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Diastereoselective Palladium-Catalyzed (3 + 2)-Cycloadditions from Cyclic Imines and Vinyl Aziridines

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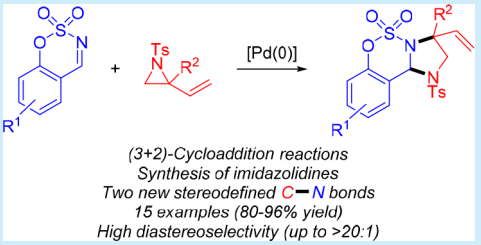
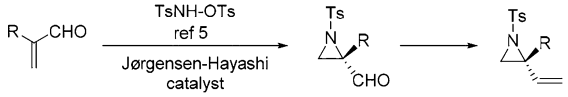
Supporting Information

ABSTRACT: The synthesis of cyclic imidazolidines via two N−C bond-forming sequences has been developed. The transformation goes through a (3 + 2)-cycloaddition reaction in the presence of catalytic amounts of palladium by combining several vinyl aziridines and cyclic *N*-sulfonyl imines. Interestingly, the use of LiCl as additive allowed the improvement of diastereoselectivities when less encumbered substrates were used. The imidazolidine derivatives that bear aminal cores are isolated in high yields (15 examples, up to 96% yield) and diastereoselectivities (up to >20:1).



Following the seminal work of Oshima et al. on palladium-catalyzed rearrangement of vinyl aziridines,[1] their reactivity as precursors of zwitterionic π-allyl palladium intermediates in (3 + 2)-cycloadditions has emerged as a powerful cycloaddition strategy, as illustrated early on by Alper using isocyanates, carbodiimides, and isothiocyanates.[2−4] Thanks to straighforward access to racemic (or enantioenriched) vinyl aziridines in two steps from α-branched enals using an organocatalyzed aziridination, followed by a Wittig reaction (Scheme 1),[5] we became interested in the use of vinyl aziridines in Pd-catalyzed (3 + 2)-cycloadditions with cyclic *N*-sulfonyl imines.

Scheme 1. Targeted Chiral Vinyl Aziridines from α-Substituted α,β-Unsaturated Enals

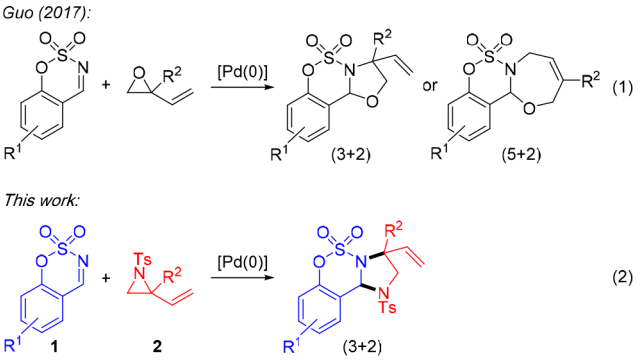


A recent paper by Guo[4f] describing the reactivity of cyclic *N*-sulfonyl imines with vinyl oxiranes (Scheme 2, eq 1) prompted us to disclose our work using vinyl aziridines. We report herein a straightforward way to access cyclic aminal cores through the synthesis of several imidazolidines by combining cyclic *N*-sulfonyl imines **1** and vinyl aziridines **2** in the presence of a Pd catalyst (Scheme 2, eq 2).

Although intrinsically unstable, aminals (*N*,*N*-acetals) can be stabilized by the presence of electron-withdrawing groups and/or when embedded in a ring. Indeed, the aminal moiety is prevalent and can be found in a wide range of natural products, drugs, and ligands (Figure 1).[6]

Starting from racemic vinyl aziridine **2a** (R^2 = Bn) and cyclic *N*-sulfonyl imine **1a**, the reaction was first investigated in the presence of $Pd(Ph_3P)_4$ in THF. Gratifyingly, at room temperature, the expected imidazolidine **3aa** was obtained in 92% yield and 14:1 diastereoselectivity (Scheme 3). The stereochemistry of the major diastereomer could be ascertained by X-ray analysis showing a *cis* relationship between the proton at the aminal position and the benzyl group (Scheme 3).

Scheme 2. Vinyl Oxiranes and Aziridines on Pd-Catalyzed (3 + 2)-Cycloaddition Reactions with Cyclic *N*-Sulfonyl Imines



The scope of the reaction has then been surveyed using variously substituted cyclic *N*-sulfonyl imines **1a−d** and vinyl aziridines **2a−d**. The results obtained in these reactions are summarized in Scheme 4. Starting from vinyl aziridine **2a**, several *ortho*-, *meta*-, and *para*-substituted cyclic *N*-sulfonyl imines **1b−d** were first tested. In all cases, the imidazolides **3aa−d** were obtained in very good yields (89−92%) and diastereoselectivities (from 11:1 to 14:1). Notably, the use of sterically more demanding substrates **2b** (R^2 = *i*Pr) was not deleterious to the reaction outcome as imidazolidines **3ba−d**

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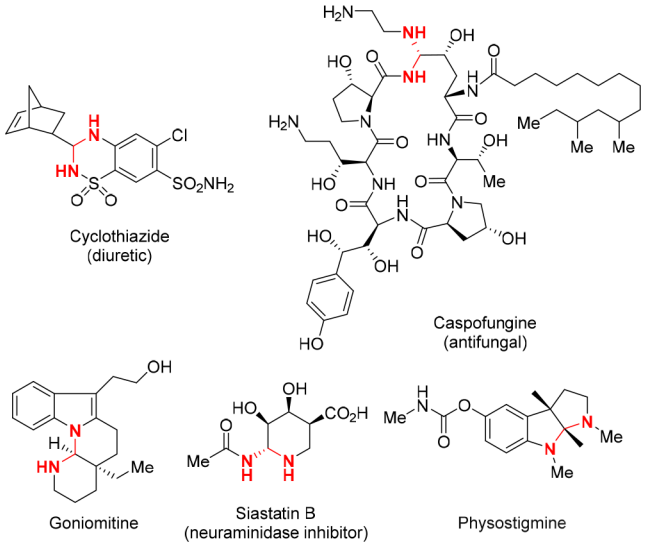
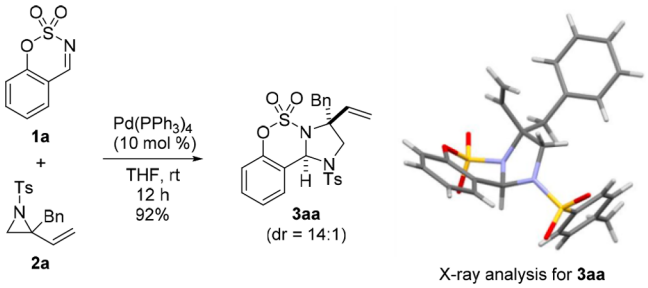


Figure 1. Selected examples of natural and biologically relevant compounds bearing aminal moieties.

Scheme 3. First Trial toward Imidazolidine 3aa via (3 + 2)-Cycloaddition Reaction between 1a and 2a



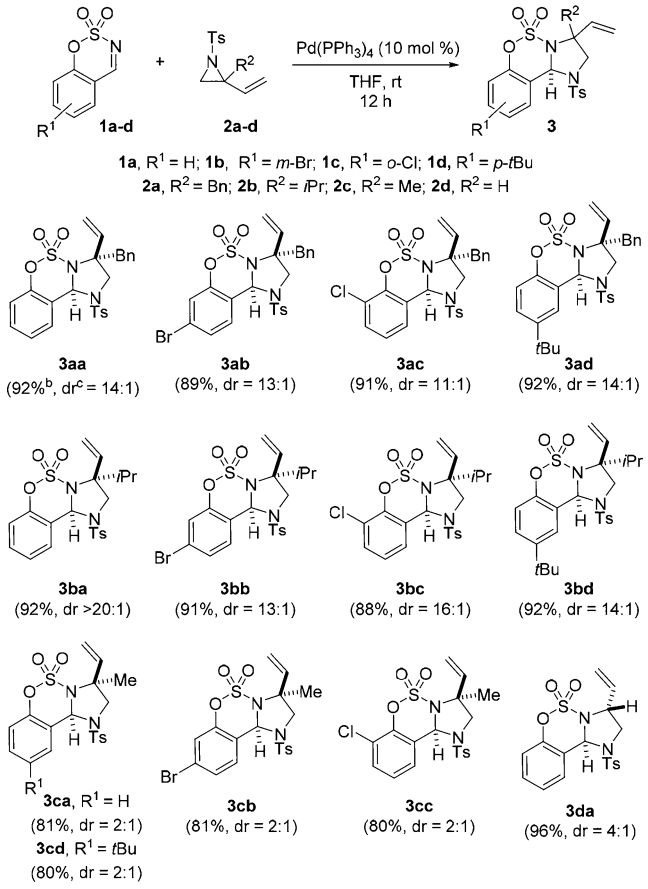
were isolated in good yields (88−92%) and diastereoselectivities (from 13:1 to >20:1). Therefore, the creation of a particularly hindered tetra-substituted carbon in the α-position of the nitrogen from the cyclic *N*-sulfonyl imine group was successfully accomplished. Limitations were, however, observed with vinyl aziridines **2c** (R^2 = Me) and **2d** (R^2 = H) for which a lower diastereoselectivity was observed (i.e., 2:1 for compounds **3ca−d** and 4:1 for compound **3da**), whereas similar good isolated yields were attained. This result prompted us to reinvestigate the reaction conditions.

The diastereoselectivity issue (see mechanistic discussion below) appears to be governed by the attack of the transient amide anion to the less hindered face of the π-allyl palladium as illustrated in the *cis* benzylic H−R^2 group relationship observed in Scheme 3 (X-ray structure of **3aa**) .

Anticipating that a rapid $\pi-\sigma-\pi$ interconversion of the π-allyl palladium intermediate could improve the diastereoselectivity,[7] the reaction between **1a** and **2c** was carried out in the presence of 2 equiv of LiCl (Table 1, entry 2). By doing so, we were able to improve the diastereomeric ratio to 5:1 maintaining a similar yield of 81%. Gratifyingly, when the temperature was decreased to −30 °C, imidazolide **3ca** was obtained with high diastereoselectivity (>20:1) and 85% yield (Table 1, entry 4).[8]

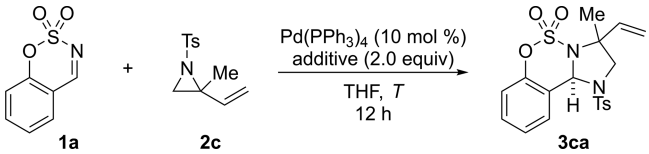
Thus, the reactivity of the vinyl aziridine **2c**, (i.e., reluctant substrate concerning diastereoselectivity issues) was reinvestigated in the presence of LiCl (Scheme 5). Pleasingly, now

Scheme 4. Scope of the (3 + 2)-Cycloaddition Reaction[a]



[a]Reaction conditions: **1** (0.16 mmol), **2** (0.13 mmol), $Pd(PPh_3)_4$ (10 mol %), THF (1.5 mL) at rt for 12 h. [b]Isolated yields of the mixture of diastereomers. [c]Diastereomeric ratios (dr) were determined on the basis of ^{1}H NMR analysis of crude reaction mixture.

Table 1. Optimization of Reaction Conditions for Less Encumbered Substrates[a]



entry	additive	T (°C)	dr[b]	yield[c] (%)
1		rt	2:1	81
2	LiCl	rt	5:1	81
3	LiCl	0	8:1	83
4	LiCl	−30	>20:1	85
5		−30	2:1	82

[a]Reaction conditions: **1a** (0.16 mmol), **2c** (0.13 mmol), $Pd(PPh_3)_4$ (10 mol %), LiCl (2.0 equiv), THF (1.5 mL) at T for 12 h. [b]Determined on the basis of ^{1}H NMR analysis of crude reaction mixture. [c]Isolated yields of the mixture of diastereomers.

imidazolides **3ca−d** were isolated in good yields and excellent diastereoselectivities (from 13:1 to >20:1). The reactivity of monosubstituted vinyl aziridine **2d** was also reconsidered. Imidazolide **3da** was obtained in 88% yield and improved diatereoselectivity (>20:1 vs 4:1 without LiCl) (Scheme 5). Nonetheless, it might be mentioned that no significant

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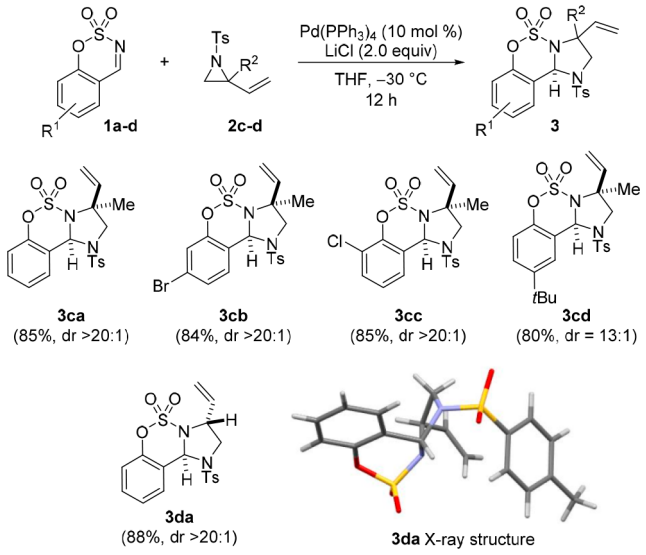
Scheme 5. Influence of LiCl in (3 + 2)-Cycloaddition Reaction between 1a−d and Vinyl Aziridines 2d and 2c

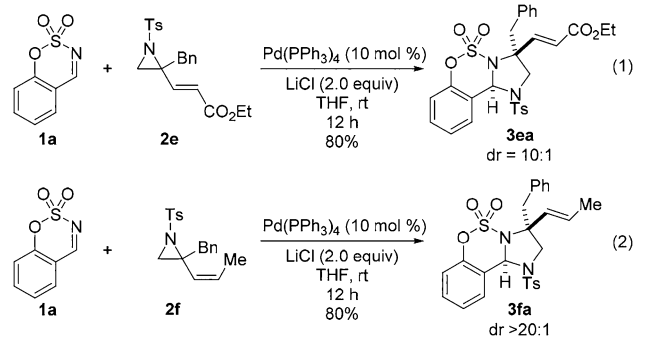


improvement of the diastereomeric outcome was observed in the model reaction **1a** + **2a** (Scheme 3) in the presence of LiCl.

Anticipating that using a vinyl aziridine with less bulky R^2 = H group might have a strong impact on the diastereoselectivity of the reaction, efforts have been undertaken to obtain an X-ray structure of **3da**. Indeed, as illustrated in Scheme 5 (X-ray structure of compound **3da**), the aminal H group and the vinyl moiety have in this case a *cis* relationship. An X-ray structure for **3ba** was also obtained (see Supporting Information), confirming the relative stereochemistry observed for **3aa**. Accordingly, the relative stereochemistry for compounds **3ab−d**, **3bb−d**, and **3ca−d** was tentatively assigned by analogy to **3aa** and **3ba**.

Thanks to the straightforward access to vinyl aziridines (Scheme 6), substituted double bonds can also be easily

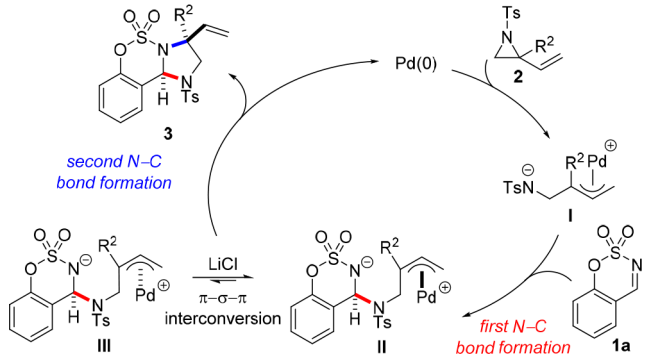
Scheme 6. (3 + 2)-Cycloaddition Reaction with Vinyl-Substituted Aziridines 2e and 2f



obtained using either Wittig or Horner−Wadsworth−Emmons (HWE) reactions. From **2e**, obtained by a HWE reaction with triethyl phosphonoacetate, the imidazolide **3ea** was isolated in 80% yield and a diastereomeric ratio of 10:1 (Scheme 6, eq 1). *Z*-Vinyl aziridine **2f**, prepared via a Wittig reaction with ethyltriphenylphosphonium bromide, gave in the presence of cyclic *N*-sulfonyl imine **1a** the expected imidazolide **3fa** in 80% yield and excellent diastereoselectivity (>20:1) as the single *E* stereoisomer. In these cases, room temperature was required to reach suitable reaction rates. The isomerization of the double bond (**2f** → **3fa**) further confirms a $\pi-\sigma-\pi$ interconversion of the transient π-allyl palladium intermediate (Scheme 6, eq 2).

Mechanistically, the first step of the reaction can be seen as the behavior of the Pd(0) source in the presence of vinyl aziridine **2** to form the zwitterionic π-allyl palladium species **I** (Scheme 7). The anion part of the complex **I** could then react

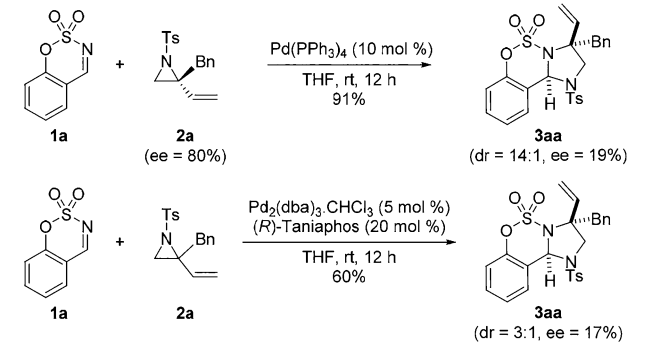
Scheme 7. Proposed Mechanism



with cyclic *N*-sulfonyl imine **1a** to give intermediate **II** that could further intramolecularly react with the π-allyl palladium to give imidazolide **3**. As highlighted by the isomerization of the *Z* double bond in **2f** → **3fa** (see Scheme 6, eq 2), and the need of LiCl to ensure high diastereoselectivities through the release of the amide anion from the positive Pd sphere,[8] one can assume a rapid $\pi-\sigma-\pi$ interconversion of the π-allyl palladium (**II** → **III**). The second N−C bond formation, which affords the tetra-substituted carbon, proceeds in high diastereoselectivities and is dependent on the first N−C bond formation (see intermediate **II**) through an intramolecular allylic amination were the amide anion attacks the π-allyl palladium on its less encumbered face, as previously mentioned.

This assumption was confirmed when enantioenriched **2a** (80% ee) was reacted in the presence of **1a** leading to **3aa** in an almost racemic form (19% ee, Scheme 8). Interestingly, the

Scheme 8. Insights toward an Asymmetric (3 + 2)-Cycloaddition Reaction in the Presence of a Chiral Ligand



rapid $\pi-\sigma-\pi$ interconversion paves the way to the development a dynamic kinetic asymmetric transformation (DYKAT). Indeed, in a preliminary experiment in the presence of a chiral ligand [i.e., (*R*)-Taniaphos], imidazolide **3aa** was obtained in 17% ee (dr = 3:1 and 60% yield).[9]

In conclusion, a Pd-catalyzed (3 + 2)-cycloaddition reaction has been developed affording a straightforward route to several functionalized cyclic imidazolidines in both high yields and

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Org. Lett. XXXX, XXX, XXX−XXX

diastereoselectivities. The cycloaddition takes place via the formation of two N−C bonds in the presence of vinyl aziridines (precursors of N^1-1,3-dipoles in the π-allyl palladium intermediates) and cyclic *N*-sulfonyl imine. Interestingly, the low-to-moderate diastereoselectivities that were first obtained with less sterically encumbered substrates could be improved through the addition of LiCl as additive. The extent to which the last N−C bond formation proceeds in high diastereoselectivities is dependent on the rapid $\pi-\sigma-\pi$ interconversion and could be explained by the ability of Li^+ to facilitate the cyclization step by strongly coordinating to the amide anion. Further studies on the synthesis of novel compounds through imidazolidines derivatization and the development of an asymmetric version are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00228.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 1589055−1589057 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(8) Interestingly, the use of LiBr has been described in (3 + 2)-cycloadditions with vinyl aziridines, however, with the opposite consequence as lower diastereoselectivity was observed; see ref 3a.

(9) These trials were done in the absence of LiCl to check a possible control by the chiral ligand (see ref 3a). The reaction in the presence of the Trost ligand was also tested, but a very low enantioselectivity was observed (ee < 10%).

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