Green Chemistry



View Article Online

PAPER

Check for updates

Cite this: *Green Chem.*, 2018, **20**, 4023

Thermal azide–alkene cycloaddition reactions: straightforward multi-gram access to Δ^2 -1,2,3-triazolines in deep eutectic solvents†

Filip Sebest, ^(D)^a Luis Casarrubios, ^(D)^{a,b} Henry S. Rzepa, ^(D)^a Andrew J. P. White ^(D)^a and Silvia Díez-González ^(D)*^a

The multi-gram synthesis of a wide range of 1,2,3-triazolines *via* azide–alkene cycloaddition reactions in a Deep Eutectic Solvent (DES) is reported. The role of DES in this transformation as well as the origin of the full product distribution was studied with an experimental/computational-DFT approach.

Introduction

Received 8th June 2018, Accepted 29th June 2018

DOI: 10.1039/c8qc01797b

rsc.li/greenchem

1,3-Dipolar cycloadditions, also known as Huisgen reactions, are convergent and atom-economical reactions that offer a convenient synthetic route for five-membered heterocyclic molecules.¹ To date, few reactions can match dipolar cycloadditions in the variety of bonds that can be involved and the increase of molecular complexity in the obtained products. Hence, the extensive research coverage received by these reactions over the years is more than justified and has notably allowed uncovering alternative catalytic routes leading to broader and more selective reactions, including enantioselective ones. A particularly high-profile example of this is the copper-mediated azide–alkyne cycloaddition reaction,² and this transformation has become the emblem of Click chemistry,³ a concept coined by Sharpless in 2001 and closely related to that of Green chemistry.

While the use of metals (mainly copper, but also ruthenium, iridium, or silver)⁴ has been instrumental for the study and application of triazoles, the preparation of 1,2,3-triazolines from azides and alkenes remains limited to highly activated alkenes, such as strained and electron-rich alkenes,⁵ and therefore out of the scope of Click chemistry. Simple alkenes do not react with azides or react very slowly and reaction times of several days or even months are not overly uncommon.⁶ Even when a triazoline can be formed, it often rearranges/ further reacts and other heterocycles (such as triazoles,⁷ pyrazolines,⁸ isoindoles,⁹ amidines,¹⁰ pyrrol- and indol-izidines¹¹) are isolated instead. In consequence, the promise of 1,2,3triazolines as versatile synthons¹² and biologically active compounds remains unfulfilled.¹³

A thermal azide-alkene cycloaddition is expected to deliver two regioisomeric triazolines, either 1,4- or 1,5-disubstituted, and the product distribution is mainly dictated by electronic factors.¹⁴ Thermodynamically, dipolar cycloadditions leading to either triazoles or triazolines are virtually identical. However, while triazoles are aromatic and highly stable, triazolines are typically more reactive than the starting materials due to the numerous decomposition pathways available to them.¹⁵ The most commonly encountered products are then imines (often hydrolysed into amines and carbonyl derivatives) and aziridines. The formation of aziridines upon nitrogen extrusion from the corresponding triazolines could be a simple alternative to metal-mediated aziridination reactions with azides as nitrene source.¹⁶ However, the formation of aziridines from the corresponding triazolines depends strongly on the position and electronic nature of the substituents on the five-membered ring,¹² which has led to apparently conflicting reports over the years.^{17,18} Unlike the reaction with alkynes, to the best of our knowledge no metal-mediated version of the azide-alkene cycloaddition has been reported and therefore the scope of this reaction remains severely limited.

On the other hand, it was recognised early on that the reaction media could play a key role in numerous non-catalysed dipolar cycloaddition reactions.¹⁹ As part of our interest in developing user-friendly and greener methodologies, we turned our attention to Deep Eutectic Solvents (DESs). DESs are combinations of two or three inexpensive, non-toxic and safe components that produce a non-flammable mixture with a much lower melting point than any of the individual com-

^aDepartment of Chemistry, Imperial College London, Exhibition Road,

South Kensington, London SW7 2AZ, UK. E-mail: s.diez-gonzalez@imperial.ac.uk ^bDepartamento de Química Organica I, Facultad de Ciencias Químicas, Universidad Complutense and Centro de Innovación en Química Avanzada (ORFEO-CINQA), 28040 Madrid. Spain

[†]Electronic supplementary information (ESI) available: FAIR data for NMR spectra, computational and crystallographic data, see ref. 48. CCDC 1843142–1843147. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8gc01797b

View Article Online

Green Chemistry

ponents. These mixtures, which are liquids at the reaction temperature, are held together *via* hydrogen bonding interactions. The interesting physico-chemical properties of DESs are often compared to those of ionic liquids, with the additional advantages of lower costs and much higher userand environment-friendliness (*i.e.* water tolerance).²⁰ The benefits of using DESs instead of ionic liquids or standard organic solvents are obviously dependent on the actual DES components. Those made of urea, glycerol, water or choline chloride are particularly promising in Green chemistry.

The applications of DESs are steadily spreading in separation, materials, organic and organometallic chemistry.²¹ In particular, DESs have been applied to several cycloaddition reactions such as Lewis acid-catalysed Diels–Alder reactions,²² formation of pyrrolidines from the corresponding azomethine ylides,²³ and isoxazoles from nitrile oxides.²⁴ From azides, either tetrazoles²⁵ or triazoles²⁶ have been prepared in DES. In many of these examples the beneficial effect of DES as reaction media was rationalised either through the Lewis acidity of one of the components, or the formation of hydrogen bonds between either of the components and the cycloaddition partners.

Herein we report straightforward azide–alkene cycloaddition reactions in Deep Eutectic Solvents to yield 1,2,3-triazoline cycloadducts, or in some cases aziridines, where organic solvents or ionic liquids only led to disappointing results. Preliminary studies to ascertain the role of DES in the azide–alkene cycloaddition reaction and the origin of the aziridine products are also presented.

Results and discussion

Optimisation of the reaction conditions

4-Trifluoromethylphenyl azide and styrene were chosen as model substrates and they were reacted at 80 °C overnight (Table 1). Mixtures of 1,5-disubstituted triazoline **3aa** and aziridine **4aa** were obtained in most reactions. A number of known decomposition products of triazolines –an imine, aniline or acetophenone (Table 1)– were evidenced by NMR in many of these reactions but only as traces. Disappointing NMR yields were obtained in all tested organic solvents independently of their characteristics due to severe decomposition of cycloadducts and/or the starting azide (up to 80% of the total mass, Table 1, entries 1–10), which made it virtually impossible to isolate any reaction product. In stark contrast with these results, a clean reaction was obtained when the model substrates were heated in a mixture 1:2 of choline chloride and urea (DES, Table 1, entry 12).

It is important to note that both reaction products are stable under the reaction conditions and they were recovered quantitatively when heated separately at 80 °C in DES for 16 h. However, partial decomposition of triazoline **3aa** was observed when heated in standard organic solvents (*i.e.* DMSO, 1,4-dioxane) at the same temperature (*vide infra*). We believe that this increased stability of triazolines in DES is key to explaining the success of these reactions.

 Table 1
 Solvent screening^{a,b}

	N₃ + Ph − − − − − − − − − − − − − − − − − − −	Solvent, 80 °C	Ar-N ^N N Ph 3aa	Ar + N Ph 4aa
Entry	Solvent	$\mathbf{1a}^{c}(\%)$	$\mathbf{3aa}^{c}(\%)$	$4aa^{c}(\%)$
1	Toluene	25	5	13
2	MeCN	23	<5	5
3	$CHCl_3$	19	<5	7
4	1,4-Dioxane	30	18	14
5	THF	14	30	13
6	TBME	37	11	10
7	Diglyme	0	10	11
8	EtOAc	38	<5	7
9	EtOH	22	5	<5
10	DMSO	16	<5	0
11	Water	12	0	0
12	DES	7	55	18

^{*a*} Reaction conditions: Azide **1a** (1 mmol), styrene **2a** (1.3 equiv.) in 2 mL of solvent. ^{*b*} Observed trace decomposition products:

$$h \xrightarrow{N \xrightarrow{Ar}} CF_3 \xrightarrow{O} Ph \xrightarrow{O}$$

^{*c* ¹}H NMR yields/recovery are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

Capitalising on this promising result, the optimisation studies then focused on cycloaddition reactions in deep eutectic solvents and different reaction times and temperatures were screened. At 80 °C no further conversion was observed when the reaction mixture was heated for 24 h instead of 16 h. Comparable conversions into **3aa** and **4aa** were observed at 90 °C after 8 h, but again the reaction did not proceed further after longer heating periods. Higher reaction temperatures led to significant formation of decomposition products.

Next, a number of commonly encountered DESs were tested (Table 2). In all cases, the starting azide was fully converted when 2 equivalents of styrene were employed and overall similar reaction outcomes were obtained with most of the tested DESs. The original choice, choline chloride/urea (1:2), led to the highest conversion into the desired triazoline 3aa. When choline iodide was used instead as the Lewis base partner, significant formation of 4-trifluoromethylaniline (~10%) was observed and the resulting DES was only liquid above 70 °C, which made its manipulation cumbersome. Other DESs remained valuable options, except when a more acidic partner such as glycolic acid was used as one of the components and only a complex mixture of decomposition products was obtained (Table 2, entry 6).27 A similar outcome was observed when a popular ionic liquid, BMIM·PF₆ (BMIM = N-butyl-N'-methylimidazolium), was used as solvent (Table 2, entry 7).

After this screening, the term DES in this article will refer solely to a 1:2 mixture of choline chloride and urea.²⁸ To date, only a handful of 1,2,3-triazolines have been structurally

Paper

1

2

3

4

5 6



Choline chloride/glycerol (1:2)	61	12
Choline chloride/glycolic acid $(1:2)$	Decom	position
BMIM·PF ₆	Decom	position

^a Reaction conditions: Azide **1a** (1 mmol), styrene **2a** (2 equiv.) in 2 mL of solvent. ^b ¹H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

characterised,²⁹ and therefore single crystals were grown for 3aa and 4aa to confirm the assigned structures (Fig. 1 and 2). Crystals of 3aa contained two independent molecules and in both of them the triazoline ring has a small envelope deformation with C5 lying ca. 0.20 Å out of the {N1,N2,N3,C4} plane in molecule 3aa-A (0.18 Å in 3aa-B), which atoms are coplanar to better than 0.01 Å in both instances. In each case, the 4-CF₃-phenyl group is almost co-planar to the {N1,N2,N3,C4} plane, while the phenyl ring on C5 is oriented such that its plane approaches eclipsed with respect to the N1-C5 bond, with the N1-C5-C16-C21 torsion angles being ca. 28° in both molecules. Aziridine scaffolds are far more common, and in the case of 4aa, the torsion angle between the two substituents is 138° (Fig. 2).



Fig. 1 Structure of one (3aa-A) of the two independent molecules present in the crystal of triazoline 3aa (50% probability ellipsoids). Most hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): N1A-N2A 1.380(6), N2A-N3A 1.241(8), N3A-C4A 1.471(8), C4A-C5A 1.538(8), N1A-C5A 1.462(7); N3A-N2A-N1A 112.2(5), C4A-C5A-C16A 113.2(4)





Fig. 2 Structure of aziridine 4aa (50% probability ellipsoids). Most hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): N1-C2 1.477(4), N1-C3 1.451(5), C2-C3 1.484(5); C3-N1-C2 60.9(2), C4-N1-C2 18.3(3).

Scope of the reaction

With a set of optimised conditions in hand, we explored the scope of the reaction with a range of aryl/heteroaryl azides and styrene (Table 3). In all cases, the desired 1,5-disubstituted triazolines were the major product in these reactions and the ¹H NMR conversions for the corresponding aziridines ranged between 6 and 36%. Proportionally, the highest formation of aziridines was observed when using azides bearing electrondonating substituent(s) (Table 3, entries 12-15). Reactions with heteroaryl azides as cycloaddition partners (Table 3, entries 16-18) were carried at lower temperatures (60-70 °C) as substantial decomposition of the reaction products was observed at 80 °C.

Even if the main purpose of this work was the preparation of 1,2,3-triazolines, many of the formed aziridines 4 were also isolated and fully characterised due to the inherent importance of this heterocyclic motif, both in chemistry and biology.³⁰ Traces of aniline derivatives were observed in many of these reactions, but such a decomposition product was only significant when a nitro substituent was present in the starting azide (Table 3, entry 2, 23% by ¹H NMR). On the other hand, imine formation was only competitive in the reaction of heteroaryl azide 1r (Table 3, entry 18). Indeed, whereas triazolines bearing ortho-electron-donor groups in their 1-aryl substituents were found relatively stable, this was not the case when the ortho substituent was an electron-withdrawing one. For example, in the reaction with 2-trifluoromethylphenyl azide, only traces of the desired triazoline were observed together

Table 3 Reaction scope – aryl and heteroaryl azides^a



^{*a*} Reaction conditions: Azide **1X**, styrene **2a** (2 equiv.) in DES (0.5 M). ^{*b*} ¹H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. ^{*c*} Isolated yields. ^{*d*} Reaction time = 8 h. ^{*e*} Reaction carried out at 70 °C for 24 h. ^{*f*} Reaction carried out at 60 °C for 32 h.

with 30% of aziridine, 18% of imine and 6% of aniline. In the case of 2-nitrophenyl azide, only formation of imine (18%) and aniline (16%) was evidenced by 1 H NMR.

While the optimisation studies were carried out using 1 mmol of aryl azide, the reactions could be easily scaled up and the scope of the cycloaddition was explored using 3 to 5 g of azide (15-27 mmol). This led to the multigram isolation of 1,2,3-triazolines, typically by simple precipitation and recrystallisation from the reaction mixture, which minimises the need for volatile organic compounds. Column chromatography was still necessary in some cases, as for the isolation of oily triazolines and aziridines, since the latter remained in the filtrate during the first recrystallization step. While triazoline 3aa and aziridine 4aa could be separated on silica, significant decomposition (~40% of the formed materials) was observed as expected for products sensitive to acidic conditions. This could be easily avoided using basified silica (triethylamine), instead. No decomposition was observed with cellulose either, although the separation of 3aa and 4aa was poor and required several columns to obtain an acceptable purity. When basified alumina or florisil were used as stationary phase only triazoline 3aa was recovered, albeit contaminated with some decomposition by-products. Finally, purification on neutral alumina resulted in the substantial decomposition of both products. Overall, basified silica led to the best separation of the formed reaction products while minimising their decomposition during purification.

Benzylic azides were also screened in DES (Table 4), although lower conversions into cycloadducts were observed in these reactions, particularly when no electron-withdrawing groups were present. Longer reactions times could be used in order to maximise azide conversion, but higher reaction temperatures only led to significant decomposition of the reaction mixture. The reaction of bis(azide) **1v** led to the formation of four different products, with that bearing a triazoline and an aziridine ring being the major product (**34va**, Table 4, entry 4).

The reaction of 1-azido-2-ethoxyethane with styrene has been reported to yield a mixture of regioisomeric triazolines after heating neat at 50 °C for 30 days.³¹ However, when we tried to reproduce this transformation, we obtained a mixture of 1,5-disubstituted triazoline and aziridine (49% and 35% ¹H NMR yield, respectively). This reaction could also be performed in DES, albeit low conversions were obtained after 16 h of stirring (Table 4, entry 5). Only starting materials were recovered from the reactions with other aliphatic azides (*i.e.* decyl

Table 4 Reaction scope – aliphatic azides^a

	1X + Ph 2a	DE	S, 80 °C 16 h Ph	N N 3Xa Ph	R N /\
Entry	Azide		$3:4^{b}$ (%)	3 ^c (%)	$4^{c}(\%)$
1^d	N ₃	1s	36:34	28	29
$2^{d,e}$	F ₃ C N ₃	1t	50:30	42	22
3	N ₃	1u	18:8	_	—
$4^{e,f}$	N ₃	1v	9:24:42:15	6 (31va) 20 (33va) 29 (34va)	1 (44va)
5^g	$\sim N_3$	1w	n.d.	16	5

^{*a*} Reaction conditions: Azide **1X**, styrene **2a** (2 equiv. per azide group) in DES (0.5 M). ^{*b*} ¹H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. ^{*c*} Isolated yields. ^{*d*} Reaction carried out at 85 °C. ^{*e*} Reaction time = 24 h. ^{*f*} Four reaction products could be isolated in this reaction:



^g Reaction carried out at 70 °C.

azide and adamantyl azide) at 80 °C. When the reaction temperature was raised to 90 °C, 8% of the desired triazoline was observed by ¹H NMR with decyl azide, but higher temperatures only led to severe decomposition of the reaction mixture.

Next, the generality of the reaction in terms of alkene substitution was studied (Table 5). Two other styrene derivatives were screened bearing either an electron-withdrawing or an electron-donating group at the para position (Table 5, entries 1 and 2). While only formation of triazoline 3dc was observed in the reaction with 4-methoxystyrene, a lower ratio of triazoline formation was observed with the 4-chloro analogue. A similar triazoline to aziridine ratio was also obtained with a naphthyl derivative (Table 5, entry 3). The structure of triazoline 3dd was confirmed by X-ray crystallography (Fig. 3) because several broad signals were observed in its ¹H NMR spectrum, which in our experience is unusual for this family of compounds. Interestingly, the reaction of 4-vinylpyridine afforded the corresponding aziridine 4de as the major reaction product (Table 5, entry 4). This was also the only product that could be isolated analytically pure from this reaction.

Table 5 Reaction scope – monosubstituted alkenes N_3 DES. 80 °C 16 – 24 h R 1d 2X 3dX 4dX COOF $3:4^{b}(\%)$ Entry 3^c (%) $4^{c}(\%)$ Alkene 1 2b 53:31 39 2 86:0 70 2c3 2d56:2542 14 4 2e 31:40 31 5 2f 44:16 41 3 6 2g 67:<5 62 7 2h 5:30 16 8^d 2i 52:1543 26 96 2j 74:0 66 10^{j} 2k 90:085 11^g 21 56:0 37

^{*a*} Reaction conditions: Azide **1d**, alkene **2X** (2 equiv.) in DES (0.5 M). ^{*b*} ¹H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. ^{*c*} Isolated yields. ^{*d*} Reaction carried out at 85 °C. ^{*e*} Reaction carried out at 75 °C. ^{*f*} Reaction carried out at 65 °C. ^{*g*} Reaction carried out at 60 °C.



Fig. 3 Structure of triazoline 3dd (50% probability ellipsoids). Most hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): N1–N2 1.3724(18), N2–N3 1.2515(19), N3–C4 1.477(2), C4–C5 1.542(2), N1–C5 1.4681(19); N3–N2–N1 111.97(14), C4A–C5A–C16A 113.99(12).

We also found that the allylic substituent has a profound impact on the cycloaddition outcome. Indeed, the reaction of allyltrimethylsilane delivered triazoline 3dg in good yields and only traces of the corresponding aziridine. However, allylic alcohol led to the formation of 30% of aziridine 4dh and only 5% of triazoline (Table 5, entries 6 and 7). Significant aniline formation (~25% ¹H NMR yield), indicative of product decomposition, was observed in all reactions with allylic derivatives. Even an alkene as non-activated as 1-octene could be successfully used under our reaction conditions (Table 5, entry 8). As expected,⁵ electron-richer alkenes led to completely selective reactions and no aziridine formation was observed (Table 5, entries 9 and 10). These alkenes were particularly reactive cycloaddition partners and triazoline 3dk could be prepared at 65 °C in high yields. This accrued reactivity was exploited with allyl vinyl ether (Table 5, entry 11), which delivered 5-(allyloxy)triazoline 3dl with only traces of the triazoline issue of the reaction of the allyl moiety. Nevertheless, the presence of an allyl group remained problematic and around 30% of the overall mass could not be accounted for in this case.

Next, the effect of introducing additional substituents on the alkene partner was explored. In general, longer reaction times and/or higher reaction temperatures were required to overcome the increased steric bulk in these reactions (Table 6). 1,1-Disubstituted alkenes led to the exclusive formation of the corresponding triazolines with the notable exception of 1,1diphenylethene (Table 6, entries 1–3). Norbornene yielded triazoline **3dp** quantitatively at room temperature (Table 6, entry 4), as expected for a strained substrate.^{5a} In stark contrast, unstrained 1,2-disubstituted alkenes led to the stereospecific formation of the corresponding aziridines (*trans*-aziridines from *E*-alkenes and *cis*-aziridines from *Z*-alkenes). The crystal structure of **4dq** confirmed the stereospecificity of the aziri-

10	+ R R	DES, T, t	Ar N N N R R' 3dX	4d	r I R' X
Entry	Alkene	Conditions	$3:4^{b}(\%)$	$3^{c}(\%)$	4^{c} (%)
1	MeO 2m	75 °C, 96 h	92:0	87	_
2	Ph 2n	90 °C, 16 h	66:0	51	—
3		100 °C, 72 h	30:17	24	11
4	2p	RT, 16 h	100:0	99	—
5	Ph Ph 2q	100 °C, 48 h	0:60	_	53
6	Ph 2r	110 °C, 16 h	0:42	_	36
7	Ph Me 2s	90 °C, 32 h	0:26	_	21
8	Me C ₅ H ₁₃ 2t	95 °C, 32 h	0:26	—	21

^{*a*} Reaction conditions: Azide **1d**, alkene **2X** (2 equiv.) in DES (0.5 M). ^{*b*} ¹ H NMR yields are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard. ^{*c*} Isolated yields.

dine formation,³² which is in agreement with the expected configurational stability of singlet biradicals (*vide infra*).³³

Aziridines **4dq-4dt** were accompanied by decomposition products, which suggests that triazolines bearing substituents on the 4-position are considerably less stable and supports the notion of aziridines being formed from 1,4-disubstituted triazolines, as discussed below.

From these results, it is clear that the product distribution is most strongly influenced by the alkene substitution, while the nature of the azide has a crucial effect on the overall conversion into cyclised products.

Finally, we screened a 1,2-diene under our reaction conditions, cyclohexylallene (Scheme 1). In this case, no aziridine formation was observed and instead two conjugated cycloadducts were obtained (together with aniline and other unidentified decomposition products), triazoline 3du and triazole 5du, issue of a double bond migration in 3du. The observed regioselectivity is in accordance with the few reports available on intermolecular azide-allene cycloadditions.³⁴

No conversion of triazoline **3du** into triazole **5du** was observed during its isolation/purification. However, attempts to grow crystals of **3du** from a hot solution in methanol led to the characterisation of peroxide **5du**' instead. While triazole **5du**' was not present in the reaction mixture, traces of it could already be evidenced in the ¹H NMR of triazoline **3du** after a pentane/diethyl ether wash, which shows its high reactivity.

Mechanistic studies and origin of the aziridines

(*A*) *The DES effect*: As mentioned in the introduction, no metalbased catalysts have been reported for azide–alkene cycloaddition reactions. We could only find two reports evoking the use of organocatalysts in this reaction. Garcia-Garibay and coworkers reported the use of dimethylurea as catalyst in the cycloaddition reaction of aryl azides and electron-poor 1,2-disubstituted alkenes.³⁵ Alternatively, tetramethylammonium hydrogen sulfate was used to mediate the cycloaddition of enones to isolate triazoles after *in situ* oxidation of the intermediate triazoline.³⁶ When we subjected one of our reactions to these reported conditions, only disappointing results were obtained (Table 7, entries 1–3). Little, if any, cycloadducts were obtained, accompanied by significant decomposition of the reaction mixture as observed by ¹H NMR.

Furthermore, in previous examples of dipolar cycloadditions in DES, an organocatalytic effect is often suggested through H-bonding interactions between the cycloaddition partners and DES components.^{23,24,26b} While such interactions might be established with any organic azide through its internal nitrogen atom, most of the alkenes screened in this work are not susceptible to forming hydrogen bonds. We nevertheless tested each of the DES components as organocatalysts for cycloaddition. In these tests, THF/water mixtures and vigorous stirring were required in order to ensure homogeneous solutions. Virtually identical results were obtained with either 15 mol% of choline chloride or urea (Table 7, entries 5 and 6) and even if the conversion of triazoline 3aa remained modest it should be noted that only decomposition was obtained when the cycloaddition was carried out in THF/ water in the absence of an additive. Using both DES components in sub-stochiometric quantities further improved the results, but none of these conditions were competitive when compared to the developed reactions in DES, which led to the highest and cleanest conversions (Table 7, entries 4 and 8).

Overall, it appears plausible that the observed "DES effect" in the azide–alkene reaction is mainly due to the increased thermal stability of the formed cycloadducts when compared to standard organic solvents. However, an organocatalytic effect of one or both DES components cannot be completely ruled out at this time.

(*B*) Formation and evolution of triazolines: It is well established that the cycloaddition of aryl azides and simple alkeness proceeds through an asynchronous concerted mechanism.³⁷ In comparison, the factors determining the final reaction product distribution are less studied.^{35,38} Accordingly, we next carried out a computational mechanistic study to rationalise the obtained experimental results and focused our efforts on 1,2,3-triazolines as the origin of the isolated aziridines. The formation of the three-membered heterocycles *via* a nitrene– alkene cycloaddition was not considered since formation of nitrenes from the reported aryl azides is highly unlikely at the reaction temperatures employed.³⁹ Indeed, azide **1d** was quantitatively recovered after heating it in DES at 80 °C for 24 h or at 90 °C for 8 h. Hence, the formation of aziridines **4** from



Scheme 1 Intermolecular azide–allene cycloaddition reaction in DES. Structures of one (5du'-A) of the two independent molecules present in the crystal of triazoles 5du' (left) and triazole 5du (right) are 50% probability ellipsoids. Most hydrogens are omitted for clarity.

Table 7 Organocatalytic tests^a

	$1X R 2a$ N_{3} $Ph Conditions A$	Ph 3Xa	$\frac{Ar}{N} + Ar - NH_2$		
Entry	Conditions (R = -COOEt)	1d (%)	3da (%)	4da (%)	$\operatorname{ArNH}_{2}(\%)$
1	Dimethylurea (10 mol%), toluene, 80 °C, 16 h	12	23	12	_
2	[NBu ₄][HSO ₄] (20 mol%), toluene, 80 °C, 16 h	58	_	_	7
3	[NBu ₄][HSO ₄] (20 mol%), DMF, 80 °C, 16 h	42	9	5	10
4	Standard conditions: DES, 80 °C, 16 h	5	63	24	7
Entry	Conditions ($R = -CF_3$)	1a (%	%) 3aa (%)	4aa (%)	$\operatorname{ArNH}_{2}(\%)$
5	Urea (15 mol%), THF/water, 80 °C, 16 h	20	19	11	6
6	ChCl (15 mol%), THF/water, 80 °C, 16 h	16	22	10	6
7	Urea (30 mol%), ChCl (15 mol%), THF/water, 80 °C, 16 h	0	42	16	5
8	Standard conditions: DES, 80 °C, 16 h	<5	72	24	<5

^{*a* ¹}H NMR yields/recoveries are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.

transient 1,4-disubstituted triazolines seems to be the most likely option. However, we could not prepare such a triazoline even when following literature procedures (*vide supra*, Table 4, entry 5). On the other hand, we observed that triazoline **3aa** was stable under our reaction conditions (Table 8, entry 1) and only minor decomposition was observed in other solvents such as DMSO and dioxane (Table 8, entries 2 and 3). At 100 °C, only 58% of the starting triazoline was recovered but the main decomposition product was the corresponding aniline and only small amounts of aziridine were formed in



^{*a* ¹}H NMR yields/recoveries are the average of two independent experiments and were determined with respect to 1,3,5-trimethoxybenzene as internal standard.



Scheme 2 Complete product distribution in the model reaction.

comparison (Table 8, entry 4). No triazoline was recovered at 100 °C in either DMSO or dioxane, with imine **6aa** being the major thermolysis product in the latter case (Table 8, entries 5 and 6).

Calculations⁴⁰ were performed at the B3LYP⁴¹+GD3BJ⁴²/ $6-311++G(d,p)^{43}$ (triple-ζ) SCRF continuum solvation level, using the CPCM⁴⁴ model and N-methylformamide mixture level parameters (ε = 181.56) to simulate the high polarity of the eutectic solvent used experimentally. Calculations using the alternative $\omega B97XD^{45}$ functional and/or the Def2-OZVPP⁴⁶ quadruple-ζ basis set are reported for selected systems. All transition states were characterised by normal coordinate analysis, revealing one imaginary mode corresponding to the intended reaction. IRC47 calculations on these transition states confirmed the identity and synchronicity of the reactions. Unless stated otherwise, all energy values are free energies $\Delta G_{353}^{\ddagger}$ (kcal mol⁻¹) for a standard state of 1 atm (0.041 M), normalized to a relative free energy of 0 kcal mol^{-1} for the reactant pre-complex. Full coordinates for all the stationary points, together with IRC animations and other data are available via a FAIR data repository.⁴⁸

The reaction between azide **1d** and styrene was chosen for the computational study. In this reaction, small quantities of imine **6da** and the corresponding aniline were also formed as minor by-products (Scheme 2). An overview of the located stationary points and transition states and their corresponding energies is shown in Scheme 3.

At the B3LYP+GD3BJ/6-311++G(d,p)/SCRF level, two concerted asynchronous cycloaddition transition states resulting in the formation of regioisomeric triazolines **3da** and **3da**' were located as **TS1**_{1,5} and **TS1**_{1,4}, respectively (Scheme 3). The basis set effect (BSE) on the difference in the activation free energies $\Delta \Delta G_{353}^{\ddagger}$ for 6-311++G(d,p) *vs*. Def-QZVPP was found to be insignificant, whilst the effect on the barrier is to increase it by ~2 kcal mol⁻¹. The regioselectivity $\Delta \Delta G_{353}^{\ddagger}$ was more sensitive to the DFT functional, ranging from 1.3 for the B3LYP method with no dispersion included, to 2.2 for the ω B97XD method which includes a built-in second generation D2 dis-



Scheme 3 Complete reaction profile with $\Delta G_{353}^{\ddagger}$ calculated at the B3LYP+GD3BJ/6-311++G(d,p)/SCRF level.

persion correction and 2.8 kcal mol⁻¹ using B3LYP with explicit inclusion of the third generation GD3BJ correction (Table 9). These differences qualitatively match the experi-

Calculated	values o	of Δ	G_{353}^{\ddagger}	for	TS1 ^a
	Calculated	Calculated values o	Calculated values of Δ	Calculated values of $\Delta G_{353}^{\ddagger}$	Calculated values of $\Delta G_{353}^{\ddagger}$ for

Method	TS1 _{1,4}	TS1 _{1,5}	$\Delta\Delta G_{353}^{\ddagger}$	$\Delta\Delta G_{353}$ ^c
B3LYP/6-311++G(d,p)	30.8	29.5	$(0.95)^{b}$	-4.9, -4.1
B3LYP+GD3BJ/6- 311++G(d.p)	24.7 (26.7) ^b	21.6 $(24.0)^{b}$	$(3.08)^{a}$ $(2.75)^{b}$	-11.1, -11.7
ω B97XD/6-311++G(d, p)	29.0	26.7	$(2.29)^{b}$	-17.5, -18.3

^{*a*} Bimolecular energetic barriers $\Delta G_{353}^{\ddagger}$ are reduced by 1.7 kcal mol⁻¹ when corrected for the 0.5 M experimental concentration. ^{*b*} Def2-QZVPP basis set. ^{*c*} $\Delta \Delta G_{353}$ product_{1,4}, product_{1,5}. Full FAIR data is available *via* a data repository at DOI: 10.14469/hpc/4325.

Table 10 Calculated values of $\Delta G_{353}^{\ddagger}$ for TS2^a

Method	$\Delta G^{\ddagger}_{353}$	$\Delta\Delta G_{353}^{\ \ b}$
TS2 _{1,5-H} TS2 _{1,5-Ph} TS2 _{1,4a} TS2 _{1,4b}	30.1 30.2 21.8 20.9	$ \begin{array}{r} -53.0 \\ -49.4 \\ -42.4 (-13.9)^c \\ -61.3 \\ \end{array} $

^{*a*} At the B3LYP+GD3BJ/6-311++G(d,p) level, relative to **3da** or **3da**' in kcal mol⁻¹. ^{*b*} Overall reaction free energies. ^{*c*} Energy of intermediate biradical. Full FAIR data is available *via* a data repository at DOI: 10.14469/hpc/4326.

mentally observed regioselectivity favouring the formation of **3da** as the major product (57% isolated yield). The reaction is predicted exoenergic by >10 kcal mol⁻¹ but only if dispersion is included in the model, since this affects both the interaction energies and the entropies, both of which propagate to the free energies.

To understand the origin of the minor products shown in Scheme 2, we next modelled the nitrogen extrusion processes. That from 1,5-disubstituted triazoline was investigated just at the B3LYP+GD3BJ/6-311++G(d,p) level, the reference (resting) state now being the product of the first reaction 3da (Table 10). No transition state for aziridine formation could be located from 3da. Instead, it was computed to evolve into two different imines 6da(H) and 8da(Ph) via TS2_{1.5-H} and TS2_{1.5-Ph}, a process that also involves the migration of either a H or Ph group to the emerging primary cation *via* relatively high energy barriers (Table 10 and Fig. 4). The presence of a dipolar "hidden intermediate"⁴⁹ is shown by the large increase in dipole moment in the region of the transition state (Fig. 4b). As previously stated, prolonged heating at 80 °C of a pure sample of a 1,5-disubstituted triazoline led to the corresponding imine as the only decomposition product (see Table 8). Partial hydrolysis of this imine during work-up would explain the detection of anilines in the reaction crudes. Competitive TS2_{1.5-Ph} would produce aldimine 8da, a more unstable product that would completely hydrolyse into aniline and an aliphatic aldehyde, which in turn is likely to oligomerise under the reaction conditions. The overall reactions are now strongly exoenergic.



Fig. 4 Computed properties along an intrinsic reaction coordinate (IRC) for (a) energy profile for **TS2**_{1,5-H}, (b) dipole moment response for **TS2**_{1,5-H}, (c) energy profile for **TS2**_{1,4-b} and (d) dipole moment response for **TS2**_{1,4-b}.

Green Chemistry

Two diastereomeric transition states (**TS2**_{1,4a} and **TS2**_{1,4b}) were located for the loss of dinitrogen from 1,4-disubstituted triazoline **3da**'. The activation free energies are now low enough to explain the absence of reactant **3da**' in the reaction products (Table 10). The IRC for **TS2**_{1,4a} revealed the formation of a singlet dipolar biradical followed by a relatively low energy (*e.g.* $\Delta G_{353trans}^{\ddagger} = 2.6$ kcal mol⁻¹) for electrocyclic ring closure to the corresponding aziridines *cis*-**4da** and *trans*-**4da**. In contrast, **TS2**_{1,4b} was found to evolve into imine **8da** upon a migration of a hydrogen atom (Fig. 4), which would be expected to easily hydrolyse into the corresponding aniline. The transition state again has transient cationic character (Fig. 4c) as revealed by the dipole moment response along the IRC.

Overall, our calculations are in good agreement with the experimental results. A thermal dipolar cycloaddition step leads to the formation of two regioisomeric triazolines. Whereas the 1,5-disubstituted triazoline 3da would be kinetically relatively stable at the reaction temperature and render only small quantities of imine by-products at most, the 1,4-disubstituted regioisomer 3da' readily reacts to form either the corresponding aziridine or imines with dinitrogen evolution. We have experimentally shown that the product distribution is also highly dependent on the aryl alkene and azide substitutions. This is consistent with the insight revealed by the calculations for nitrogen extrusion in particular, which show significant dipolar/ionic character localised in the region of the transition state for this step. It has indeed been established that variation in the substituents may indeed induce dramatic changes in reaction mechanisms.⁵⁰ A full study of the influence of such substituents upon the reactions described here will be reported separately.

Conclusions

A range of di- and tri-substituted Δ^2 -1,2,3-triazolines have been prepared and fully characterised. The studied azide–alkene cycloadditions in DES typically led to mixtures of 1,2,3-triazolines and aziridines, although the overall product distributions were largely influenced by the alkene substitution. The benefits of DES in this context are twofold. First, the DES employed herein is non-flammable and it is composed of two safe and inexpensive components, urea and choline chloride. Secondly, much cleaner reaction crudes were obtained in DES when compared to standard organic solvents, and typically several grams of the desired triazolines could then be isolated analytically pure after a simple recrystallisation step.

Furthermore, a mechanism for the reaction between aromatic azides and olefins to yield triazolines and/or aziridines has been proposed. All our calculations have shown that this interesting process can proceed through two divergent pathways, cycloaddition followed by simple loss of dinitrogen to a biradical intermediate and then cyclization to the corresponding aziridines or loss of dinitrogen together with concomitant group migration to form imines. The process seems to be highly dependent on the nature of both the starting azide and the alkene and might also be dynamically controlled. Further studies on DES applications and dynamic calculations are underway in our laboratories.

Experimental section

General procedure for the dipolar cycloadditions

Azide (1.0 equiv.) and alkene (2.0 equiv.) were stirred in deep eutectic solvent (choline chloride/urea = 1:2; 0.5 M) at 80 °C for 16 h, unless stated otherwise. The reaction mixture was cooled down to room temperature, diluted with water (2 mL per mmol of azide) and pentane/Et₂O (3:1; 1 mL per mmol of azide) and stored at -18 °C overnight. If triazoline precipitated overnight, this was triturated at room temperature, collected by filtration, washed three times with ice cold pentane/Et₂O and recrystallised from boiling ethanol if necessary. Occasionally, the washings and/or filtrate from this recrystallisation were further purified by column chromatography as described next, either to improve the triazoline recovery, or to isolate the corresponding aziridine. If no solid precipitated at -18 °C, the mixture was extracted with EtOAc, the combined organic phases were washed with water and brine, dried over MgSO₄, filtered, concentrated under reduced pressure and purified by column chromatography on basified silica (eluent: petroleum ether/EtOAc 0 \rightarrow 25% gradient basified with 2% v/v NEt₃ unless stated otherwise; reaction crude was dry-loaded onto stationary phase). Occasionally, the product recovered after column chromatography required washing with ice-cold pentane/Et₂O (1:1).

3aa: Following the general procedure from 1-azido-4trifluoromethylbenzene (5.00 g, 26.7 mmol) and styrene (6.18 mL, 53.4 mmol), the title compound was isolated as a white solid (3.68 g after recrystallisation, 0.82 g after column: 58% overall). From this reaction, aziridine **4aa** was also isolated as a white solid (1.28 g, 18%) after column chromatography and recrystallisation from pentane at -18 °C.



3aa: Single crystals for X-ray diffraction were grown from Et₂O, CCDC 1843142;[†] Mp 88.0–90.0 °C; $R_f = 0.49$ (petroleum ether/ EtOAc = 80 : 20); IR: ν_{max} 1612 (m), 1523 (m), 1502 (m), 1458, 1431, 1365 (m), 1316 (m), 1193, 1153 (m), 1111 (s), 1067 (s), 1010 (m), 990 (m), 963 (m), 926 (m), 841 (m), 820 (s), 751 (s), 698 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.45 (d, J = 8.5 Hz, 2H, H²), 7.35–7.24 (m, 5H, H^{Ar}), 7.15 (d, J = 8.5 Hz, 2H, H³), 4.94 (dd, J = 12.5; 8.0 Hz, 1H, H⁶), 4.88 (dd, J = 17.5; 12.5 Hz, 1H, H⁵), 4.37 (dd, J = 17.5; 8.0 Hz, 1H, H⁵); ¹³C NMR (CDCl₃, 101 MHz): δ 142.9 (C⁴), 139.5 (C⁷), 129.5 (C⁹), 128.4 (C¹⁰), 126.5 (q, J = 3 Hz, C²), 125.9 (C⁸), 124.3 (q, J = 269 Hz, C¹¹), 124.0 (q, J = 33 Hz, C¹), 114.4 (C³), 76.1 (C⁵), 57.4 (C⁶); ¹⁹F NMR (CDCl₃, 377 MHz): δ –61.9 (s); HRMS (ES+) calculated for $C_{15}H_{13}N_3F_3$ 292.1062, found 292.1058 ([M + H]⁺); elemental analysis calculated for $C_{15}H_{12}N_3F_3$: C, 61.85; H, 4.15; N, 14.43, found: C, 61.95; H, 4.27; N, 14.27.



4aa: Single crystals for X-ray diffraction were grown from Et₂O, CCDC 1843144; † Mp 85.0–87.0 °C; $R_f = 0.83$ (petroleum ether/ EtOAc = 80:20); IR: ν_{max} 3053, 1614 (m), 1516, 1464, 1418, 1389, 1327 (s), 1279 (s), 1185, 1163 (m), 1127 (m), 1101 (s), 1076 (m), 1065 (s), 1010 (m), 981 (m), 914, 867, 843 (s), 790, 767 (m), 758 (s), 714 (s), 698 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.50 (d, J = 8.5 Hz, 2H, H²), 7.38–7.36 (m, 4H, H^{Ar}), 7.34–7.29 (m, 1H, H^{Ar}), 7.11 (d, J = 8.5 Hz, 2H, H^3), 3.16 (dd, J = 6.5; 3.5 Hz, 1H, H⁶), 2.49 (dd, J = 6.5; 1.0 Hz, 1H, H⁵), 2.47 (dd, J = 3.5; 1.0 Hz, 1H, H⁵); ¹³C NMR (CDCl₃, 101 MHz) δ 157.6 (C⁴), 138.6 (C⁷), 128.6 (C⁹), 127.7 (C¹⁰), 126.3 (q, J = 3 Hz, C^2), 126.2 (C^8), 124.6 (q, J = 32 Hz, C^1), 124.4 (q, J =269 Hz, C¹¹), 120.7 (C³), 41.7 (C⁶), 37.7 (C⁵); ¹⁹F NMR (CDCl₃, 377 MHz): δ -61.8 (s); HRMS (ES+) calculated for C₁₅H₁₃NF₃ 264.1000, found 264.0988 ($[M + H]^+$); elemental analysis calculated for C₁₅H₁₂NF₃: C, 68.44; H, 4.59; N, 5.32, found: C, 68.39; H, 4.69; N, 5.29.

Conflicts of interest

There are no conflict to declare.

Acknowledgements

This research was financially supported by Imperial College London and the EPSRC (DTP studentship to F. S. and EP/ K030760). L. C. gratefully acknowledges financial support of the Spanish government for a grant in the 2017 Salvador de Madariaga program.

Notes and references

- 1 (a) 1,3-Dipolar Cycloaddition Chemistry, ed. A. Padwa, Wiley-Interscience, New York, 1984, vol. 1 and 2; (b) R. Huisgen, *Proc. Chem. Soc.*, 1961, 357–369.
- For selected, complementary reviews, see: (a) C. J. Pickens, S. N. Johnson, M. M. Pressnall, M. A. Leon and C. J. Berkland, *Bioconjugate Chem.*, 2018, 29, 686–701; (b) S. Chassaing, V. Bénéteau and P. Pale, *Catal. Sci. Technol.*, 2016, 6, 923–957; (c) E. Haldón, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, 2015, 13, 9528–9550; (d) S. Díez-González, *Catal. Sci. Technol.*, 2011, 1, 166–178;

(*e*) Special issue on Click chemistry, Chem. Soc. Rev., 2010, 39, 1221–1408; (*f*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015.

- 3 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem.*, *Int. Ed.*, 2001, **40**, 2004–2021.
- 4 C. Wang, D. Ikhlef, S. Kahlal, J.-Y. Saillard and D. Astruc, *Coord. Chem. Rev.*, 2016, **316**, 1–20.
- 5 (a) P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey and G. P. Nowack, J. Am. Chem. Soc., 1965, 87, 306-311;
 (b) R. Huisgen, L. Möbius and G. Szeimies, Chem. Ber., 1965, 98, 1153-1158; (c) M. E. Munk and Y. K. Kim, J. Am. Chem. Soc., 1964, 86, 2213-2217; (d) Y. Nomura, Y. Takeuchi, S. Tomoda and M. M. Ito, Bull. Chem. Soc. Jpn., 1981, 54, 261-266; (e) P. K. Kabada, J. Org. Chem., 1992, 57, 3075-3078; (f) X. Zhang, Q. Zhang, Y. Wu, C. Feng, C. Xie, X. Fan and P. Li, Macromol. Rapid Commun., 2016, 37, 1311-1317; (g) T. Slagbrand, A. Volkov, P. Trillo, F. Tinnis and H. Adolfsson, ACS Catal., 2017, 7, 1771-1775.
- 6 (a) P. Scheiner, *Tetrahedron*, 1967, 24, 349–356;
 (b) P. K. Kadaba and S. B. Edelstein, *J. Org. Chem.*, 1990, 55, 5891–5894.
- 7 For selected examples, see: (a) D. R. Roque, J. L. Neill, J. W. Antoon and E. P. Stevens, *Synthesis*, 2005, 2497–2502;
 (b) S. S. van Berkel, A. J. Dirks, M. F. Debets, F. L. van Delft, J. J. L. M. Cornelissen, R. J. M. Nolte and F. P. J. T. Rutjes, *ChemBioChem*, 2007, 8, 1504–1508; (c) D. Gangaprasad, J. P. Raj, T. Kiranmye, R. Sasikala, K. Karthikeyan, S. K. Rani and J. Elangovan, *Tetrahedron Lett.*, 2016, 57, 3105–3108.
- 8 (a) R. Huisgen, G. Szeimies and L. Möbius, *Chem. Ber.*, 1966, 99, 475–490; (b) J. S. Yadav, B. V. Subba Reddy and V. Geetha, *Synlett*, 2002, 513–515.
- 9 B. Wei-Qiang and S. Chiba, Org. Lett., 2009, 11, 729-732.
- 10 S. Xie, S. A. Lopez, O. Ramström, M. Yan and K. N. Houk, J. Am. Chem. Soc., 2015, 137, 2958–2966.
- 11 W. H. Pearson, S. C. Bergmeier, S. Degan, K.-C. Lin, Y.-F. Poon, J. M. Scheryantz and J. P. Williams, *J. Org. Chem.*, 1990, 55, 5719–5738.
- 12 J. Bourgois, M. Bourgois and F. Texier, *Bull. Soc. Chim. Fr.*, 1978, **9–10**, 485–527.
- 13 P. K. Kadaba, Curr. Med. Chem., 2003, 10, 2081-2108.
- 14 R. Huisgen, in 1,3-Dipolar Cycloaddition Chemistry, ed. A. Padwa, Wiley-Interscience, New York, 1984, vol. 1, pp. 1–176.
- 15 (a) P. K. Kadaba, B. Stanovnik and M. Tišler, Adv. Heterocycl. Chem., 1984, 37, 217–361; (b) P. Scheiner, in Selective Organic Transformations, ed. B. S. Thyagarajan, Wiley-Interscience, New York, 1970, vol. 1, pp. 327–362.
- 16 (a) N. Jung and S. Bräse, Angew. Chem., Int. Ed., 2012, 51, 5538–5540; (b) D. M. Jenkins, Synlett, 2012, 1267–1270.
- 17 For examples of aziridines isolated from the corresponding fused Δ²-triazolines, see: (a) F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 1925, **127**, 1307–1311; (b) A. Mustafa, S. M. A. D. Zayed and S. Khattab, *J. Am. Chem. Soc.*, 1956, **78**, 145–149; (c) P. Scheiner, *J. Org. Chem.*, 1965, **30**, 7–10; (d) P. Scheiner, *J. Am. Chem. Soc.*, 1968, **90**, 988–992; (e) D. Belei, E. Bicu, P. G. Jones and M. L. Birsa, *J. Heterocycl. Chem.*, 2011, **48**, 129–134.

- 18 For examples that showed no aziridine formation from the corresponding 1,2,3-triazolines, see: (a) D. Pocar, P. Trimarco and G. Bombieri, *J. Heterocycl. Chem.*, 1998, 35, 687–692; (b) S. Fantauzzi, E. Gallo, A. Caselli, F. Ragaini, P. Macchi, N. Casati and S. Cenini, *Organometallics*, 2005, 24, 4710–4713.
- 19 P. K. Kadaba, Synthesis, 1973, 71-84.
- 20 Q. Zhang, K. De Oliveira Vigier, S. Royer and F. Jérôme, *Chem. Soc. Rev.*, 2012, 41, 7108–7146.
- 21 (a) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena,
 I. M. Partor and D. J. Ramón, *Eur. J. Org. Chem.*, 2016, 612–632; (b) J. García-Álvarez, *Eur. J. Inorg. Chem.*, 2015, 5147–5157.
- 22 A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Green Chem.*, 2002, 4, 24–26.
- 23 R. Singh and A. Singh, J. Iran. Chem. Soc., 2017, 14, 1119-1129.
- 24 J. M. Pérez and D. J. Ramón, ACS Sustainable Chem. Eng., 2015, 3, 2343–2349.
- 25 S. A. Padvi and D. S. Dalal, Synth. Commun., 2017, 47, 779– 797.
- 26 (a) F. Ilgen and B. König, *Green Chem.*, 2009, 11, 848–854;
 (b) M. A. P. Martins, G. C. Paveglio, L. V. Rodrigues, C. P. Frizzo, N. Zantta and H. G. Bonacorso, *New J. Chem.*, 2016, 40, 5989–5992.
- 27 1,2,3-Triazolines are notoriously acid sensitive, although synthetically useful reactions have been developed under controlled conditions, see: (a) D. S. Reddy, W. R. Judd and J. Aubé, Org. Lett., 2003, 5, 3899–3902; (b) K. B. Hong, M. G. Donahue and J. N. Johnston, J. Am. Chem. Soc., 2008, 130, 2323–2328; (c) T. L. Troyer, H. Mucalski, K. B. Hong and J. N. Johnston, Org. Lett., 2011, 13, 1790–1792.
- 28 A. P. Abbott, G. Capper, D. L. Davies, R. K. Rasheed and V. Tambyrajah, *Chem. Commun.*, 2003, 70–71.
- 29 (a) A. Gieren, Chem. Ber., 1973, 106, 288–311; (b) K. Kaas, Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem., 1973, 29, 1458–1463; (c) S. Murata, Y. Mori, Y. Satoh, R. Yoshidome and H. Tomioka, Chem. Lett., 1999, 28, 597–598; (d) G. Mlostoń, K. Urbaniak, A. Linden and H. Heimgartner, Helv. Chim. Acta, 2002, 85, 2644–2656. See also ref. 18b.
- 30 (a) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe and H.-J. Ha, *Chem. Soc. Rev.*, 2012, 41, 643–665; (b) C. Botuha, F. Chemla, F. Ferreira and A. Perez-Luna, in *Heterocycles in Natural Product Synthesis*, ed. K. C. Majumdar and K. S. Chattopadhyay, John Wiley & Sons, 2011, pp. 3–39; (c) G. S. Singh, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2007, 107, 2080–2135.
- 31 L. A. Lanovaya, M. F. Mishchenko and E. D. Korniets, *Chem. Heterocycl. Compd.*, 1987, 23, 660–664.
- 32 See ESI† for full crystallographic details.
- 33 P. Scheiner, J. Am. Chem. Soc., 1966, 88, 4759-4760.
- 34 (a) R. F. Bleinholder and H. Shechter, J. Am. Chem. Soc., 1968, 90, 2131–2137; (b) P. Battioni, L. Vo-Quang and Y. Vo-Quang, Bull. Soc. Chim. Fr., 1978, Part II, 415–427; (c) D. K. Wedegaertner, R. K. Kattal, I. Harrison and S. K. Cristie, J. Org. Chem., 1991, 56, 4463–4467.

- 35 T. S. Chung, S. A. Lopez, K. N. Houk and M. A. Garcia-Garibay, *Org. Lett.*, 2015, **17**, 4568–4571.
- 36 (a) N. Singh, S. K. Pandey and R. P. Tripathi, *Carbohydr. Res.*, 2010, 345, 1641–1648. See also; (b) J. Zhang and C.-W. T. Chang, *J. Org. Chem.*, 2009, 74, 685–695.
- 37 (a) R. Sustmann, Tetrahedron Lett., 1971, 12, 2717–2720;
 (b) K. N. Houk, Acc. Chem. Res., 1975, 8, 361–369;
 (c) A. K. Chandra, T. Uchimaru and M. T. Nguyen, J. Chem. Soc., Perkin Trans. 2, 1999, 2117–2121; (d) J.-C. Fan, J. Liang, Y. Wang and Z.-C. Shang, J. Mol. Struct.: THEOCHEM, 2007, 821, 145–152; (e) G. O. Jones and K. N. Houk, J. Org. Chem., 2008, 73, 1333–1342;
 (f) D. H. Ess and K. N. Houk, J. Am. Chem. Soc., 2008, 130, 10187–10198; (g) B. Braida, C. Walter, B. Engels and P. C. Hiberty, J. Am. Chem. Soc., 2010, 132, 7631–7637;
 (h) S. A. Lopez, M. E. Munk and K. N. Houk, J. Org. Chem., 2013, 78, 1576–1582.
- 38 (a) C. Silva López, O. Nieto Faza, K. S. Feldman, M. R. Iyer and D. K. Hester II, *J. Am. Chem. Soc.*, 2007, **129**, 7638– 7646; (b) A. Contini and E. Erba, *RSC Adv.*, 2012, **2**, 10652– 10660.
- 39 (a) P. A. S. Smith and J. H. Hall, J. Am. Chem. Soc., 1962, 84, 480–485; (b) L. Horner and A. Christmann, Angew. Chem., Int. Ed. Engl., 1963, 2, 599–607.
- 40 (a) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 16, Revision A.03, Gaussian, Inc., Wallingford CT, 2013.
- 41 (a) A. D. Becke, J. Chem. Phys., 1993, 98, 1372–1377;
 (b) A. D. Becke, J. Chem. Phys., 1993, 98, 5648–5652;
 (c) A. D. Becke, Phys. Rev., 1998, A38, 3098–3100;
 (d) P. J. Stevens, F. J. Devlin, C. F. Chablowski and M. J. Frish, J. Phys. Chem., 1994, 98, 11623–11627.
- 42 (a) S. Grimme, J. Antony, S. Ehrlich and H. Krieg, J. Chem. Phys., 2010, 132, 154104; (b) S. Grimme, S. Ehrlich and L. Goerigk, J. Comput. Chem., 2011, 32, 1456–1465.
- 43 (a) W. J. Hehre, L. Random, P. V. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986; (b) W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Phys. Chem.*, 1972, 56, 2257–2261;

(c) P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, 1973, **28**, 213–222.

- 44 (a) V. Barone and M. Cossi, J. Phys. Chem. A, 1998, 102, 1995–2001; (b) M. Cossi, N. Rega, G. Scalmani and V. Barone, J. Comput. Chem., 2003, 24, 669–681.
- 45 J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615–6620.
- 46 (a) F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, 7, 3297–3305; (b) F. Weigend, *Phys. Chem. Chem. Phys.*, 2008, 8, 1057–1065.
- 47 (a) K. Fukui, Acc. Chem. Res., 1981, 14, 363–368;
 (b) H. P. Hratchian and H. B. Schlegel, in Theory and

Applications of Computational Chemistry: The First 40 Years, ed. C. E. Dykstra, G. Frenking, K. S. Kim and G. Scuseria, Elsevier, Amsterdam, 2005, pp. 195–249.

- 48 F. Sebest, L. Casarrubios, H. S. Rzepa, A. J. P. White and S. Díez-González, *Imperial College Research Services Data Repository*, 2018, DOI: 10.14469/hpc/4062 and sub-collections therein.
- 49 (a) D. Cremer and E. Kraka, Acc. Chem. Res., 2010, 43, 591–601; (b) H. S. Rzepa and C. Wentrup, J. Org. Chem., 2013, 78, 7565–7574.
- 50 C. D.-T. Nielsen, W. J. Mooij, D. Sale, H. S. Rzepa, J. Burés and A. C. Spivey, submitted for publication.