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Palladium-catalysed enantio- and regioselective (3 + 2) cycloaddition reactions of sulfamidate imine-derived 1-azadienes towards spirocyclic cyclopentanes†

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An enantio- and diastereoselective Pd-catalysed (3 + 2) cycloaddition of bis(trifluoroethyl) 2-vinyl-cyclopropane-1,1-dicarboxylate (VCP) with cyclic sulfamidate imine-derived 1-azadienes (SDAs) has been developed. These reactions provide highly functionalized spiroheterocycles having three contiguous stereocentres, including a tetrasubstituted carbon bearing an oxygen functionality. The two geminal trifluoroethyl ester moieties can be manipulated in a facially selective manner to afford more diversely decorated spirocycles with four contiguous stereocentres. In addition, diastereoselective reduction of the imine moiety can also afford a fourth stereocentre and exposes the important 1,2-amino alcohol functionality.

Introduction

The sterically congested and highly functionalised cyclopentane scaffold is among the most encountered architectural features in natural products, bioactive compounds, and medicinally relevant molecules (Fig. 1).[1–3] Due to their importance, synthetic protocols enabling efficient access to this privileged motif with high stereocontrol are indispensable and highly sought after. Among these, a commonly employed strategy concerns the use of donor–acceptor cyclopropanes (DACs) as C3 synthons in (3 + 2) cycloaddditions, which allow the effective construction of these five-membered carbocycles[4–8] as well as their heterocyclic counterparts[9–13] in a stereoselective and atom economical fashion. Within the array of structurally diverse DACs lies the vinylcyclopropane (VCP) scaffold, which readily ring-open in the presence of a transition metal catalyst such as palladium to afford a metal-bound zwitterionic π-allyl dipole that can undergo (3 + 2) cycloaddition with an array of dipolarophiles to furnish five-membered rings bearing a synthetically valuable vinyl handle.[14–20]

A wide range of dipolarophiles have been utilised in conjunction with VCP-derived 1,3-dipoles,[21–43] enabling the synthesis of fused-[23–26,30,43] and spirocyclic cyclopentanes and 5-membered heterocycles *via* (3 + 2) cycloaddition reactions.[33,37,39,41,42] Among these, benzofuran-derived azadienes (BDAs) are an intriguing potential class of dipolarophiles for Pd-catalysed (3 + 2) reactions for cyclopentane synthesis.[31,34] However, BDAs often act as four-atom synthons in (4 + *n*) cycloadditions to give larger ring systems *via* an aromatic benzofuran intermediate **I** (Fig. 2a).[44–55] In comparison, their employment as two-atom synthons has been scarcer,[31,34,47,50] among which there are only two examples of (3 + 2) cycloaddition reactions with BDAs known, with chemoselectivity for C=N *versus* C=C addition being a potential challenge.[31,34] The preference for (4 + *n*) reactions of BDAs is due to the favoured attack of the intermediate sulfonamide anion on the pendant Pd-

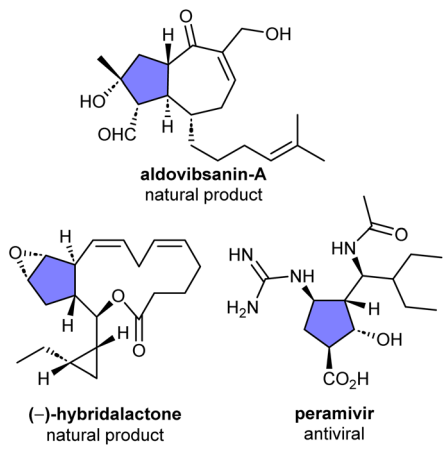

Fig. 1 Selected examples of naturally occurring and medicinally relevant compounds containing a densely functionalized cyclopentane core.

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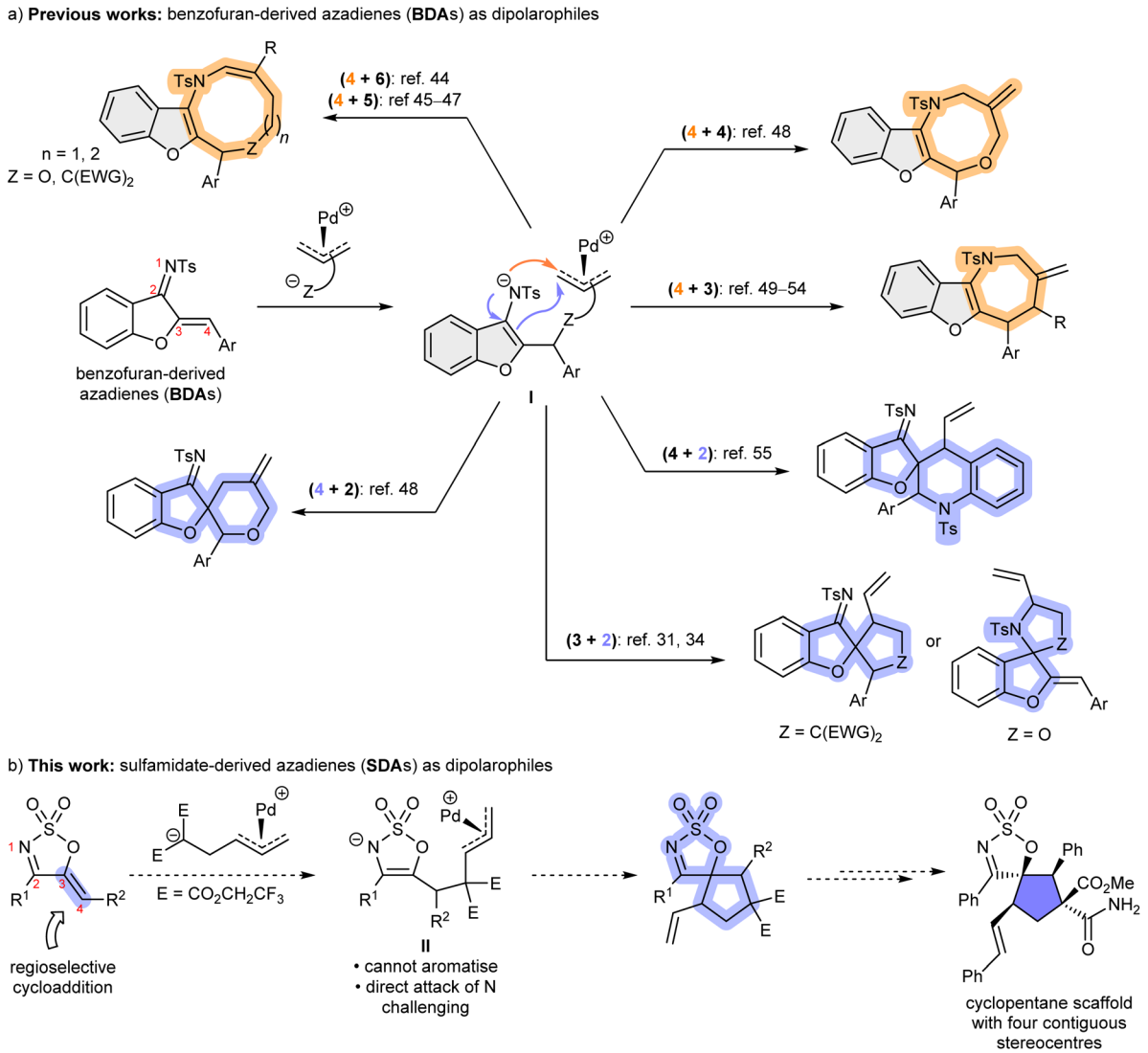


Fig. 2 (a) Prior work on the different reaction modes of BDAs as dipolarophiles in Pd-catalysed cycloadditions. (b) This work: SDA scaffolds as dipolarophiles in Pd-catalysed (3 + 2) cycloadditions with VCP-derived 1,3-dipoles.

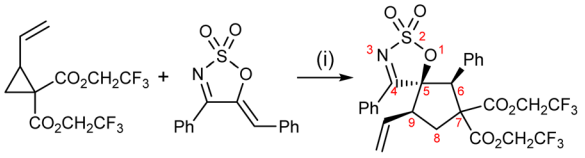
allyl complex to preserve the aromatic benzofuran moiety (highlighted in grey). We therefore designed a new azadiene dipolarophile that would completely preclude $(4 + n)$ reactivity and enable reliable (3 + 2) processes with VCPs to be realised. From our experience with cyclic sulfamidate imines,[56] we envisaged that sulfamidate imine-derived azadienes (SDAs) would be an intriguing alternative to the BDA system that would completely preclude the $(4 + n)$ reaction mode and give highly functionalised cyclopentanes (Fig. 2b).[57,58] Such (3 + 2) cycloadditions would proceed *via* a non-aromatic intermediate **II**, where attack by the nitrogen on the pendant π-allyl palladium complex would be unlikely as it would result in a strained bicyclic product. Furthermore, in contrast to BDA cycloaddition products, the oxygen substituent in the SDA-derived cyclopentanes would not be attached to an aromatic ring. We envision that this method will open up new (3 + 2) reaction manifolds for aza-dienes and find wide application in target synthesis of densely functionalised bioactive cyclopentanes.

Herein, we report this new class of dipolarophiles successfully undergoing chemo- and enantioselective (3 + 2) cycloaddition with the exocyclic C=C bond to give exclusively stereodefined and densely functionalised spirocyclic cyclopentanes containing three-contiguous stereogenic centres. In addition, we can demonstrate that these cycloadducts—having a structurally rigid skeleton decorated with useful synthetic handles such as the imine, vinyl, and geminal diester moieties—can undergo further stereoselective transformations to create an additional stereogenic centre.

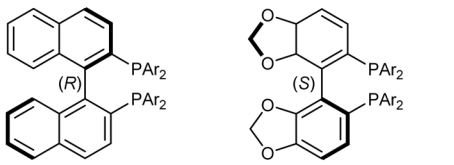
Results and discussion

A preliminary optimisation, carried out using VCP **1a** [59] and cyclic 1-azadiene **2a** as model substrates, identified toluene as the solvent of choice (see the ESI† for full optimisation details). Azadiene **2a** was readily accessible from the corresponding C5-unsubstituted cyclic sulfamidate imine *via* a Knoevenagel condensation.[60] A selection of C_2 symmetric chiral ligands were then screened in

Table 1 Ligand screen of the Pd-catalysed (3 + 2) cycloaddition reaction of VCP **1a** with 1-azadiene **2a** with toluene as solvent[a]



1a **2a** **3aa**



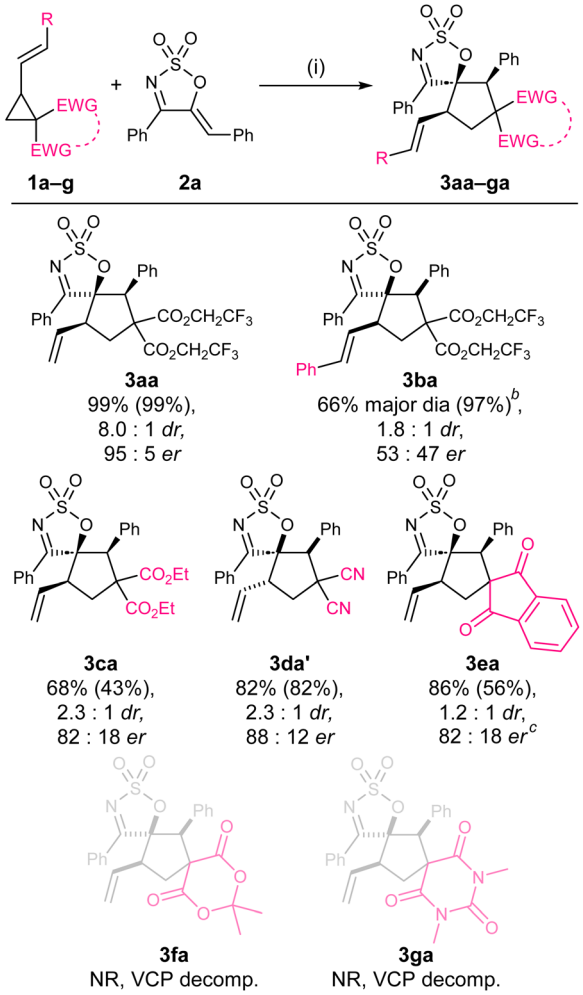
L1: Ar = Ph
L2: Ar = 4-MePh
L3: Ar = 3,5-Me_2Ph
L4: Ar = Ph
L5: Ar = 3,5-Me_2Ph
L6: Ar = 3,5-tBu_2-4-OMePh

Entry	Ligand	Yield[b]	dr[c]	er[d]
1	**L1**	36% (71%)	7.2 : 1	7 : 93
2	**L2**	81% (87%)	8.7 : 1	11 : 89
3	**L3**	74% (91%)	7.1 : 1	12 : 88
4	**L4**	76% (80%)	7.1 : 1	90 : 10
5	**L5**	84% (98%)	7.3 : 1	94 : 6
6	**L6**	34% (31%)	1 : 1.2	94 : 6
7[e]	**L5**	92% (84%)	3.8 : 1	90 : 10
8[f]	**L5**	85% (81%)	2.7 : 1	81 : 91
9[g]	**L5**	84% (88%)	5.4 : 1	93 : 7
10[h]	**L5**	77% (83%)	8.5 : 1	94 : 6
11[h,i]	**L5**	99% (99%)	8.0 : 1	95 : 5

[a] Reaction conditions: **1a** (0.15 mmol, 1.2 equiv.), **2a** (0.1 mmol, 1.0 equiv.), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), ligand (7.5 mol%), PhMe (0.067 M w.r.t. **2a**), rt, 24 h. [b] Calculated yields are provided in parentheses and were determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric ratio was determined by chiral HPLC. [e] Reaction was carried out at 0 °C. [f] Reaction was carried out at −10 °C. [g] Reaction concentration was doubled (0.134 M w.r.t. **2a**). [h] Reaction concentration was halved (0.034 M w.r.t. **2a**). [i] 1.5 Equiv. of **1a** used.

toluene (Table 1). BINAP analogues **L2** and **L3** both performed well, furnishing the product in high yields and drs, but slightly lower ers compared to **L1** (entries 1–3). Among the three SEGPHOS-type ligands **L4–6** tested (entries 4–6), (*S*)-DM-SEGPHOS **L5** was found to be the most suitable candidate, affording the desired product in high yield, good dr and high er (entry 5). Encouraged by the results obtained with **L5**, further fine tuning of other reaction conditions was attempted with this ligand. Performing the transformation at 0 °C or −10 °C led to a significant decline in dr, er and yield (entries 7 and 8). The diastereoselectivity of the reaction was found to be concentration-dependent: performing the reaction at a higher concentration resulted in a significant decline in dr (entry 9), whereas a lower reaction concentration allowed for better diastereocontrol (entry 10). Gratifyingly, a slight increase in the amount of VCP (from 1.2 to 1.5 equivalents), to account for any potential polymerisation, allowed the reaction to achieve near quantitative yield (entry 11). The results obtained by variations of the Pd^0 source and catalytic loadings were all inferior to that outlined in entry 11 (see the ESI†).

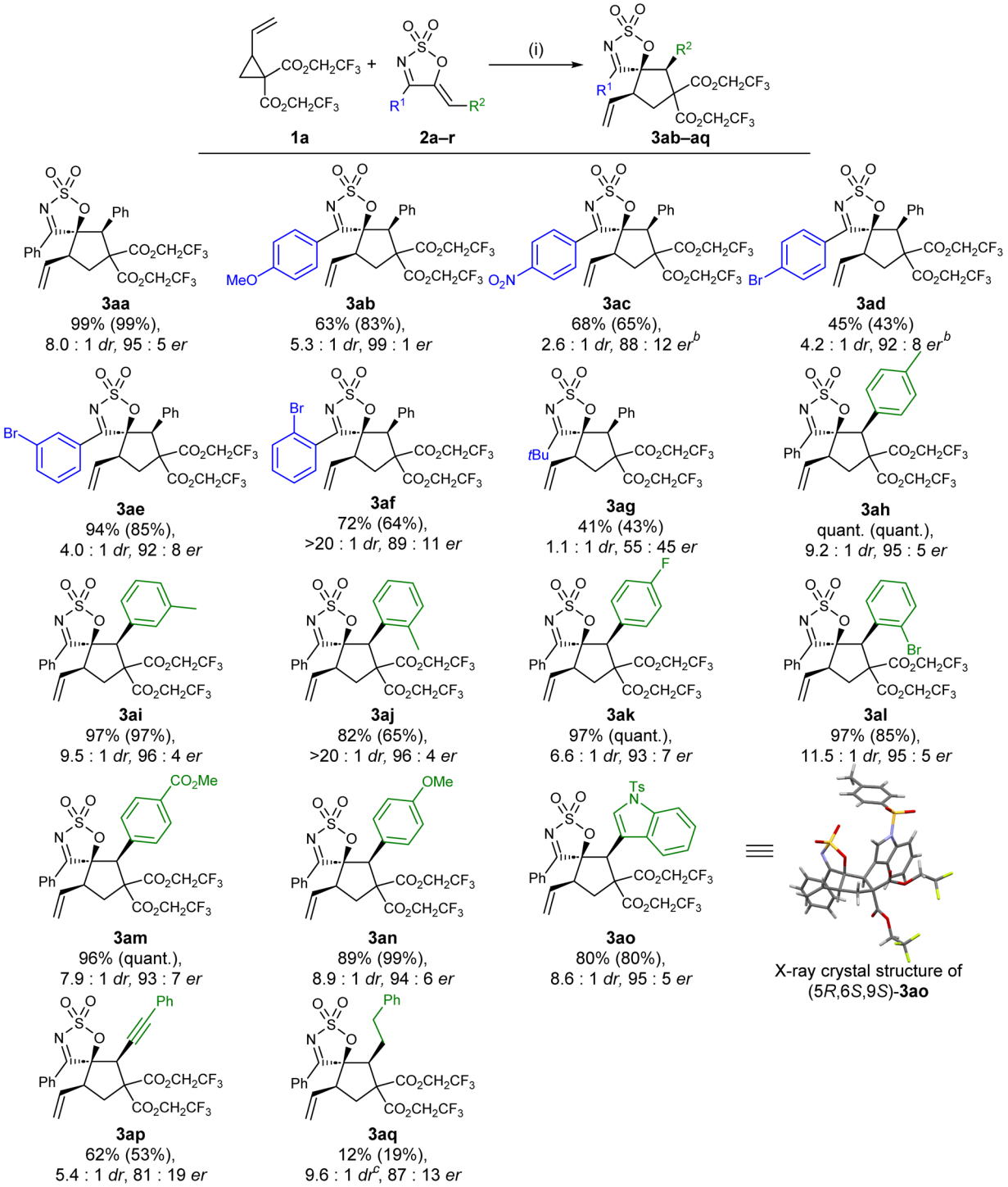
The optimum VCP was then examined (Scheme 1). The styryl derivative **1b** was found to have comparable reactivity to **1a**, affording the product in excellent yield, although in significantly poorer dr and er. The reaction of the diethyl malonate substrate **1c** was remarkably lower yielding compared to its bis(trifluoro)ethyl counterparts **1a** and **1b**, affording **3ca** in a modest 43% yield, 2.3 : 1 dr and 82 : 12 er. Interestingly, when the malononitrile derivative **1d** was tested, the *trans*-diastereoisomer **3da′** was formed preferentially.[59] Among the three spirocyclic VCPs **1e–g** subjected to the optimised reaction conditions, only **1e** reacted to afford the desired product (**3ea**) but in moderate yield, poor dr, and modest er. No reaction took place when either **1f** or **1g** was employed as the



Scheme 1 Screening of various VCPs. [a]Reaction conditions: (i) **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol, 1.0 equiv.), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), **L5** (7.5 mol%), PhMe (0.034 M w.r.t. **2a**), rt, 24 h. Calculated yields are provided in parentheses and were determined by ^{1}H NMR integration against an internal standard (1,2,3-trimethoxybenzene). The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric ratio was determined by chiral HPLC. [b]The two diastereoisomers are separable by chromatography. [c]Lowest estimation due to HPLC traces of the two diastereoisomers being undistinguishable.

reactant, and the decomposition of these VCPs was noted in both cases. These results highlight the VCP as the optimum reactant.

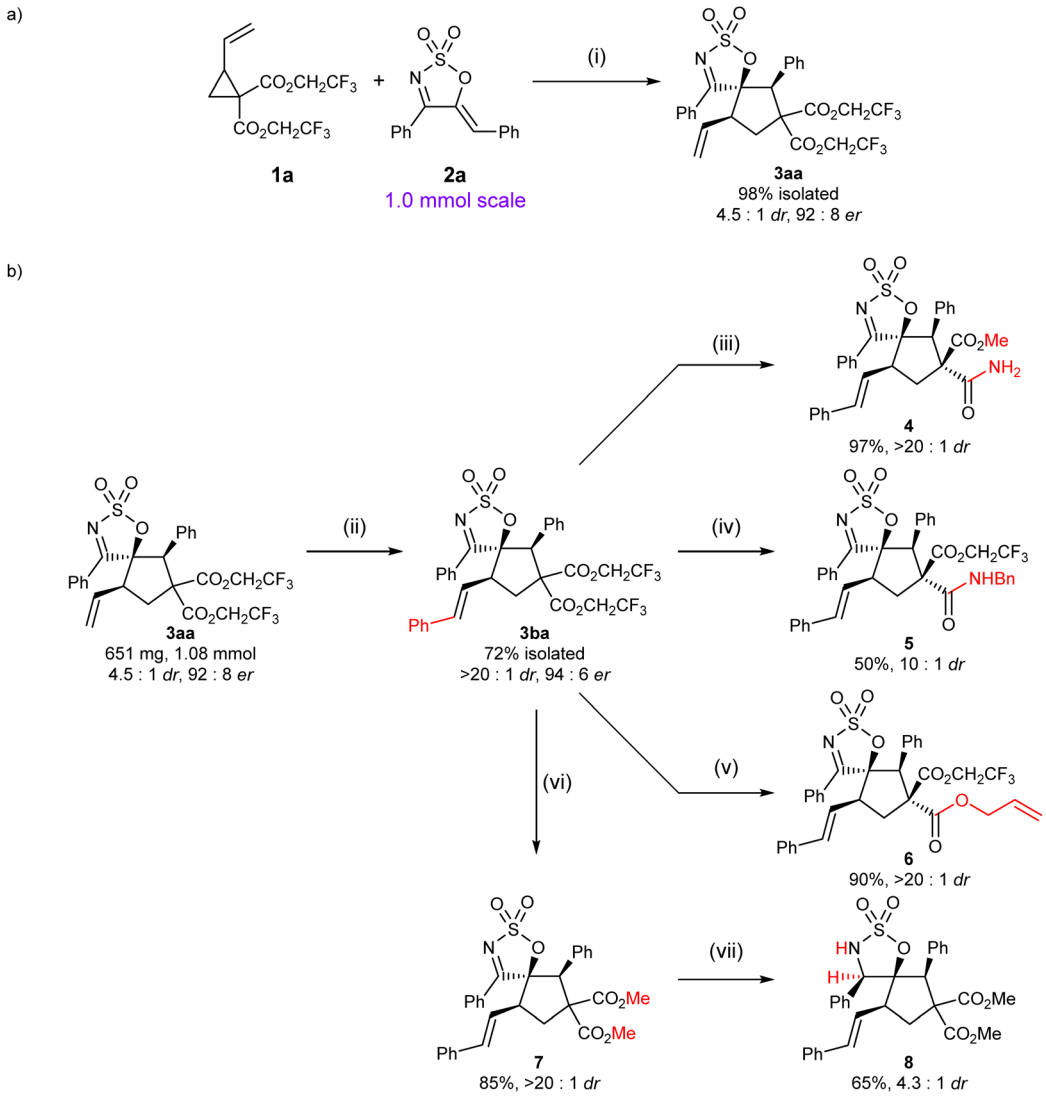
With the optimised conditions and VCP in hand, the scope of cyclic sulfamidate imine-derived 1-azadiene was next investigated (Scheme 2). 1-Azadienes with electronically diverse aryl substituents at the C4 position (R^1) were first examined, and were generally well tolerated. Almost all of these substrates (with the exception of **2f**) furnished the desired (3 + 2)



Scheme 2 Substrate scope of cyclic 1-azadienes. [a]Reaction conditions: (i) **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol, 1.0 equiv.), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), **L5** (7.5 mol%), PhMe (0.034 M w.r.t. **2a**), rt, 24 h. Calculated yields are provided in parentheses and were determined by ^{1}H NMR integration against an internal standard 1,2,3-trimethoxybenzene. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric ratio was determined by chiral HPLC. [b]Reaction was carried out at reflux. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis of the purified product.

cycloaddition product in lower drs compared to the parent substrate **2a**. While electron rich 1-azadiene **2b** reacted smoothly under the optimised reaction conditions, the reactions of **2c** and **2d**—each bearing an electron deficient C4 aryl moiety—were both sluggish at rt; therefore, heating under reflux conditions was required. In stark contrast to the low reactivity of **2d**, the reactions of its analogues **2e** and **2f** were significantly more efficient, furnishing the desired products in good yields, drs, and ers. The excellent diastereocontrol achieved with substrate **2f** was particularly remarkable, which is hypothesised to be due to the sterically demanding *ortho*-bromophenyl moiety being twisted out of the plane with the cyclic sulfamidate imine ring, exerting additional facial selectivity that favours the formation of the major diastereoisomer. A single 4-alkyl substrate, the *tert*-butyl derivative **2g** was tested and was poorly tolerated under the optimised reaction conditions, as shown by the poor dr and er of the product **3ag**.

Cyclic sulfamidate 1-azadienes with a range of electronically and sterically diverse phenyl and heteroaryl groups at the olefinic terminal (**2h–o**) were next subjected to the optimised reaction conditions (Scheme 2). Gratifyingly, all the tested substrates underwent the transformation efficiently, affording the desired (3 + 2) products in good to high yields and in high ers, suggesting that the impact of either electronic or steric effects on both the efficiency and the enantioselectivity of the transformation was minor. The diastereocontrol of the reaction seemed to be more prone to these variations in the electronic and steric properties of the substrate, as illustrated by the minimal erosion in diastereoselectivity observed for substrates with electron deficient aryl groups (**2k** and **2m**), as well as the notable increase in dr noted with substrates bearing more sterically demanding aryl moieties (**2j** and **2l**). The alkynyl substituted 1-azadienyne **2p** was found to be a competent substrate, furnishing the desired product **3ap** in respectable



Scheme 3 Scale up and derivatisation of products **3aa** and **3ba**. [a]Reaction conditions: (i) **1a** (0.15 mmol, 1.5 equiv.), **2a** (0.1 mmol, 1.0 equiv.), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), **L5** (7.5 mol%), PhMe (0.034 M w.r.t. **2a**), rt, 24 h. (ii) Styrene (200 equiv.), Grubbs catalyst 2nd generation (3.5 mol%), CH_2Cl_2, reflux, overnight. (iii) NH_3 (7 N in MeOH), 40 °C, 88 h. (iv) $BnNH_2$ (1.9 equiv.), THF, reflux, 24 h. (v) K_2CO_3 (3.1 equiv.), allyl alcohol, rt, 66 h. (vi) $Na_{(s)}$ (2.4 equiv.), MeOH, rt, 23 h. (vii) $NaBH_3CN$ (8.4 equiv.), 1 : 1 MeOH/CH_2Cl_2, rt, 65 h.

yield, dr, and er. In comparison, the reaction of its saturated analogue **2q** gave the product **3aq** in poor yield, but in slightly higher dr and er.

The absolute configuration of the major diastereomeric cycloadduct was determined *via* X-ray crystallographic analysis of the enantiopure crystal of **3ao**, which allowed the absolute configuration of other substrates to be assigned by analogy.

To demonstrate the synthetic viability of our optimised protocol, the reaction of VCP **1a** and 1-azadiene **2a** was carried out on a 1 mmol scale (Scheme 3a). Delightfully, the cycloadduct **3aa** was obtained in comparably high yield and enantioselectivity to that observed on a smaller scale, although a significant decline in dr was observed. Although direct manipulation of a diastereoenriched mixture of **3aa**/**3aa**′ was possible, it was soon realised that the resulting diastereomeric mixture—which would likely consist of more than two species—might pose a significant analytical challenge. Aiming to avoid the challenging task of analysing these complex mixtures, cycloadduct **3aa** was first converted to its styryl analogue *via* olefin cross-metathesis, allowing the major diastereomer **3ba** to be isolated in 72% isolated yield without any erosion in er. With a substantial amount of **3ba** in hand, several post-synthetic transformations were then attempted to illustrate the versatility of this scaffold (Scheme 3b).

The distinction in the reactivity of the geminal esters provided opportunities for some chemoselective reactions to be conducted and allowed a fourth stereogenic centre to be readily created. Treatment of spirocyclic cyclic imine **3ba** with ammonia in methanol allowed a double transesterification to take place, followed by a regioselective amidation of the more reactive ester moiety *trans*- to the SO_2 bridge, furnishing amide **4** in high yield and dr (relative configuration of **4** was determined by 2D NOESY, see the ESI†). These differences in reactivity of the two ester moieties of **3ba** were further exploited for the preparation of amide **5** and diester **6**—*via* chemoselective amidation and transesterification, respectively. These reactions occurred in moderate to high yields and good to high drs, with that of **5** being diminished relative to that of **4**, presumably due to the higher reaction temperature (reflux in THF). In addition to the selective functionalisation of the *gem* diesters, construction of an additional stereogenic centre could be otherwise achieved *via* the functionalisation of the reactive imine moiety. Reduction of **7**—readily obtained by a double transesterification of **3ba** with NaOMe—by $NaBH_3CN$ afforded cyclic sulfamidate **8** in moderate yield and dr (relative stereochemistry of the major diastereoisomer was established by 2D NOESY analysis, see the ESI†). Attempts to subject **3ba** to a variety of other common hydride reducing agents were complicated by the highly reactive nature of the bis(trifluoroethyl) diester moieties.

The stereochemical outcomes of the transformation can be rationalised using a quadrant analysis, generated based on X-ray data for analogous Pd–Segphos complexes (Fig. 3).[61,62] Ionisation of the racemic VCP by the chiral [(*S*)-DM-Segphos]Pd^0 complex can afford either diastereomeric complex **A** or **B**, which can interconvert *via* π–σ–π isomerisation. Of these two, complex **A** is likely more favoured due to the lower steric interaction between the dipole fragment and the equatorial xylyl group from the ligand. In line with established literature, the Michael addition of the dipole to the dipolarophile is likely a reversible process,

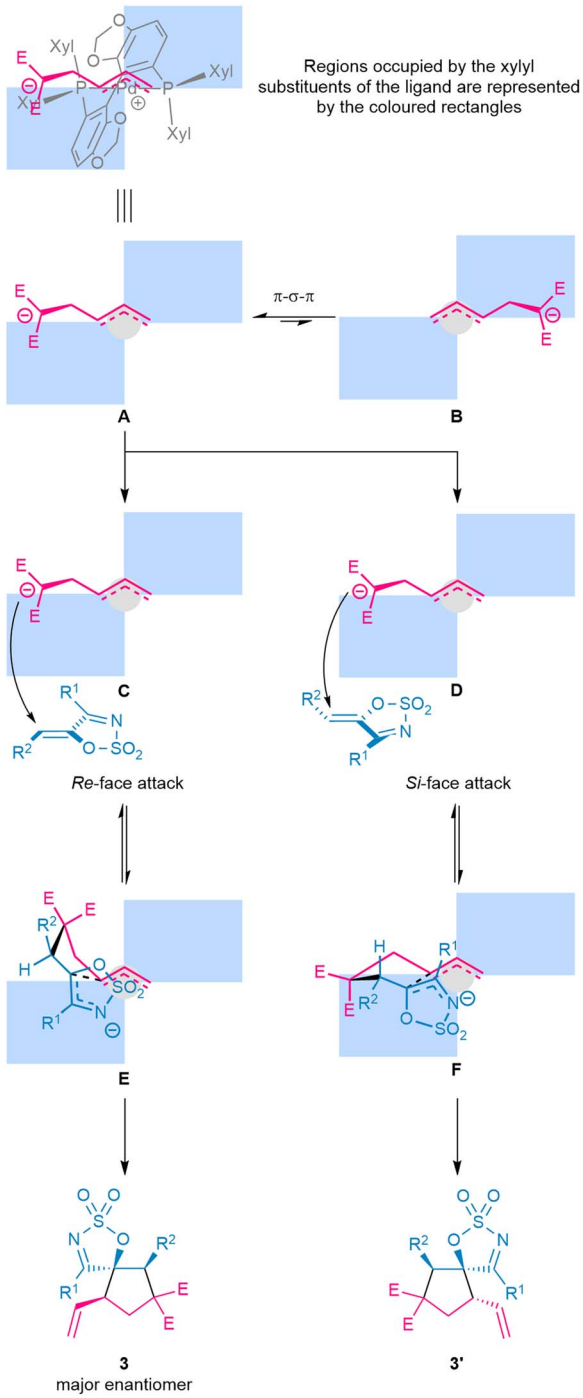


Fig. 3 Rationalisation of the observed stereochemical outcomes using a quadrant analysis. For clarity, in complexes **A**–**F**, the chiral ligand scaffold is omitted and the cationic metal centre is represented by the light grey circle.

whereas the ring-closure occurs irreversibly and under the control of the ligand to determine the configuration [stereochemistry] of the cycloadduct. Specifically, addition of **A** to the *Re*-face of 1-azadiene *via* **C** should form the pre-cyclisation conformer **E**—where the R^2 moiety is placed in the pseudo-equatorial position—followed by irreversible ring closure to furnish the major diastereomeric product with the observed

absolute configuration. In contrast, addition of **A** to the *Si* face of 1-azadiene *via* **D** gives pre-cyclisation conformer **F**—with the R^2 substituent similarly occupying the pseudo-equatorial position—and then ring closure of **F** provides an enantiomer of the minor diastereomeric product. For pre-cyclised conformer **E**, it is likely that the more favourable disposition of a significant portion of the intermediate in the open quadrant of the chiral ligand space may have allowed the cyclisation to proceed faster than that of **F**, thus leading to high stereocontrol.

Conclusions

In conclusion, SDAs have been demonstrated to be competent partners in stereo- and regioselective Pd-catalysed (3 + 2) cycloaddition reactions with vinylcyclopropane derived 1,3-dipoles. The ability of this dipolarophile to avoid (4 + *n*) reaction manifolds has implications for reactions with a myriad of other Pd-stabilised dipoles and in organocatalysed processes,[63,64] which can also be utilised with BDAs but are far less explored, with no (3 + 2) processes known. The cycloaddition provides a rapid assembly of highly substituted and stereodefined cyclopentanes as part of a spirocyclic system, with sp^3-rich systems being privileged structures in pharmaceutical development. The transformation is scalable and post-synthetic modifications targeting different functional handles demonstrate the synthetic utility of the cycloadduct. Many of these transformations allow an additional stereocentre to be readily installed *via* either chemoselective manipulations of geminal diester functionalities or *via* diastereoselective reduction of the imine moiety.

Data availability

Data for all compounds reported in this manuscript are available in the ESI,† which includes experimental details, characterisation, copies of ^{1}H and ^{13}C NMR spectra as well as HPLC traces. Crystallographic data for compounds has been deposited at the CCDC under CCDC 2224300.

Author contributions

HP, CH, and SP conceptualised the project. CH and SP were involved with supervision, funding acquisition and writing – reviewing and editing. HP carried out the investigation and formal analysis of the data and was involved with writing the original draft of the manuscript. AT was involved in writing – reviewing and editing and formal analysis of data. MGG and CR carried out the X-ray crystallography.

Conflicts of interest

There are no conflicts to declare.

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