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The Pd-catalysed asymmetric allylic alkylation reactions of sulfamidate imines†

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The Pd-catalysed asymmetric allylic alkylation (Pd-AAA) of prochiral enamide anions derived from 5*H*-oxathiazole 2,2-dioxides has been developed. Various 4,5-disubstituted and 4-substituted cyclic sulfamidate imines have participated in the transformation with a range of allyl carbonates—as well as 2-vinyl oxirane, 2-vinyl-*N*-tosylaziridine, and 2-vinyl-1,1-cyclopropane dicarboxylate—to furnish the desired C-allylated products in moderate to high yields, with high regioselectivities and generally high enantioselectivities. Conversion between *N*- and C-allyl products was observed, with the *N*-allylated products converting to the C-allylated products over time. The resulting high-value allylated heterocyclic products all bear a tetrasubstituted stereogenic centre and can be reduced to an allylated chiral sulfamidate or an amino alcohol.

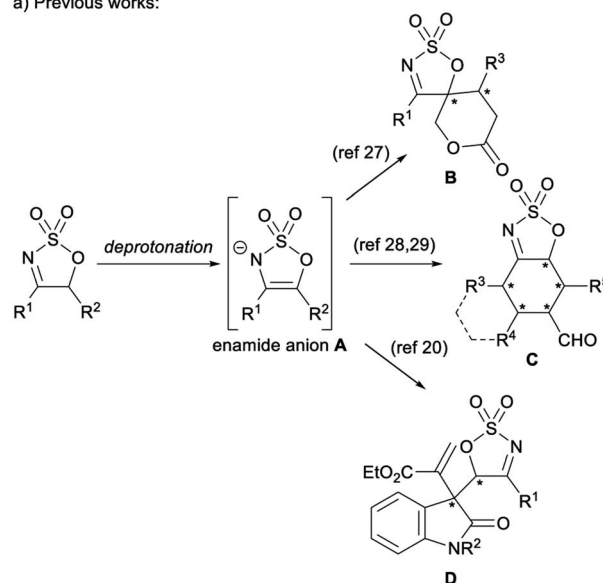
Introduction

Sulfamidate imines are versatile heterocyclic building blocks that have been utilised in a range of reactions.¹ The reactivity of these heterocycles is dominated by nucleophilic attack and reduction of the activated imine portion of the ring to provide sulfamidates – themselves valuable precursors to a myriad of heteroatom containing molecules.^{2–5} A number of metal-catalysed hydrogenation^{6–9} and transfer-hydrogenation^{10–16} reactions disclosed in recent years offer a convenient and efficient pathway to synthetically useful chiral sulfamidates with an α -secondary amine moiety. Similarly, the successful development of various Rh-,^{17–22} Ir-,²³ and Pd-catalysed²⁴ nucleophilic addition reactions allows for the preparation of sulfamidates with an α -tertiary amine. A number of these transformations have been employed in the syntheses of bioactive and medically relevant scaffolds such as norephedrine and norpseudoephedrine,²⁵ a medically relevant piperazinone derivative,⁷ a potent β -secretase 1 inhibitor,²⁶ and the potential Alzheimer's medication, verubecestat.²⁴

While the electrophilic reactivity of sulfamidate imines is well developed, their reactions as nucleophilic enamide anions *A* via deprotonation of the acidic proton(s) adjacent to the imine moiety are not well developed – especially with regard to stereoselective transition metal-catalysed reactions (Fig. 1a). The only reports of such reactions are from the groups of Vicario

and Samanta, who have both demonstrated organocatalyzed diastereo- and/or enantio-selective reactions of sulfamidate imines to provide stereodefined scaffolds, such as spiro

a) Previous works:



b) This work:

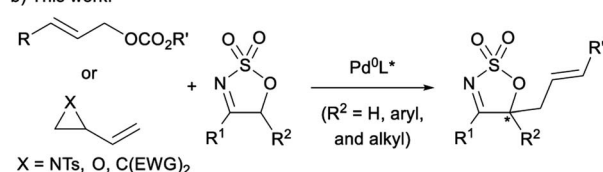


Fig. 1 Deployment of cyclic sulfamidate imines as nucleophilic enamide anions.

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sulfamate imine-fused δ -lactone **B**,²⁷ sulfamate imine-fused cyclohexanes and *trans*-decalins **C**,^{28,29} and 3,3-disubstituted oxindoles **D**.³⁰ None of these reactions involve reaction of a 5-substituted cyclic imine to directly form a tetra-substituted stereogenic centre in the product. Further, to the best of the authors' knowledge, there are no transition metal-catalysed processes harnessing enamide anion **A**. Given the range of nucleophiles deployed in Pd-catalysed asymmetric allylic (Pd-AAA) reactions, it was envisaged that the enamide anion **A** would be an intriguing and useful prochiral nucleophile in this powerful methodology (Fig. 1b).^{31–35} While enolates and enamines have been deployed as nucleophiles in Pd-AAA reactions, enamide anions have not been explored.³⁶ The use of **A** in the Pd-AAA reaction provides the opportunity to introduce a heterocyclic nucleophile with multiple heteroatoms,^{37–42} and given the availability of 5-substituted sulfamate imines, Pd-AAA products bearing an enantiodefined tetra-substituted carbon centre could be obtained. Furthermore, the imine moiety would still be present in the allylated products, providing a handle for further synthetic manipulation.

Herein, we report the successful application of cyclic sulfamate imines in Pd-catalysed asymmetric allylic alkylation to produce high-value allylated heterocycles.

Results and discussion

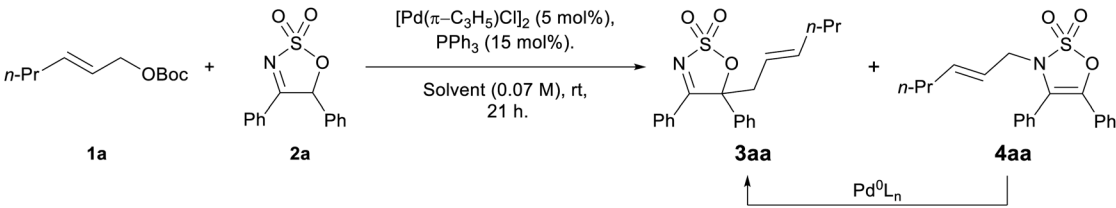
Preliminary proof of principle for the proposed enamide anion allylation was carried in a racemic sense using allyl carbonate **1a** and 4,5-diphenyl cyclic imine **2a** with $[\text{Pd}(\pi\text{-C}_3\text{H}_5)\text{Cl}]_2/\text{PPh}_3$ as the catalyst system. The imine substrates **2** are readily prepared from α -hydroxyketones and chlorosulfonyl isocyanate (see ESI† for full details†). The reaction proceeded as predicted, however

an interesting regioselectivity issue was encountered, with both the desired *C*-allylated product **3aa** and the *N*-allylated species **4aa** being formed (Table 1, entry 1—structures unambiguously assigned by X-ray crystallography, see the ESI†). It was postulated that due to the weaker C–N bond, the *N*-allylation process should be reversible, and gratifyingly, when re-subjecting the *N*-allyl product **4aa** to the reaction conditions, the thermodynamically more stable *C*-allyl product **3aa** was obtained in high yield (Table 1, entry 2).

A number of solvents were tested to find the best for generating the desired *C*-allylated product selectively, and while the reaction progressed well in a range of solvents such as MeCN, DMF, and DMSO—with both *C*- and *N*-allylated products being formed in good combined yields (Table 1, entries 1, 5–8)— CH_2Cl_2 and THF were the only two options allowing the regioselective synthesis of the *C*-allylated product **3aa** in good to high yields (70% and 89%, entries 2 and 3, respectively).

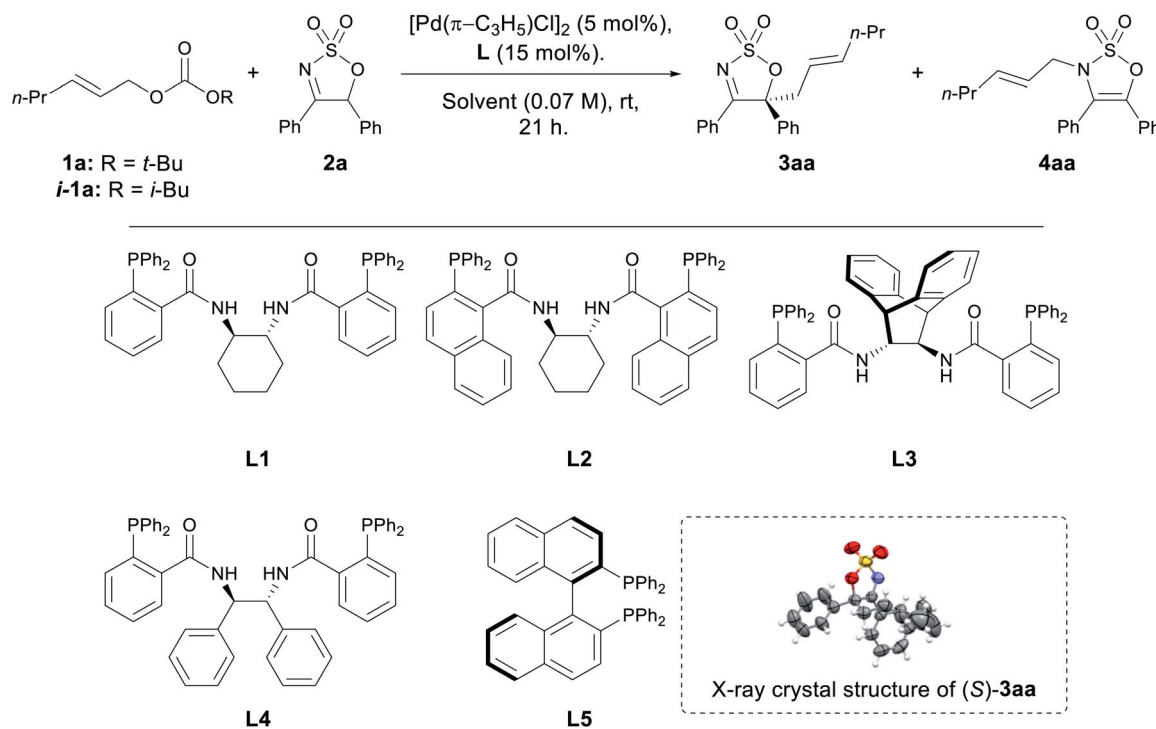
With two optimum solvents for the *C*-allylated product identified, screening of several chiral ligands was carried out (Table 2). A range of Trost ligands **L1–4** was screened, and **L1** was found to have excellent performance in both THF and CH_2Cl_2 , affording the desired *C*-allylated product **3aa** in high yields and high enantiomeric ratios (ers) (Table 2, entries 1 and 6). Analysis of the progress of the reaction in this case also showed formation of the *N*-allyl product **4aa**, which slowly disappeared over time, indicating it is a possible reaction intermediate. Trost ligand **L4** performed well in both solvents, affording **3aa** in moderate to good yields and good ers, although a small amount of **4aa** was observed in both cases (entries 4 and 9). (*R*)-BINAP (**L5**) performed very well in THF, affording **3aa** in excellent yield and high er (entry 5), but was almost completely inactive in CH_2Cl_2 (entry 10). Trost ligands **L2** and **L3** were

Table 1 Selected optimisation results of the racemic Pd-AAA reactions of cyclic imine **2a** with allyl carbonate **1a** using triphenylphosphine^a

|  | | | |
|--------------------------------------------------------------------------------------|--------------------------|------------------------|-----------------|
| Entry | Solvent | Yield ^b (%) | |
| | | 3aa | 4aa |
| 1 | MeCN | 49 ^c | 30 ^c |
| 2 ^{d,e} | MeCN | 77 | — |
| 3 | CH_2Cl_2 | 70 | — |
| 4 | THF | 89 | — |
| 5 | PhMe | NR | |
| 6 | MeOH | 16 | 17 |
| 7 | DMF | 41 | 22 |
| 8 | DMSO | 61 | 12 |

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.22 mmol, 1.1 equiv.), $[\text{Pd}(\pi\text{-C}_3\text{H}_5)\text{Cl}]_2$ (5 mol%), PPh_3 (15 mol%), solvent (0.07 M w.r.t. **1a**), rt, 21 h. ^b Yield determined by ¹H NMR integration against an internal standard (1,2,3-trimethoxybenzene). ^c Isolated yield. ^d **4aa** was employed as the SM. ^e Reaction time: 17 h.



Table 2 Selected optimisation of the Pd-AAA reactions of cyclic imine **2a** with allyl carbonate **1a** with chiral bidentate phosphine ligands^a

| Entry | Ligand | Solvent | Yield ^b (%) | | er ^c |
|-------------------|-----------|---------------------------------|------------------------|------------|----------------------|
| | | | 3aa | 4aa | |
| 1 ^d | L1 | THF | 90 | — | 93 : 7 |
| 2 | L2 | THF | NR | — | — |
| 3 | L3 | THF | NR | — | — |
| 4 | L4 | THF | 73 | 6 | 83 : 17 |
| 5 | L5 | THF | 97 | — | 91 : 9 |
| 6 ^e | L1 | CH ₂ Cl ₂ | 90 | — | 91 : 9 |
| 7 | L2 | CH ₂ Cl ₂ | 17 | 10 | 84 : 16 |
| 8 | L3 | CH ₂ Cl ₂ | 6 | 9 | 62 : 38 |
| 9 | L4 | CH ₂ Cl ₂ | 54 | 6 | 85 : 15 |
| 10 | L5 | CH ₂ Cl ₂ | 7 | — | 35 : 65 ^f |
| 11 ^{e,g} | L1 | CH ₂ Cl ₂ | 78 | — | 91 : 9 |
| 12 ^{e,h} | L1 | CH ₂ Cl ₂ | 86 | — | 91 : 9 |
| 13 ^{e,i} | L1 | CH ₂ Cl ₂ | 84 | — | 92 : 8 |
| 14 ^{e,j} | L1 | CH ₂ Cl ₂ | 85 | — | 93 : 7 |
| 15 ^{e,k} | L1 | CH ₂ Cl ₂ | 61 | — | 91 : 9 |

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.22 mmol, 1.1 equiv.), [Pd(π-C₃H₅)Cl]₂ (5 mol%), **L** (15 mol%), solvent (0.07 M w.r.t. **1a**), rt, 21 h.

^b Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone or *trans*-stilbene oxide). ^c Enantiomeric ratio determined by chiral HPLC. ^d Reaction reached completion after 3 h. ^e Reaction reached completion after 1 h. ^f Reversed enantioselectivity compared to entry 5.

^g [Pd(π-C₃H₅)Cl]₂ (2.5 mol%), **L** (7.5 mol%). ^h Reaction concentration halved (0.04 M w.r.t. **1a**). ⁱ *i*-**1a** (1.0 equiv.) used instead of **1a**.

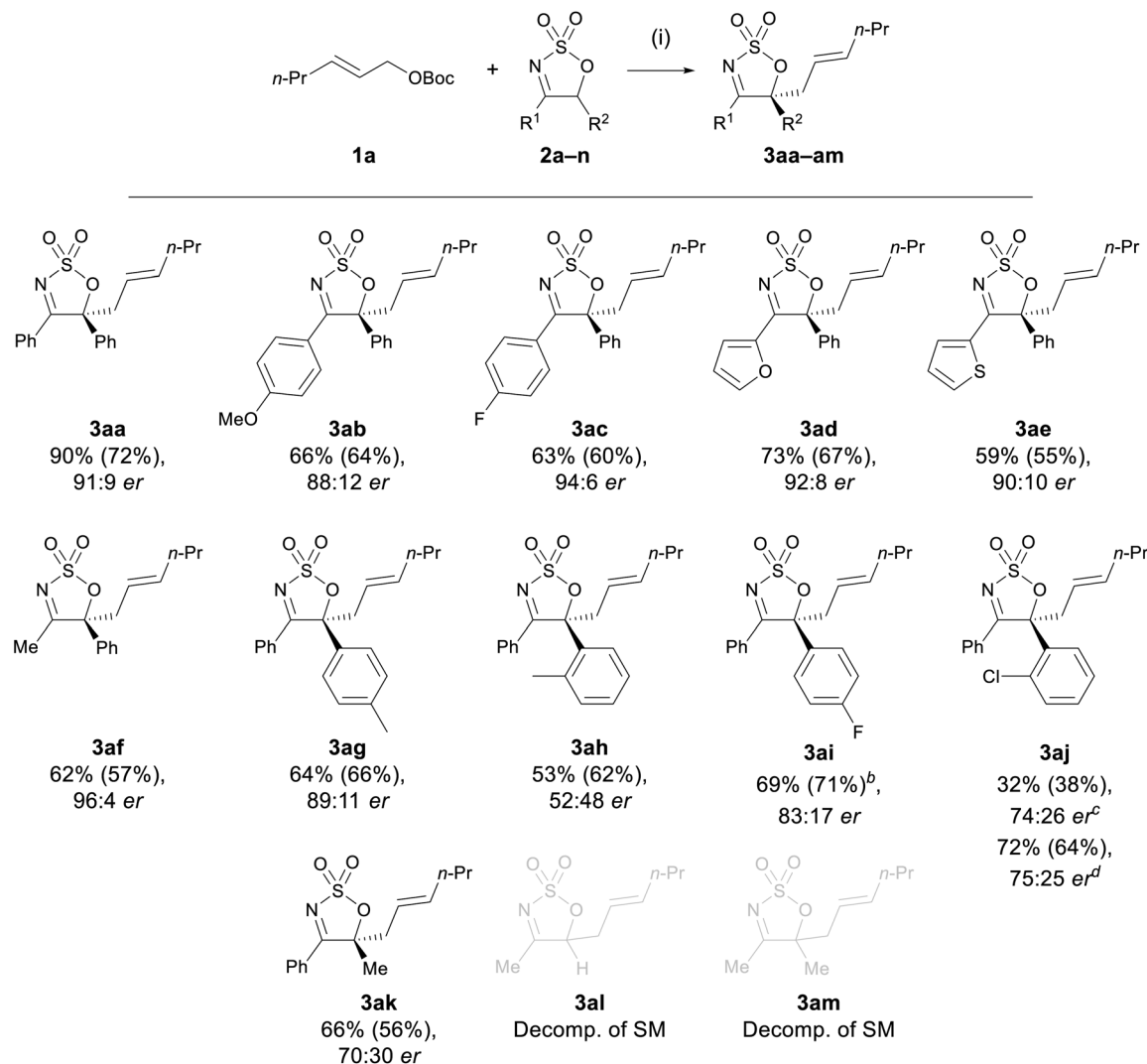
^j Pd₂dba₃·CHCl₃ (5 mol%). ^k **4aa** was employed as SM.

found to be completely inactive in THF (entries 2 and 3, respectively), and performed poorly in CH₂Cl₂ (entries 7 and 8, respectively).

Further optimisation was carried out with **L1** in CH₂Cl₂ due to a faster rate of reaction compared to THF (Table 2). A slight decline in yield was observed when the catalytic load was halved to 2.5 mol% (entry 11), while no noticeable impacts on either yield or enantioselectivity were observed when the reaction was

performed at a more dilute concentration (entry 12). The nature of the *in situ* generated alkoxide seemed to be insignificant, as indicated in the reaction employing *i*-**1a** in place of **1a** (entry 13). No appreciable changes to the performance of the reaction were observed when employing Pd₂dba₃·CHCl₃ as the Pd(0)-source, suggesting that it can be a viable alternative to the allylpalladium(II) chloride dimer (entry 14).⁴³ Finally, subjecting the isolated *N*-allyl product **4aa** to the optimised reaction conditions





Scheme 1 Substrate scope of cyclic sulfamidate imines.^a ^a Reaction conditions: (i) **1a** (1.0 equiv.), **2** (1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (5 mol%), **L1** (15 mol%), CH₂Cl₂, rt, 1 h. Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone or *trans*-stilbene oxide), isolated yield in parentheses. Enantiomeric ratio determined by chiral HPLC. ^b Combined yield of a 7:1 : 1 mixture of **3aj** and **3ac** (see ESI†). ^c *N*-Allylated species **4aj** detected in 21% yield by NMR. ^d Modified procedure: **1a** (1.1 equiv.), **2** (1.0 equiv.), Pd₂dba₃·CHCl₃ (5 mol%), **L1** (15 mol%), CH₂Cl₂, rt, 24 h.

furnished the *C*-allyl product **3aa** in moderate yield and with comparable er, confirming that this conversion occurs enantioselectively (entry 15).

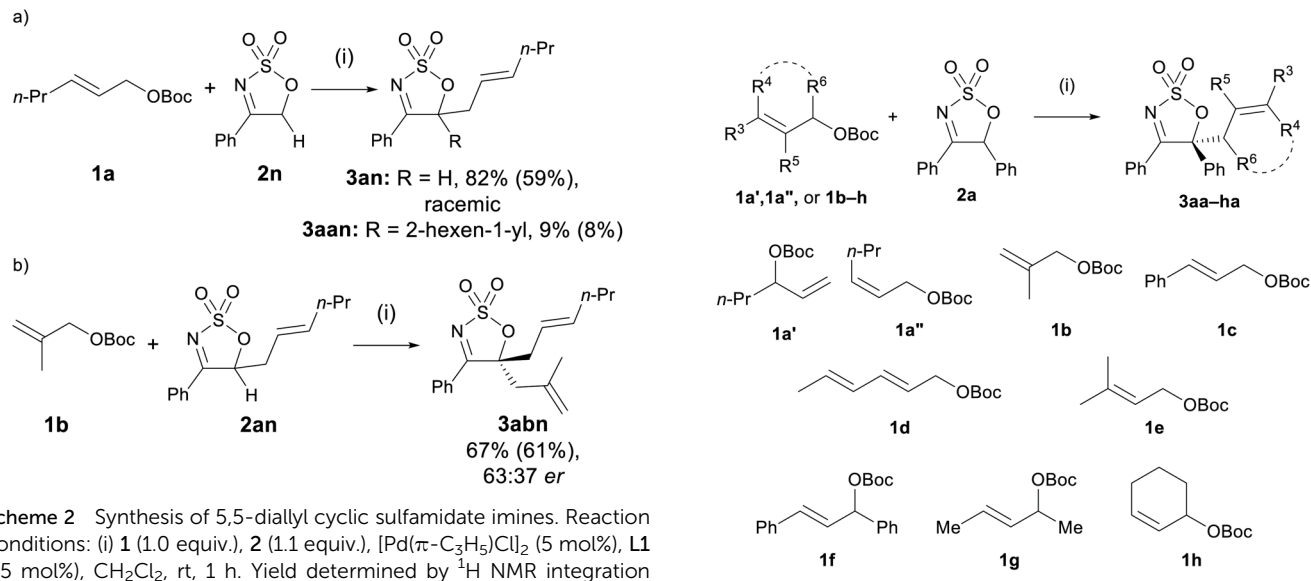
The absolute (*S*)-configuration of the *C*-allylated product was determined *via* X-ray crystallographic analysis of the enantiopure crystal of **3aa**. For all other enantioenriched substrates, the absolute configuration was assigned by analogy.

With the optimised Pd-AAA of **2a** established (Table 2, entry 6), the generality of the allylation reaction with other cyclic sulfamidate imines was pursued (Scheme 1). The electronic effect of the substituent at the C4 position of the cyclic imine was first probed. A range of cyclic imines **2a–e** bearing different aryl and heteroaryl substituents at the C4 position—either electron rich or poor—reacted efficiently with allyl carbonate **1a** to furnish the desired products **3aa–ae** in moderate to high yields (59–90%), and in high ers (88 : 12–94 : 6 er). Notably,

imine **2f** bearing a 4-methyl group was found to be well tolerated, selectively producing the allylated product **3af** in 62% yield and 96 : 4 er with no by-products arising from the competitive deprotonation of the C4 methyl group detected, as had been the case in previous methods.⁴⁴

Cyclic sulfamidate imines bearing substituents with varying electronic and steric properties at the C5 position (**2g–k**) were subjected to the reaction conditions to investigate the impact of these two factors on reaction efficacy. All the tested substrates afforded the *C*-allylated product in moderate to good yields (53–72%), suggesting neither electronic nor steric factors had a significant impact on the reaction yields. No appreciable change in er was observed when varying the electronic properties of the substituent on C5 (**3ag** and **3ai**); however, a significant drop in er was observed with substrates bearing more sterically hindered substituents (**3ah**, **3aj**, and **3ak**). In the case





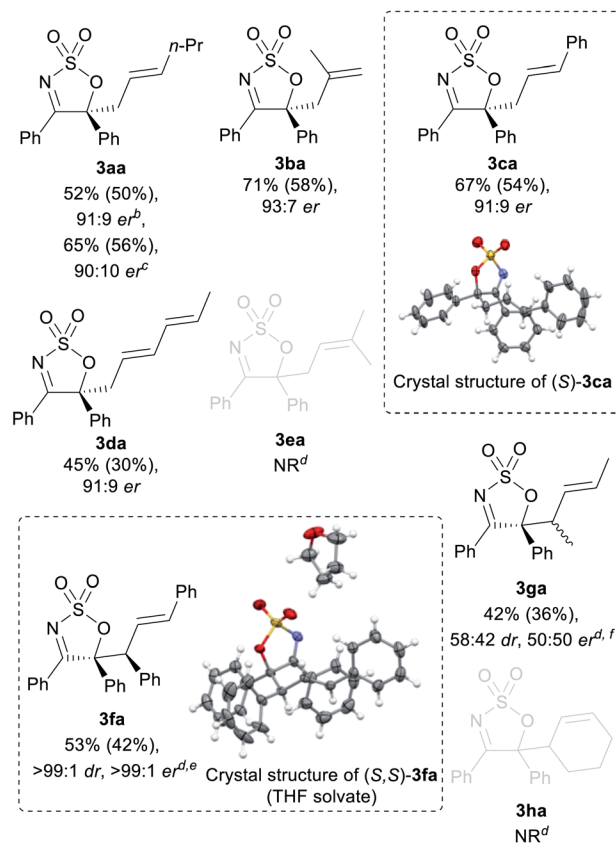
Scheme 2 Synthesis of 5,5-diallyl cyclic sulfamidate imines. Reaction conditions: (i) **1** (1.0 equiv.), **2** (1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (5 mol%), **L1** (15 mol%), CH₂Cl₂, rt, 1 h. Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone or *trans*-stilbene oxide). Enantiomeric ratio determined by chiral HPLC.

of imine **2j**, a diminished yield of **3aj** was obtained under the optimised conditions and a significant amount of the *N*-allylated product **4aj** (21% by NMR analysis) was detected in the crude reaction mixture. Prolonging the reaction time of **2j** to 24 h afforded exclusively **3aj** in 72% yield with an er of 75 : 25. The unchanged er observed for substrate **3aj** further confirmed that the conversion from the *N*- to the *C*-allyl species is an enantioselective process.

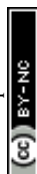
Sulfamidate imine **2n**, lacking a substituent at C5, engaged in the allylation reaction to yield the corresponding mono-allylated product **3an** in 82% yield as a racemate, accompanied by a small amount of di-allylated **3aan** (Scheme 2a). The complete lack of enantioselectivity is not surprising, as the presence of an acidic proton at C5 of the mono-allylated product allows rapid racemisation of **3an** to occur under the basic reaction conditions. Inspired by the formation of the diallylated product **3aan**, product **3an** was reacted with allyl carbonate **1b**, and the diallylated product **3abn** was afforded in good yield and low er (Scheme 2b).

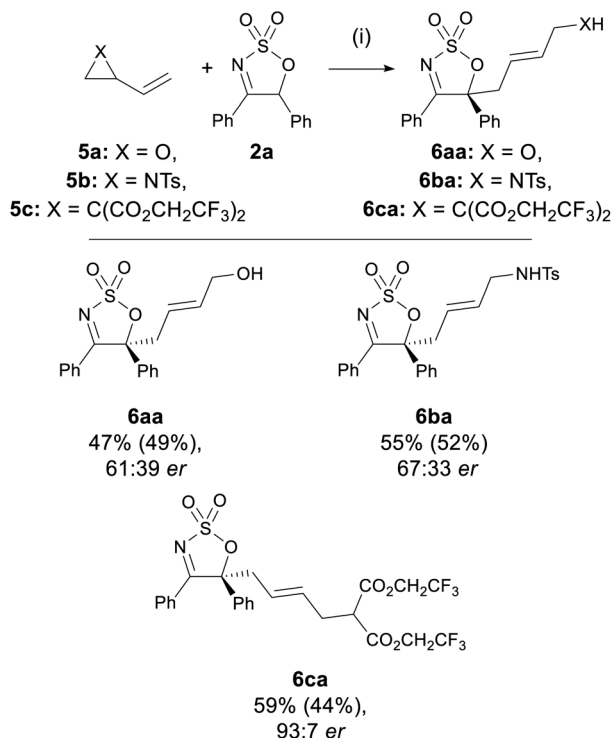
To explore the scope further, a range of monosubstituted allyl carbonates were also examined (Scheme 3). Allyl carbonates **1a'** and **1a''** were viable substrates, as both furnished imine **3aa** in excellent er but in lower yields compared to **1a** (52% and 65%, respectively). Carbonates **1b** and **1c** were also competent substrates, affording the corresponding products **3ba** and **3ca** in good yields of 71% and 67%, respectively, and very high ers (93 : 7 and 91 : 9, respectively). X-ray crystallographic analysis carried out on **3ca** confirmed the absolute (*S*)-configuration of this product. Conjugated diene substrate **1d** provided **3da** in only 45% yield, but in high enantioselectivity (91 : 9 er) and without the formation of any other regioisomeric products. No reaction was observed when prenyl carbonate **1e** was employed.

A number of disubstituted allyl carbonates (**1f–h**) were also tested, however, none of these were reactive under the



Scheme 3 Substrate scope of allyl carbonates.^a Reaction conditions: (i) **1** (1.0 equiv.), **2a** (1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (5 mol%), **L1** (15 mol%), CH₂Cl₂, rt, 1 h. Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone or *trans*-stilbene oxide), isolated yield in parentheses. Enantiomeric ratio determined by chiral HPLC. ^b**1a'** employed as substrate. ^c**1a''** employed as substrate. ^dReaction time: 24 h. ^eModified procedure: **1** (1.0 equiv.), **2a** (1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (5 mol%), (*S*)-BINAP (15 mol%), THF, rt, 24 h. ^fIsolated yield, diastereomeric ratio, and enantiomeric ratio determined from the recrystallised material. ^gDiastereomeric ratio determined from the ¹H NMR spectrum of the crude reaction mixture.





Scheme 4 Substrate scope with *in situ* generated 1,3-dipoles.^a

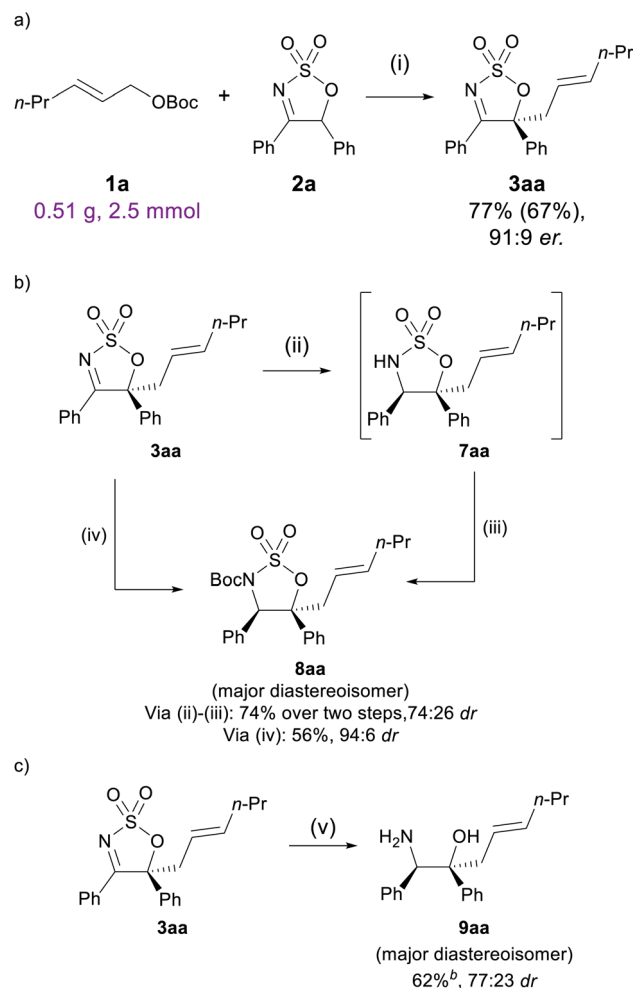
^aReaction conditions: (i) **4** (1.0 equiv.), **2a** (1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (5 mol%), **L1** (15 mol%), CH₂Cl₂, rt, 24 h. Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone or *trans*-stilbene oxide), isolated yield in parentheses. Enantiomeric ratio determined by chiral HPLC.

optimised reaction conditions. Allyl carbonates **1f** and **1g**, however, showed moderate reactivity when the alternate (*S*)-BINAP/THF (see Table 2, entry 5) conditions were employed, providing **3fa** and **3fg**. Interestingly, the major diastereoisomer of **3fa** was obtained as a single enantiomer following recrystallisation, and X-ray crystallographic analysis of this enantiopure sample confirmed the (*S,S*)-configuration of the two stereogenic centres. Allyl carbonates **1e** and **1h** were also subjected to this modified procedure, but no products were obtained in either case. Notably, however, racemic **3ea** and **3ha** were obtained when Ph₃P was employed as the ligand—indicating that the more sterically encumbered chiral bidendate ligands were inhibiting the reaction for these substrates (see the ESI†).

The compatibility of *in situ* generated Pd-stabilised zwitterionic 1,3-dipoles in the allylation of **3** was also investigated (Scheme 4).⁴⁵ Under the optimised conditions, dipole precursors 2-vinyl oxirane **5a**, *N*-tosyl-2-vinylaziridine **5b**, and 2-vinyl-1,1-cyclopropane dicarboxylate (VCP) **5c** all reacted with imine **2a** to deliver the corresponding linear products **6aa–ca** in moderate yields (44–52%). Interestingly, while **6aa** and **6ba** were both obtained in modest *ers* of 61 : 39–67 : 33, the VCP-derived product **6ca** was formed with a very high *er* of 93 : 7, which is comparable to those obtained in previously reported VCP-specific Pd-AAA protocols.^{38,46} It is also worth noting that there have been few examples on the use of vinyl oxiranes and 2-

vinylaziridines as substrates in Pd-AAA with carbon nucleophiles.^{47–50}

To demonstrate the synthetic practicality of this method, the reaction of **1a** with **2a** was performed at a 2.5 mmol scale, with a reduced catalytic loading of 2.5 mol% of [Pd(π -C₃H₅)Cl]₂ and 7.5 mol% of **L1**. Gratifyingly, the allylated product **3aa** was obtained in good yield (77% by NMR analysis, 67% isolated) and comparable enantioselectivity (91 : 9 *dr*, Scheme 5a). A number of post-synthetic modifications were then attempted to showcase the utility of the sulfamate imine allylated product. First, **3aa** was reduced by NaBH₄ to the corresponding sulfamate **7aa**, and following an *N*-Boc protection step,⁵¹ sulfamate **8aa** was obtained in 74% yield and 74 : 26 *dr* (Scheme 5b, absolute



Scheme 5 Scale-up reaction and derivatisation of allylated product **3aa**.^a Reaction conditions: (i) **1** (2.5 mmol, 1.0 equiv.), **2a** (2.8 mmol, 1.1 equiv.), [Pd(π -C₃H₅)Cl]₂ (2.5 mol%), **L1** (7.5 mol%), CH₂Cl₂, rt, 1 h. Yield determined by ¹H NMR integration against an internal standard (dimethyl sulfone), isolated yield in parentheses. (ii) **3aa** (1.0 equiv.), NaBH₄ (4.5 equiv.), MeOH, 0 °C, 1 h. (iii) Boc₂O (1.3 equiv.), DMAP (0.4 equiv.), CH₂Cl₂, rt, overnight. (iv) (a) **3aa** (1.0 equiv.), K-Selectride® (2.2 equiv.), THF, −10 °C, 1 h. (b) Boc₂O (2.3 equiv.), DMAP (14 mol%), −10 °C to rt, overnight. (v) LiAlH₄ (3.1 equiv.), THF, reflux, 1.5 h. Isolated yield. Diastereomeric ratio determined from the ¹H NMR spectrum of the crude reaction mixture. ^bMinor diastereoisomer also isolated in 19% yield.



configuration of **8aa** was determined by 1D NOE, see the ESI†). A one-pot reduction/*N*-Boc protection procedure can be carried out using the more sterically hindered reducing reagent K-Selectride®, in which **8aa** was afforded in 56% yield and 94 : 6 dr. Compared to the hydrogenation products obtained from reduction of the imine, this method can provide more substituted products having two contiguous stereocentres.

Lastly, treatment of **3aa** with LiAlH_4 under reflux conditions successfully furnished β -amino alcohol **9aa** in 62% yield, which was readily separable by chromatography from its diastereomer, which was isolated in 19% yield (Scheme 5c). This synthetic sequence therefore offers efficient access to highly functionalised allylated β -amino alcohols, which can serve as useful synthetic building blocks.^{52,53}

The stereochemical outcomes of the allylated products can be rationalised using Trost's well established "wall and flap" model (Fig. 2).^{54,55} Following this predictive tool, ionisation of achiral allyl substrates by the chiral Pd(0)-complex should provide the kinetically favoured π -allyl complex **E** that is rapidly attacked by the sterically bulky enamide anion of **2** under the flap, rather than under the Pd-allyl (Fig. 2a). The enamide anion

is oriented such as to avoid steric interaction between the ligand wall and R^1 and R^2 . A similar stereochemical model has been postulated by Trost and co-workers for the allylation of pro-chiral tetralones.^{56,57} The experimentally determined (*S*)-configuration of the allylated products **3** aligns with that predicted by this model.

In the case of allyl carbonates **1f** and **1g**—the ionisation of which should provide the pseudo-*meso* π -allyl complex **F**—the presence of an additional substituent on the other terminus of the π -allyl complex might have been prohibitive to the approaching sterically hindered enamide nucleophile, therefore explaining their inactivity under the optimised reaction conditions (Fig. 2b). As for the prenyl carbonate **1e** and cyclohexenyl carbonate **1h**, it is likely that the steric hindrance caused by the anti-substituent(s) on the corresponding π -allyl complexes may have been the cause of their inertness.

A clear explanation for the discrepancies in *er* observed in the reactions employing dipole precursors is unfortunately elusive at this stage, and further experimental and computational investigation is needed. However, it is possible that the varying stability of the *in situ* generated Pd-stabilised zwitterionic dipoles under

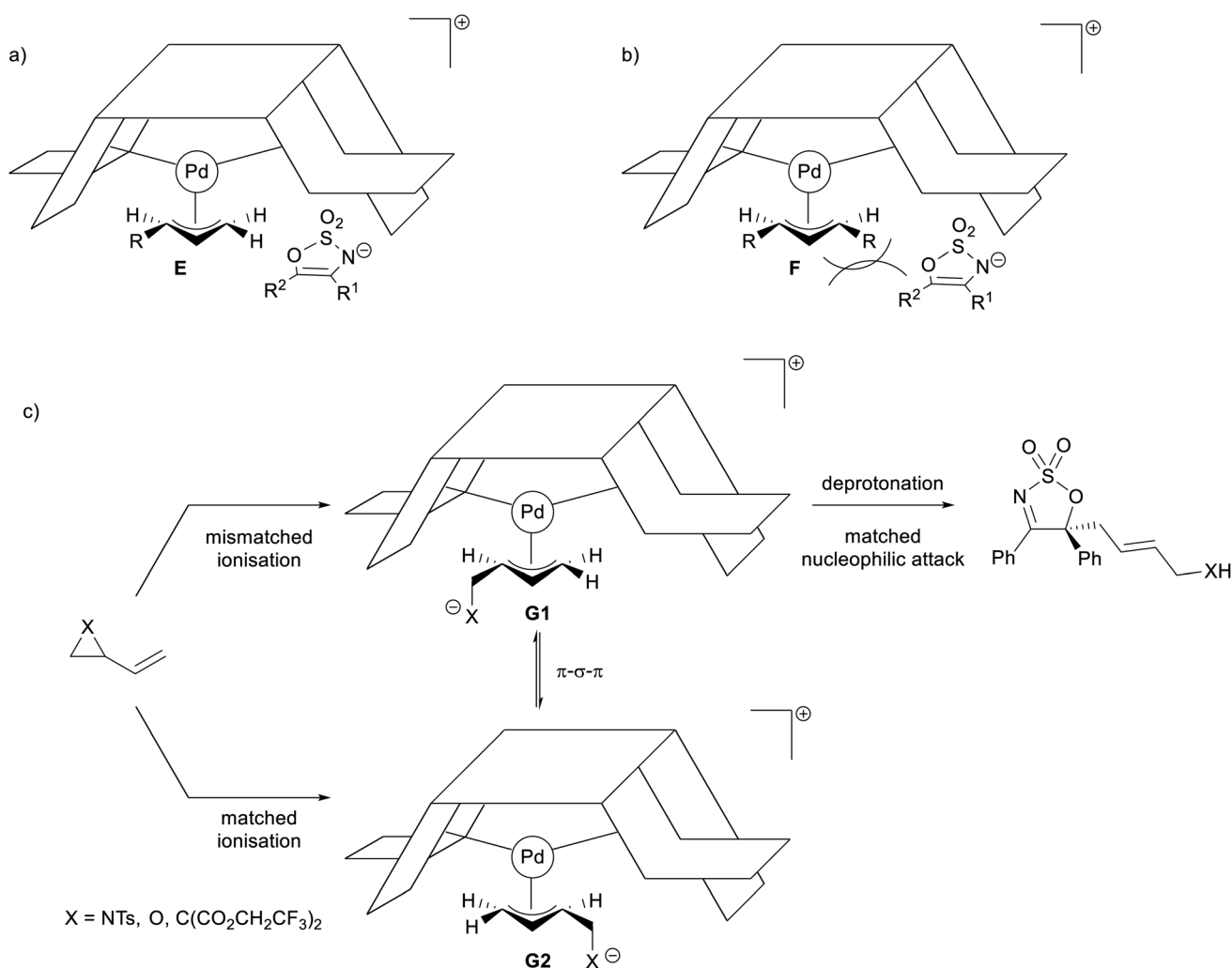


Fig. 2 Rationalising the stereochemical outcomes observed for the various allyl substrates.



the reaction conditions may influence the rate of interconversion between the two diastereomeric π -allyl complexes **G1** and **G2** (Fig. 2c), with the equilibration rate in the VCP case being more rapid compared to the rate of nucleophilic attack, and therefore furnishing the allylated product in higher er.

Conclusions

In conclusion, the Pd-AAA reactions of 4,5-disubstituted cyclic sulfamidate imines have been successfully developed, which is the first example where enamide anions are utilised in a metal-catalysed reaction. The protocol was found to tolerate a wide range of imines, allyl carbonates, as well as several related vinylic substrates. Under optimised reaction conditions, *C*-allylated products were exclusively produced in generally high enantiomeric ratios and good yields. Reactions with *in situ* generated 1,3-dipoles gave exclusively linear products. The allylation reactions can be readily performed efficiently on a 2.5 mmol scale with 5 mol% Pd catalyst without appreciable loss in chemical yield or enantiomeric purity. The allylated products can serve as precursors to chiral 1,2-amino alcohols through reduction reactions, which are useful synthetic building blocks that can be utilised in the preparation of more complex scaffolds containing N- and O-heteroatoms. Other methods are available to prepare trisubstituted β -amino alcohol derivatives similar to **8aa**. For example *via* the addition of aryl or alkyl organometallics to chiral *N,N*-protected α -amino ketones⁵⁸ or the aminolysis of trisubstituted epoxides.⁵⁹ However, the former method is expected to result in racemic products when α -aryl- α -amino ketones are used and the latter method expected to suffer from regiochemical issues when 2-alkyl-2,3-diaryl-epoxides are employed. The new methodology reported here avoids these problems in an enantioselective and efficient manner, and is readily amenable to the synthesis of the enantiomeric series of compounds by using the enantiomeric Trost catalyst. Compound **8aa** also comprises a tetrasubstituted carbinol stereocentre – other methods for preparing such alcohols are of recent interest, especially using kinetic resolution.^{60,61}

Data availability statement

Data for all compounds in this manuscript are available in the ESI,[†] which includes experimental details, characterisation and copies of ¹H and ¹³C NMR spectra. Crystallographic data for compounds has been deposited at the CCDC under CCDC 2087721–2087725.

Author contributions

CH and SP were involved with conceptualisation of the project, supervision, funding acquisition and writing – reviewing and editing. HP carried out the investigation, formal analysis of 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. CR collected the X-ray structures and was involved in writing – reviewing and editing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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