.* **2008**, *37*, 740 – 741.
[15] a) A. G. M. Barrett, M. R. Crimmin, M. S. Hill, P. A. Procopiou, *Proc. R. Soc. London Ser. A* **2010**, *466*, 927 – 963; b) S. Harder, *Chem. Rev.* **2010**, *110*, 3852 – 3876; c) M. Arrowsmith, M. S. Hill, *Alkaline earth Chemistry: Applications in Catalysis in Comprehensive Inorganic Chemistry II, Vol. 1* (Ed.: T. Chivers), Elsevier, Amsterdam, **2013**, pp. 1189 – 1216; d) M. R. Crimmin, M. S. Hill, *Alkaline Earth Metal Compounds: Oddities and Applications, Topics in Organometallic Chemistry, Vol. 45*, Springer-Verlag, Berlin Heidelberg, **2013**, pp. 191 – 241.
[16] a) M. Crimmin, I. Casely, M. Hill, *J. Am. Chem. Soc.* **2005**, *127*, 2042 – 2043; b) J. Spielmann, F. Buch, S. Harder, *Angew. Chem. Int. Ed.* **2008**, *47*, 9434 – 9438; *Angew. Chem.* **2008**, *120*, 9576 – 9580; c) J. Spielmann, S. Harder, *Eur. J. Inorg. Chem.* **2008**, 1480 – 1486; d) F. Buch, J. Brettar, S. Harder, *Angew. Chem. Int. Ed.* **2006**, *45*, 2741 – 2745; *Angew. Chem.* **2006**, *118*, 2807 – 2811; e) C. Brinkmann, A. G. M. Barrett, M. S. Hill, P. A. Procopiou, S. Reidt, *Organometallics* **2012**, *31*, 7287 – 7297.
[17] a) M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, I. J. Casely, M. S. Hill, P. A. Procopiou, *J. Am. Chem. Soc.* **2009**, *131*, 9670 – 9685; b) S. Datta, P. W. Roesky, S. Blechert, *Organometallics* **2007**, *26*, 4392 – 4394; c) S. Datta, M. T. Gamer, P. W. Roesky, *Organometallics* **2008**, *27*, 1207 – 1213; d) F. Buch, S. Harder, *Z. Naturforsch B J. Chem. Sci.* **2008**, *63*, 169 – 177; e) P. Horrillo-Martínez, K. C. Hultzsch, *Tetrahedron Lett.* **2009**, *50*, 2054 – 2056.
[18] B. M. Day, W. Knowelden, M. P. Coles, *Dalton Trans.* **2012**, *41*, 10930 – 10933.
[19] J. F. Dunne, S. R. Neal, J. Engelkemier, A. Ellern, A. D. Sadow, *J. Am. Chem. Soc.* **2011**, *133*, 16782 – 16785.
[20] V. Leich, T. P. Spaniol, L. Maron, J. Okuda, *Chem. Commun.* **2014**, *50*, 2311 – 2314.
[21] B. Liu, J.-F. Carpentier, Y. Sarazin, *Chem. Eur. J.* **2012**, *18*, 13259 – 13264.
[22] B. Liu, T. Roisnel, J.-F. Carpentier, Y. Sarazin, *Angew. Chem. Int. Ed.* **2012**, *51*, 4943 – 4946; *Angew. Chem.* **2012**, *124*, 5027 – 5030.
[23] B. Liu, T. Roisnel, J.-F. Carpentier, Y. Sarazin, *Chem. Eur. J.* **2013**, *19*, 13445 – 13462.
[24] B. Liu, T. Roisnel, J.-F. Carpentier, Y. Sarazin, *Chem. Eur. J.* **2013**, *19*, 2784 – 2802.

[25] D. Mukherjee, A. Ellern, A. D. Sadow, *Chem. Sci.* **2014**, *5*, 959 – 964.
[26] S. R. Neal, A. Ellern, A. D. Sadow, *J. Organomet. Chem.* **2011**, *696*, 228 – 234.
[27] T. D. Nixon, B. D. Ward, *Chem. Commun.* **2012**, *48*, 11790 – 11792.
[28] N. Romero, S.-C. Rosca, Y. Sarazin, J.-F. Carpentier, L. Vendier, S. Mallet-Ladeira, C. Dinoi, M. Etienne, *Chem. Eur. J.* **2015**, *21*, 4115 – 4125.
[29] R. J. Schwamm, M. P. Coles, *Organometallics* **2013**, *32*, 5277 – 5280.
[30] R. J. Schwamm, B. M. Day, N. E. Mansfield, W. Knowelden, P. B. Hitchcock, M. P. Coles, *Dalton Trans.* **2014**, *43*, 14302 – 14314.
[31] J. S. Wixey, B. D. Ward, *Dalton Trans.* **2011**, *40*, 7693 – 7696.
[32] J. S. Wixey, B. D. Ward, *Chem. Commun.* **2011**, *47*, 5449 – 5451.
[33] M. S. Hill, D. J. Liptrot, M. F. Mahon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5364 – 5367; *Angew. Chem.* **2013**, *125*, 5472 – 5475.
[34] M. Arrowsmith, W. M. S. Shepherd, M. S. Hill, G. Kociok-Köhn, *Chem. Commun.* **2014**, *50*, 12676 – 12679.
[35] M. Arrowsmith, M. R. Crimmin, M. S. Hill, S. L. Lomas, M. S. Heng, P. B. Hitchcock, G. Kociok-Köhn, *Dalton Trans.* **2014**, *43*, 14249 – 14256.

Received: April 4, 2015
Published online on June 11, 2015