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Stereoselective Synthesis of Fused Vinylcyclopropanes by Intramolecular Tsuji−Trost Cascade Cyclization

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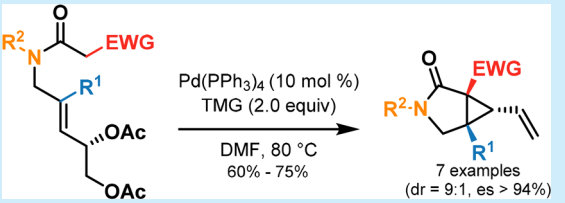
Supporting Information

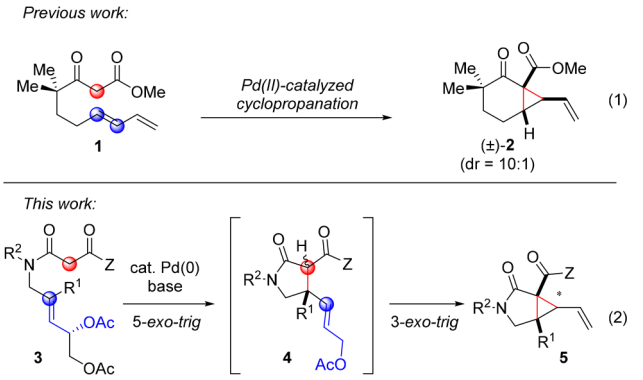
ABSTRACT: A stereoselective intramolecular Tsuji−Trost cascade cyclization of (homo)allylic vicinal diacetates with a pendant β-ketoamide or related carbon nucleophile to give γ-lactam-fused vinylcyclopropanes is reported. In addition to two new rings, the products contain three new C−C stereocenters (two of which are quaternary) with a 9:1 dr. Moreover, the reaction proceeds in >94% enantiospecificity with optically enriched starting materials, using an inexpensive carbohydrate as the source of chirality.



Donor−acceptor (DA) cyclopropanes are widely recognized as highly versatile intermediates in modern synthetic chemistry.[1] DA cyclopropanes with a vinyl group as the donor moiety have garnered specific interest as a result of the wide variety of transformations they can undergo,[2] including vinylcyclopropane−cyclopentene (VC−CP) rearrangement[3] and [3 + 2]-,[4] [3 + 3]-,[5] [4 + 2]-,[6] and intramolecular [5 + 2]-cycloaddition,[7] providing access to a broad range of structurally diverse scaffold structures. However, progress in this area has been limited by a lack of suitable stereoselective methods for the synthesis of DA vinylcyclopropanes, especially those fused to other ring systems and/or containing one or more quaternary stereocenters. The current methods often involve precursors already containing a cyclopropane moiety.[8] Syntheses from linear precursors include ruthenium-catalyzed cyclopropanation of electron-rich alkenes using diazocarbonyls,[9] formal [2 + 1] addition of carbenes to electron-deficient alkenes,[10] and dialkylation of malonates with 1,4-dihalo-2-butenes.[11] Unfortunately, these reactions provide limited control over relative and absolute stereochemistry. Despite recent progress in catalytic asymmetric cyclopropanations with chiral transition metal complexes,[12] their application to highly substituted and/or ring-fused vinylcyclopropanes remains a challenge.

Given our interest in cascade reactions and palladium catalysis,[13] we envisioned the intramolecular double Tsuji−Trost cyclization of (homo)allylic vicinal diacetates **3** bearing a β-dicarbonyl moiety as an efficient entry into fused vinylcyclopropanes. Previously, the Pd-catalyzed allylic alkylation has proven to be a useful strategy in the synthesis of cyclic compounds,[14] e.g. γ-lactones and γ-lactams.[15] Furthermore, a Tsuji−Trost allylation/retro-Claisen/Tsuji−Trost cyclization sequence was recently reported to afford a range of vinylcyclopropanes.[16] In our strategy, the allylic acetate in **3** is activated by the Pd(0) catalyst, resulting in a 5-*exo*-*trig* cyclization in the presence of a base with concomitant migration of the olefin to give **4** (Scheme 1, eq 2). Then,

Scheme 1. Synthesis of Ring-Fused Vinylcyclopropanes



activation of the new allylic acetate moiety by Pd(0) should lead to 3-*exo*-*trig* cyclization, as 5-*endo*-*trig* cyclization is believed to be hampered by the *E*-geometry of the allylpalladium intermediate.[17] The feasibility of this strategy is supported by a report by Lambert et al. demonstrating the cascade cyclization of diene-functionalized β-ketoesters under Pd(II) catalysis (Scheme 1, eq 1).[18]

We decided to investigate this Tsuji−Trost cascade cyclization using **3a** as the benchmark cyclization substrate.

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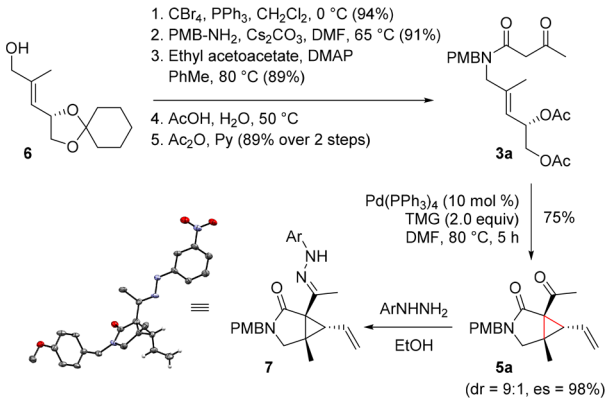
A ketoamide system was selected for ease of synthetic access and variability. Starting from known alcohol **6**[19] (derived from D-mannitol), we synthesized **3a** in five steps (bromination, substitution, amidation, acetal hydrolysis, and acetylation) in 68% overall yield (Scheme 2). To our delight, after

Scheme 2. Precursor Synthesis and Cyclization[a]

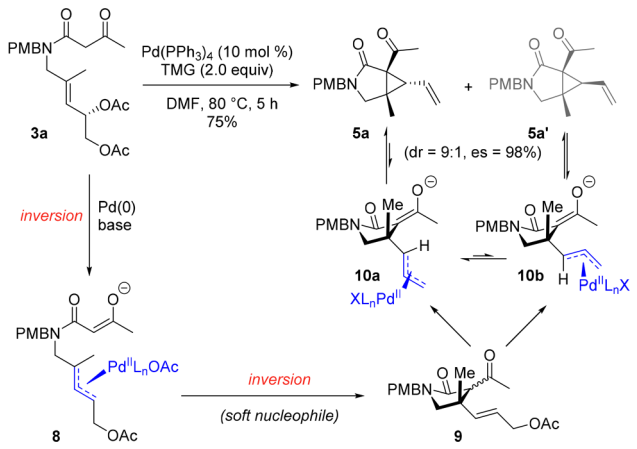


[a]Ar = 3-nitrophenyl; PMB = 4-methoxybenzyl.

optimization of various reaction parameters (for details, see the Supporting Information (SI)), **3a** underwent smooth conversion in the presence of $Pd(PPh_3)_4$ (10 mol %) and *N,N,N′,N′*-tetramethyl-guanidine (TMG, 2.0 equiv) in DMF at 80 °C within 5 h to give **5a** in 75% isolated yield as a 9:1 diastereomeric mixture. Moreover, the product proved to be optically enriched, with an ee nearly identical to the starting material (90% for **5a** vs 92% for **3a**[20]), indicating the reaction proceeds with 98% enantiospecificity. X-ray crystallographic analysis of the *m*-nitrophenylhydrazone derivative **7** unambiguously confirmed the absolute and relative stereochemistry.

The observed stereochemical outcome can be rationalized based on the mechanism (Scheme 3). Initial displacement of

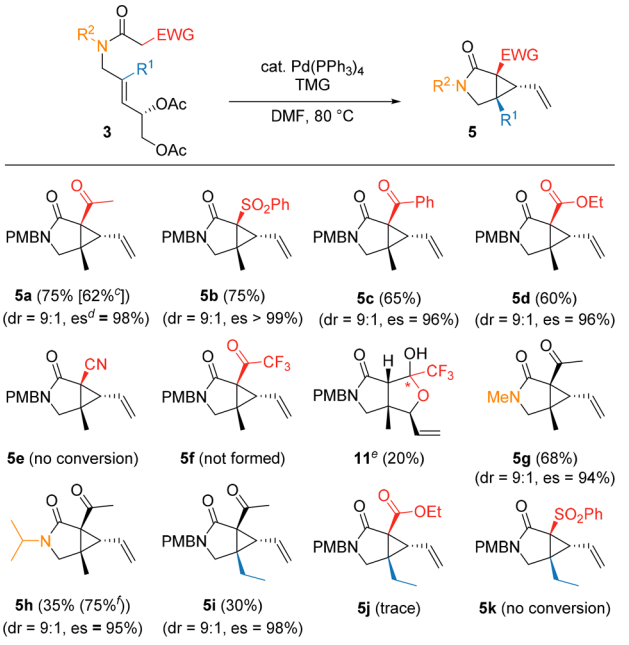
Scheme 3. Rationalization of Observed Stereochemistry



the allylic acetate by oxidative addition of Pd(0) proceeds with inversion of the stereochemistry.[21] Next, the resulting chiral π-allyl-Pd complex is trapped by the deprotonated β-dicarbonyl moiety (a relatively soft nucleophile), closing γ-lactam intermediate **9** (again with inversion), resulting in net retention of the stereochemistry with regard to **3a**.[21] The second oxidative addition of Pd(0) to the newly formed allylic acetate in **9** likely forms a mixture of diastereomeric π-allyl-Pd complexes **10a** and **10b**, with no apparent steric or electronic preference for either. Tsuji–Trost cyclization then produces **5a** and **5a′** in a 9:1 ratio. In an attempt to rationalize this rather remarkable diastereoselectivity, the isolated diastereomers **5a** and **5a′** were separately subjected to the cascade cyclization conditions resulting in both cases in the re-establishment of a 9:1 mixture of **5a** and **5a′**. This result suggests a thermodynamic equilibrium of **5a** and **5a′** via a retro-Tsuji–Trost/Tsuji–Trost sequence. Interestingly, during optimization (see the SI) we observed that the use of DPEPhos as the Pd ligand [$Pd(OAc)_2$ (10 mol %), DPEPhos (25 mol %)] provides **5a** and **5a′** in a 3:7 ratio, plausibly representing the kinetic product mixture. This observation suggests that the interconversion of **10a** and **10b** and/or the retro-Tsuji–Trost does not occur under these conditions. Indeed, when the isolated diastereomers **5a** and **5a′** were resubjected to these reaction conditions using DPEPhos, no such interconversion was observed.

With the mechanistic model in hand, we explored the scope of the cyclization cascade (Scheme 4). We first examined the

Scheme 4. Scope of the Tsuji–Trost Cascade Cyclization[a,b]



[a]Standard conditions: **3** (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), TMG (2.0 equiv) in DMF (0.2 M), 80 °C, 5 h. [b]Isolated yields. [c]1.0 mmol scale. [d]es (enantiospecificity) = ee (**5**)/ee (**3**). [e]Using DBU (2.0 equiv) as a base in PhMe (0.2 M). [f]Yield based on recovered starting material.

effect of electron-withdrawing groups (EWGs) α to the amide. We hypothesized that increased electron-withdrawing capacity (and thus increased acidity) would facilitate ring closure by increasing the concentration of the enolate nucleophile. Although most of the tested substrates (other ketones, sulfone, ester) underwent conversion to the desired fused vinylcyclopropanes **5**, we did not observe any correlation between the reaction rate and the electron-withdrawing capacity. Gratifyingly, the sulfone derivative **5b** was obtained in the same yield as the benchmark product **5a**. Also the phenyl ketone **3c** and ester **3d** were converted to the corresponding

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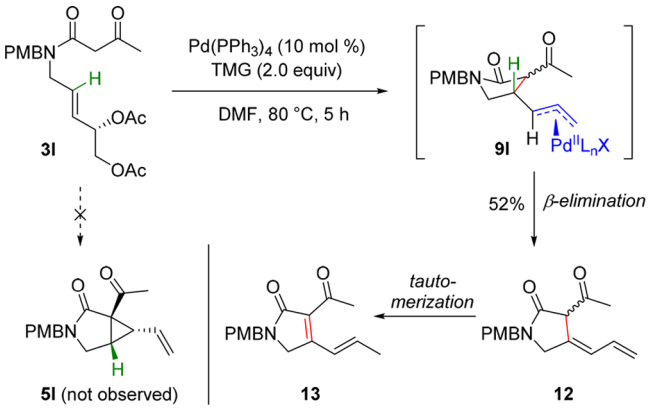
vinylcyclopropanes **5c** and **5d**, respectively, in reasonable yield. Surprisingly, the nitrile analog **3e** did not show any conversion. Furthermore, reaction of the trifluoromethyl ketone **3f** provided bicyclic hemiacetal **11** (resulting from the attack of the enol oxygen on the π-allyl-Pd intermediate) as the sole isolable product rather than the expected vinylcyclopropane **5f**.

Next, we hypothesized that increasing the steric bulk on the amide substituent would promote cyclization by favoring the productive rotamer of the tertiary amide. In contrast to our expectations, the *N*-*i*Pr derivative **3h** showed significantly slower conversion, resulting in a rather modest isolated yield after a 5 h reaction time. However, the yield with respect to conversion was comparable to that for **5a**. On the other hand, *N*-Me derivative **3g** was converted to **5g** with similar efficiency as the *N*-PMB derivative **3a**.

We then investigated the influence of the substituent at the ring junction. Further increasing the steric bulk is challenging considering the dense substitution of the products **5**. Moreover, significant additional allylic strain is imposed on the allylpalladium intermediate **8**. We were pleased to see **3i** (R^1 = Et) was converted to **5i**, albeit more slowly and in lower yield. Unfortunately, in this case the nature of the EWG proved to have more impact on the reaction outcome, as ester **3j** and sulfone **3k** showed little to no conversion to the corresponding fused vinylcyclopropanes **5**.

A different result was observed using cyclization precursor **3l** (R^1 = H, Scheme 5). Rather than the expected fused

Scheme 5. Formation of Dienes by β-H-Elimination[a]

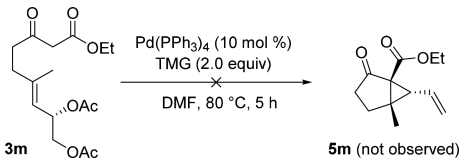


[a]Products **12** and **13** were obtained as a 1:2 inseparable mixture.

vinylcyclopropane **5l**, we obtained a mixture of **12** and **13** in modest yield. Plausibly, after the initial formation of γ-lactam intermediate **9l**, in this case β-H-elimination takes precedence over 3-*exo*-*trig* Tsuji–Trost cyclization, leading to product **12**, which is (partially) tautomerized under the basic reaction conditions to its conjugated isomer **13**.

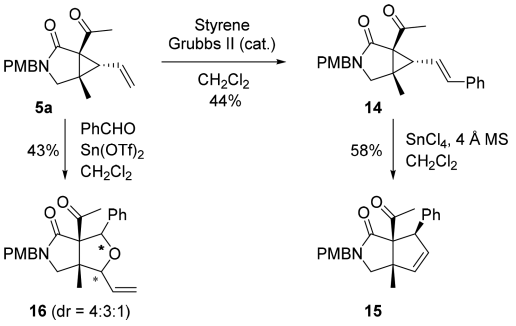
In an attempt to further expand the scope of the reaction, we synthesized ketoester **3m** featuring a methylene spacer (Scheme 6). Unfortunately, **3m** did not undergo the cascade cyclization under the standard conditions. This ketone, which has considerably more conformational freedom than the tertiary amides **3a–l**, apparently does not adopt the turn-like conformation required for the initial cyclization. Likely, additional conformational constraints (e.g., *gem*-dimethyl substitution, cf. ref 18/Scheme 1, eq 1) are required for this class of substrates to react.

Scheme 6. Cyclization Attempt with Ketoester Precursor



In order to verify that our cyclization products display characteristic DA cyclopropane reactivity, we subjected **5a** to typical VC–CP rearrangement conditions. Unfortunately, initial attempts only showed degradation of the starting material. Therefore, **5a** was first converted by cross metathesis to styrylcyclopropane **14** which subsequently underwent $SnCl_4$-mediated rearrangement to give cyclopentene **15** as a single diastereomer in moderate yield (58%, Scheme 7).

Scheme 7. Postmodification of Vinylcyclopropanes



Moreover, the $Sn(OTf)_2$-catalyzed cycloaddition of benzaldehyde and **5a** provided tetrahydrofuran-fused γ-lactam **16** as a partially separable mixture of diastereomers (dr = 4:3:1) in moderate yield (43%).

Finally, we wished to address the control over the absolute stereochemistry. We demonstrated that our Tsuji–Trost cascade reaction proceeds with near-complete retention of optical purity starting from nonracemic substrates derived from carbohydrates. Cyclization precursors **3a–l** were ultimately derived from (*R*)-glyceraldehyde cyclohexylidene acetal (or the corresponding acetonide), which, in turn, were derived from D-mannitol.

Advantageously, the opposite enantiomers are also available from the chiral pool. We accordingly prepared *ent*-**3a** from L-gulonolactone and demonstrated it is indeed converted to *ent*-**5a** under the optimized reaction conditions (Scheme 8; for details, see the SI). However, based on the proposed mechanism (Scheme 3) we realized that there may be an alternative way to control the absolute stereochemistry of the product not depending on the availability of both antipodes of the chiral pool material, i.e. the geometry of the alkene moiety. According to our mechanistic hypothesis, changing the alkene geometry from *E* to *Z* should lead to the formation of a pseudoenantiomeric π-allyl-Pd intermediate, ultimately resulting in the formation of the enantiomeric product. To verify this hypothesis, we synthesized *Z*-configured precursor *Z*-**3a**, starting from the same chiral pool material but employing a Still–Gennari reaction instead of the Wittig olefination in the initial stage of the precursor synthesis. After subjection of *Z*-**3a** to the optimized Tsuji–Trost cyclization conditions, we indeed obtained *ent*-**5a** (Scheme 8), although conversion was

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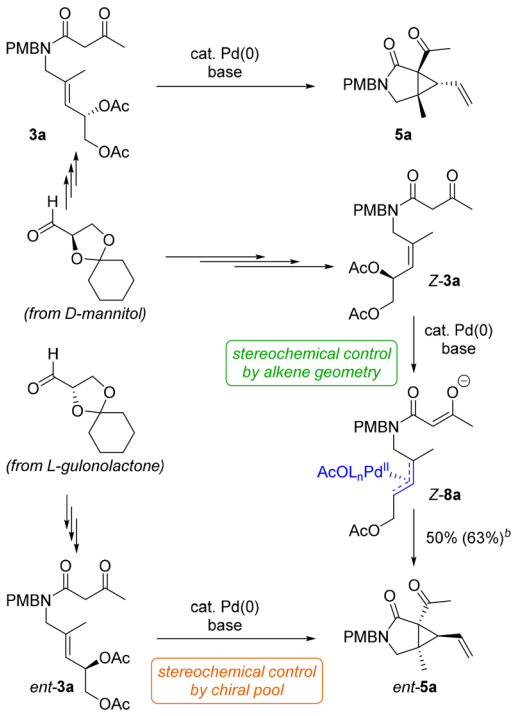
Scheme 8. Absolute Stereochemistry Control[a]



[a]Standard conditions: $Pd(PPh_3)_4$ (10 mol %), TMG (2.0 equiv) in DMF (0.2 M), 80 °C, 5 h. [b]Yield based on recovered starting material.

slower, presumably due to increased allylic strain in the π-allylpalladium intermediate *Z*-**8a**.

In conclusion, we have developed a novel intramolecular Tsuji−Trost cascade cyclization affording γ-lactam-fused vinylcyclopropanes. The reaction proceeds with high diastereoselectivity (~9:1) and a high degree of stereospecificity. The absolute configuration may be controlled either by selection of the appropriate inexpensive carbohydrate starting material or alternatively by the geometry of the alkene moiety in the cyclization precursor. The products of the reaction undergo typical vinylcyclopropane transformations leading to highly functionalized bicyclic scaffolds with full stereocontrol. Studies toward extension of the substrate scope of the reaction and its application in the synthesis of selected natural products are currently ongoing 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.8b02232.

Optimization experiments, experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1856030 contains 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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