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### syn-1,2-Diaminobenzocyclobutenes from [2+2] cycloaddition of 2-imidazolones with arynes<sup>†</sup>

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Formal [2+2] cycloaddition of arynes with 2-imidazolones affords syn-1,2-diaminobenzocyclobutenes. The transformation can also be conducted as a one-pot, three-stage process direct from simple propargyl amines and isocyanates to afford the new stereochemically defined benzocyclobutene frameworks.

The bicyclo[4.2.0]octa-1,3,5-triene structural motif (commonly known as benzocyclobutene, BCB) occurs in many bioactive natural products and pharmaceutically active compounds (Scheme 1a).<sup>1</sup> BCBs also represent attractive building blocks for generating diverse carbo- and hetero-cyclic frameworks and in the preparation of polymeric materials. This is due to the thermally activated electrocyclic ring-opening of cyclobutene that reveals valuable o-quinonedimethide intermediates. These reactive species are trapped via intra- and inter-molecular Diels-Alder reactions in the synthesis of natural products and drug-like scaffolds,<sup>2</sup> as well as undergoing a range of polymerization reactions to afford high-performance resins with broad applications in materials chemistry.3 BCBs have been prepared using many different methods, including 1,4-elimination from *o*-difunctionalised arenes,<sup>4a,b</sup> Parham cyclisation,<sup>4c</sup> [2+2+2] cyclotrimerisations,<sup>4d</sup> photochemical cycloadditions,<sup>4e</sup> extrusion reactions<sup>4f</sup> and cyclopropene ring expansion.<sup>4g</sup>

Conceptually, the simplest approach to accessing BCBs 3 is through formal [2+2] cycloaddition between alkenes 1 and arynes 2 (Scheme 1b).<sup>5-8</sup> Arynes are versatile reactive intermediates that rapidly afford valuable benzenoid and heterocyclic frameworks.9 They have experienced a recent resurgence in interest due to the advent of aryne precursors that act under mild conditions, such as the o-trimethylsilylaryl triflates (oSATs),<sup>10</sup> hexadehydro-Diels-Alder reaction of polyalkynes<sup>11</sup> and the development of arenes bearing onium ion leaving groups.<sup>12</sup> With a few exceptions,<sup>5</sup> the reaction between simple

alkenes and arynes typically affords BCBs in low yields as a result of competing ene reactions.<sup>6</sup> However, more polarised alkenes favour cycloaddition; the introduction of a single nitrogen atom proving successful with enamide and enamine-type coupling partners.<sup>7</sup> For example, Hsung and co-workers reported an elegant ringexpansion methodology used for the total synthesis of chelidonine and norchelidonene that operates via a tandem aryne-enamide [2+2] cycloaddition – electrocyclic ring-opening – intramolecular



can ring-open cyclic urea in product BCBs can operate as one-pot process direct from propargylic amine novel stereochemically defined *syn*-1,2-diamine framework (ligands, catalysis, polymers)

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Scheme 1 (a) Benzocyclobutenes in medicinal chemistry. (b) and (c) Synthetic approaches to BCBs via formal [2+2] cycloaddition between alkenes and arvnes

Diels–Alder reaction.<sup>7b,c</sup> Silyl ketene acetals and enol ethers have also shown to be productive substrates for BCB formation; more specifically *cis*-enol ethers underwent preferential [2+2] cycloaddition whereas *trans*-enol ethers favoured ene reaction.<sup>8</sup> Lakshman and co-workers exploited these observations by employing cyclic enol ethers 5 to furnish a range of stereochemically defined *syn*-1,2-disubstituted BCBs 6 in good yields with a range of arynes accessed *via o*SAT precursors.<sup>8e</sup>

Given our interest in the chemistry of arynes,<sup>13</sup> we postulated that suitably protected cyclic 1,2-diaminosubstituted alkenes (9) would give rise to *syn*-1,2-diaminoBCBs (10) *via* formal [2+2] cycloaddition with arynes (Scheme 1c). Inspired by the previous work of Lakshman with cyclic enol ethers<sup>8e</sup> and reports using mono-substituted cyclic enamine equivalents,<sup>7e,f</sup> our strategy would afford novel stereochemically defined 1,2-diamino frameworks. Chiral 1,2-diamines are important structural motifs in bio- and pharmaceutically active compounds.<sup>14a,b</sup> They also act as privileged ligands in asymmetric transition metal catalysis and are key components of chiral organocatalysts.<sup>14c,d</sup> It follows that methods to access new 1,2-diamino motifs are of significant synthetic interest. Furthermore, the development of a differently functionalized BCB derivative should offer exciting opportunities in polymer research.

To test our hypothesis, 2-imidazolones 9 were selected as the cyclic 1,2-diaminosubstituted alkenes.<sup>15</sup> These N-heterocycles are easily prepared from commercially available propargylic amines and isocyanates, as reported by Van der Eycken.<sup>16</sup> In addition to the synthetic accessibility of these 1,2-diaminosubstituted alkenes, the urea moiety was chosen with a view to attenuating potential competing aryne reactivity at nitrogen. As such, N-phenyl-N-methyl-2-imidazolone 11a was exposed to 2-trimethylsilylphenyl triflate 12a under a variety of common aryne-forming conditions (see Table 1 for selected optimisation studies). Pleasingly, treatment with CsF in acetonitrile afforded the desired syn-1,2-diaminoBCB 13aa as the major product in 41% yield (entry 1). A small amount of starting material was recovered, along with a by-product identified as benzodiazepine 14aa.<sup>17</sup> This is proposed to form via aryne insertion into either of the C-N sigma bonds of the urea; analogous ring-expansion having previously been described with the related saturated cyclic urea, N.N-dimethylimidazolidone.<sup>18</sup> Increasing the reaction temperature, the molar ratio of CsF to oSAT 12a and the number of equivalents of 12a all resulted in reduced BCB formation and a more complex reaction mixture (entries 2-4). Employing different salts and/or additives to modify fluoride solubility did not improve BCB formation; instead, higher levels of benzodiazepine were observed (entries 5-10). With the rate of aryne formation seemingly playing a key role in determining product selectivity, slow addition of precursor 12a was performed. Whilst BCB 13aa remained the major product, the yield from dropwise addition was lowered compared to adding in one portion (entry 11 vs. entry 1). Finally, altering the reaction concentration did not have a significant effect on the amount of BCB produced, however the relative quantities of benzodiazepine increased (entries 12 and 13).

With optimised conditions in hand for the formation of BCBs and having established that there is a fine balance

Table 1 Selected optimization studies for the preparation of syn-1,2-diaminoBCBs<sup>a</sup>



	Fluoride				$\operatorname{Yield}^{b}(\%)$		
Entry	source	Additive	Solvent	$T(^{\circ}C)$	11a	13aa	14aa
1	CsF	_	MeCN	50	12	41	7
2	CsF		MeCN	70	9	24	1
3 <sup>c</sup>	CsF		MeCN	50	23	32	14
$4^d$	CsF		MeCN	50	11	12	2
5	CsF	18-Crown-6	MeCN	50	12	12	35
6	KF	18-Crown-6	THF	50	4	14	14
7	TBAF	_	THF	50	20	12	22
8	TBAT		THF	50	37	20	46
9	CsF		PhMe/MeCN $(3:1)$	110	61	8	8
10	CsF		PhMe/MeCN $(3:1)$	50	8	21	19
$11^e$	CsF		MeCN	50	11	21	12
$12^{f}$	CsF	_	MeCN	50	14	43	29
$13^g$	CsF	_	MeCN	50	9	36	22

<sup>*a*</sup> Reaction conditions: *o*SAT **12a** (1.0 equiv.), fluoride source (3.0 equiv.), additive (3.0 equiv.), solvent [0.15 M], 14 h, N<sub>2</sub> atmosphere. <sup>*b*</sup> <sup>1</sup>H NMR yield *vs.* CH<sub>2</sub>Br<sub>2</sub> internal standard. <sup>*c*</sup> 5.0 equiv. of CsF. <sup>*d*</sup> 3.0 equiv. of *o*SAT **12a** & 9.0 equiv. of CsF. <sup>*e*</sup> 1.0 equiv. of *o*SAT **12a** added dropwise *via* syringe pump over 1 h. <sup>*f*</sup> 0.03 M in MeCN. <sup>*g*</sup> 0.3 M in MeCN.

between competing reaction pathways, attention turned to investigating the influence of substitution around the 2-imidazolone framework (Scheme 2). Firstly, the effect of the N-substituent introduced by the isocyanate starting material was studied. Pleasingly, N-aryl moieties with electronwithdrawing groups (p-NO<sub>2</sub> 11b, p-F 11e) and electrondonating groups (p-OMe 11c, p-Me 11d, m-OMe 11f, o-OMe 11g) all afforded the corresponding BCBs in similar yields to the parent N-Ph derivative 13aa. Interestingly, the difference between m-OMe (13fa, 22%) and o-OMe (13ga, 57%) derivatives suggests that sterics at nitrogen do not play a key role in product selectivity. The transformation was also amenable to N-alkyl imidazolones, affording N-ethyl BCB 13ha and N-benzyl BCB 13ia in 27% and 39% yields respectively. Next, several modifications were made to the imidazolone scaffold via the propargylic amine component. Changing from an N-methyl to *N*-benzyl imidazolone (11j) had little effect on the yield, with N-benzyl BCB 13ja obtained in 39% yield. Likewise, replacing the exocyclic methyl group on the imidazolone alkene with a larger substituent did not significantly alter the yield of the [2+2] cycloaddition; the benzyl BCB 13ka isolated in 32% yield. Finally, the transformation was attempted with a fully substituted imidazolone 11l. Intriguingly this afforded no trace of the expected BCB 13la, instead the corresponding regioisomeric benzodiazepines were produced in a separable 1.2:1.0 ratio (combined 55% NMR yield, see ESI<sup>†</sup>). This observation offered an insight into the mechanism of the [2+2] cycloaddition, suggesting that initial attack of the aryne occurs at the unsubstituted end of the imidazolone alkene. When the aryne-alkene



Scheme 2 Synthesis of syn-1,2-diaminoBCBs 13 with different 2-imidazolone derivatives 11a–L. Reaction conditions: imidazolone 11 (1.0 equiv.), oSAT 12a (1.0 equiv.), CsF (3.0 equiv.), MeCN (0.15 M), 50 °C, 14 h, N<sub>2</sub> atmosphere. Yields of isolated products throughout. <sup>a</sup>Afforded 1.2:1.0 ratio of corresponding regioisomeric benzodiazepines (55% combined NMR yield).

approach is too hindered, in the case of tetra-substituted alkene **11**, attack at nitrogen takes precedence and leads to formal aryne insertion into the N–C(O) sigma bonds.

We next investigated the effect of substitution on the aryne (Scheme 3). Electron-donating and withdrawing groups (**12b-f**) typically afforded the corresponding arene-functionalised BCBs **13** in comparable yields to benzyne precursor **12a**. It is noteworthy that the most electron deficient aryne (3,4-difluoro, **12d**) proved to be the most proficient coupling partner overall, furnishing BCB **13ad** in excellent yield (83%). Finally, when imidazolone **11a** was exposed to unsymmetrical *o*-methoxy aryne precursor **12f**, *o*-Me BCB **13af** was isolated as a single regioisomer in 38% yield. Given the established preference for nucleophilic attack at the distal position of *o*-methoxy aryne, the exclusive formation of BCB **13af** suggests that the imidazolone reacts at the least substituted end of the alkene. This observation supports the previous mechanistic insight drawn from the tetrasubstituted alkene **11j** (see Scheme 2).

Having synthesised a range of *syn*-1,2-diaminoBCBs **13** from the corresponding 2-imidazolones **11**, we postulated whether

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Scheme 3 Synthesis of syn-1,2-diaminoBCBs 13 with different aryne derivatives 12a–f. Reaction conditions: imidazolone 11 (1.0 equiv.), oSAT 12 (1.0 equiv.), CsF (3.0 equiv.), MeCN (0.15 M), 50 °C, 14 h, N<sub>2</sub> atmosphere. Yields of isolated products throughout. <sup>a</sup>Single regioisomer observed.

the stereochemically defined BCBs could be accessed directly from propargyl amines 7 and isocyanates 8. This would streamline the process by removing the isolation and purification of intermediate imidazolones. To this end, N-methyl propargyl amine 15 and phenyl isocyanate 16 were subjected to the ureaformation - cyclisation procedure described by Van der Eycken (Scheme 4a).<sup>16</sup> Upon complete conversion to the imidazolone 11a, CsF and oSAT 12a were added and the reaction heated at 50 °C for 14 hours. Pleasingly, the desired BCB 13aa was isolated in 36% yield from propargyl amine 15 via the onepot, three-stage process. This compares favourably to performing two separate steps, first to isolate the imidazolone (94%) and then to generate the BCB (41%). Finally, the cyclic urea within the product BCBs could be ring-opened via a two-step reduction and acetylation procedure, to reveal the general syn-1,2-diaminoBCB framework 17 for future applications (Scheme 4b).

In conclusion, the formal [2+2] cycloaddition of 2-imidazolones and arynes has been achieved, delivering novel *syn*-1,2-diaminoBCBs. The transformation can also be conducted as a one-pot, three-stage process direct from commercially available propargylic amines and isocyanates, offering simple access to imidazolone substrate variation. Overcoming competing reactivity at nitrogen, in addition to other deleterious reaction pathways, proved a challenge for the methodology and accounts for the moderate yields typically observed. Nevertheless, these new stereochemically defined BCB frameworks offer attractive synthetic potential for use in asymmetric catalysis – as chiral ligands for transition metals or key components in



**Scheme 4** (a) One-pot formation of BCBs from propargyl amine. (b) Imidazolidone ring-opening.

organocatalysts – and as building blocks for both the synthesis of complex molecules and the preparation of polymeric materials.

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#### Data availability

The data supporting this article have been included as part of the ESI.<sup>†</sup>

### Conflicts of interest

There are no conflicts to declare.

#### Notes and references

- Selected reviews: (a) G. Mehta and S. Kotha, *Tetrahedron*, 2001, 57, 625; (b) A. K. Sadana, R. K. Saini and W. E. Billups, *Chem. Rev.*, 2003, 103, 1539; (c) S. Kotha, K. Lahiri and Y. Tangella, *Asian J. Org. Chem.*, 2021, 10, 3166.
- 2 Selected examples: (a) Y. Matsuya, S. Masuda, T. Itoh, T. Murai and H. Nemoto, J. Org. Chem., 2005, 70, 6898; (b) Z. X. Ma, J. B. Feltenberger and R. P. Hsung, Org. Lett., 2012, 14, 2742; (c) M. Mazurais, C. Lescot, P. Retailleau and P. Dauban, Eur. J. Org. Chem., 2014, 66; (d) P. Maurina, D. Moraledab, H. Pellissier, R. Rodriguez and M. Santelli, Synlett, 2015, 725.
- 3 Selected examples: (a) M. F. Farona, Prog. Polym. Sci., 1996, 21, 505;
  (b) J. Yang, Y. Huang and K. Cao, in Polymerisation, ed. A. De Silva Gomes, IntechOpen, 2012, vol. 9, p. 201; (c) C. Pugh, J. S. Baker and W. K. Storms, Synlett, 2014, 148.
- Selected examples: (a) H. Finkelstein, Chem. Ber., 1959, 92, xxxvii;
   (b) M. P. Cava and D. R. Napier, J. Am. Chem. Soc., 1956, 78, 500;
   (c) M. S. Sardessai and H. N. Abramson, Org. Prep. Proced. Int., 1991,
   23, 419; (d) S. Kotha and P. Khedkar, J. Org. Chem., 2009, 74, 5667;
   (e) Y. Wada, T. Tago, K. Sugata and J. Nishimura, J. Org. Chem., 1992,
   57, 5955; (f) H. Higuchi, T. Otsubo, F. Ogura, H. Yamaguchi, Y. Sakata and S. Misumi, Bull. Chem. Soc. Jpn., 1982, 55, 182; (g) P. Muller,
   G. Bernardinelli, Y. Jacquier and A. Ricca, Heb. Chim. Acta, 1989, 72, 1618.
- 5 (a) Z. Chen, X. Han, J. H. Liang, J. Yin, G. A. Yu and S. H. Liu, *Chin. Chem. Lett.*, 2014, **25**, 1535; (b) X. Que, Y. Yan and Z. Qiu, *Eur. Polym. J.*, 2018, **103**, 410.
- 6 Y. Yang and C. R. Jones, Synthesis, 2022, 5042.

- 7 (a) M. E. Kuehne, J. Am. Chem. Soc., 1962, 84, 837; (b) J. B. Feltenberger, R. Hayashi, Y. Tang, E. S. C. Babiash and R. P. Hsung, Org. Lett., 2009, 11, 3666; (c) Z.-X. Ma, J. B. Feltenberger and R. P. Hsung, Org. Lett., 2012, 14, 2742; (d) A. Picard, S. Ciblat and Y. K. Ramtohul, Synlett, 2020, 507; (e) X. Cheng, N. Yang, W. Zeng, L. Wang, P. Li and H. Li, Chem. Commun., 2021, 57, 7047; (f) D. F. Dewez, C. Diacofotaki and G. Evano, Org. Chem. Front., 2021, 8, 6699.
- 8 (a) R. V. Stevens and G. S. Bisacchi, J. Org. Chem., 1982, 47, 2393;
  (b) P. Maurin, M. Ibrahim-Ouali and M. Santelli, Tetrahedron Lett., 2001, 42, 8147; (c) T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, J. S. Siegel, K. K. Baldridge and K. Suzuki, J. Am. Chem. Soc., 2006, 128, 10032; (d) C. Pugh, J. S. Baker and W. K. Storms, Synlett, 2014, 148; (e) V. R. Yedulla, P. Pradhan, L. Yang and M. K. Lakshman, Eur. J. Org. Chem., 2015, 750.
- 9 Selected reviews: (a) R. Sanz, Org. Prep. Proced. Int., 2008, 40, 215;
  (b) P. M. Tadross and B. M. Stoltz, Chem. Rev., 2012, 112, 3550;
  (c) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, Org. Biomol. Chem., 2013, 11, 191; (d) R. W. Hoffmann and K. Suzuki, Angew. Chem., Int. Ed., 2013, 52, 2655; (e) D. Pérez, D. Peña and E. Guitían, Eur. J. Org. Chem., 2013, 5981; (f) J.-A. García-López and M. F. Greaney, Chem. Soc. Rev., 2016, 45, 6766; (g) O. J. Diamond and T. J. Marder, Org. Chem. Front., 2017, 4, 891; (h) F. I. M. Idiris and C. R. Jones, Org. Biomol. Chem., 2017, 15, 9044; (i) J. Shi, L. Li and Y. Li, Chem. Rev., 2021, 121, 3892.
- 10 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211. 11 T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods,
- Nature, 2012, 490, 208.
  12 Selected examples: (a) M. Lanzi, T. Rogge, T. S. Truong, K. N. Houk and J. Wencel-Delord, J. Am. Chem. Soc., 2023, 145, 345; (b) R. A. Roberts, B. E. Metze, A. Nilova and D. R. Stuart, J. Am. Chem. Soc., 2023, 145, 3306; (c) B. E. Metze, R. A. Roberts, A. Nilova and D. R. Stuart, Chem. Sci., 2023, 14, 13885; (d) O. Smith, M. J. Hindson, A. Sreenithya, V. Tataru, R. S. Paton, J. W. Burton and M. D. Smith, Nat. Synth., 2024, 3, 58.
- (a) P. Trinchera, W. Sun, J. E. Smith, D. Palomas, R. Crespo-Otero and C. R. Jones, Org. Lett., 2017, 19, 4644; (b) F. I. M. Idiris, C. E. Majesté, G. B. Craven and C. R. Jones, Chem. Sci., 2018, 9, 2873; (c) W. Sun, P. Trinchera, N. Kurdi, D. Palomas, R. Crespo-Otero, S. Afshinjavid, F. Javid and C. R. Jones, Synthesis, 2018, 4591; (d) Y. Yang, Y. Xu and C. R. Jones, Eur. J. Org. Chem., 2019, 5196; (e) E. A. Neal, A. Y. R. Werling and C. R. Jones, Chem. Commun., 2021, 57, 1663; (f) W. Sun, M. Uttendorfer, F. I. M. Idiris, A. W. Y. Werling, K. Siddiq and C. R. Jones, Chem. Commun., 2023, 59, 11823.
- 14 Selected examples: (a) D. Lucet, T. Le Gall and C. Mioskowski, Angew. Chem., Int. Ed., 1998, 37, 2580; (b) S. R. Saibabu Kotti, C. Timmons and G. Li, Chem. Biol. Drug Des., 2006, 67, 101; (c) J.-C. Kizirian, Chem. Rev., 2008, 108, 140; (d) A. Mishra and S. Hanessian, Synthesis, 2024, 56, 2747.
- Selected reviews: (a) K. Lauder, A. Toscani, N. Scalacci and D. Castagnolo, *Chem. Rev.*, 2017, **117**, 14091; (b) S. Farshbaf, L. Sreerama, T. Khodayari and E. Vessally, *Chem. Rev. Lett.*, 2018, **1**, 56.
- 16 V. A. Peshkov, O. P. Pereshivkov, S. Sharma, T. Meganathan, V. S. Parmar, D. S. Ermalot'ev and E. V. Van der Eycken, J. Org. Chem., 2011, 76, 2867.
- 17 Unable to isolate a pure sample of 14aa for unequivocal characterisation, due to apparent instability of trisubstituted alkene in product. However, benzodiazepines 14la and 14la' (containing a tetrasubstituted alkene and obtained from the reaction of imidazolone derivative 11l with aryne 2a) were isolable and fully characterised (see ESI† for details). Benzodiazepine 14aa was therefore proposed by analogy with the NMR spectroscopic data of 14la and 14la' and supported by mass spectrometric data. Note: assignment of regioisomers was not possible for 14aa.
- 18 (a) H. Yoshida, E. Shirakawa, Y. Honda and T. Hiyama, Angew. Chem., Int. Ed., 2002, 41, 3247; (b) N. Saito, K. I. Nakamura, S. Shibano, S. Ide, M. Minami and Y. Sato, Org. Lett., 2013, 15, 386.