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Stereoselective Pd-Catalyzed Decarboxylative Allylation: Assembly of Highly Functionalized Allylic Amines Bearing a Quaternary Center

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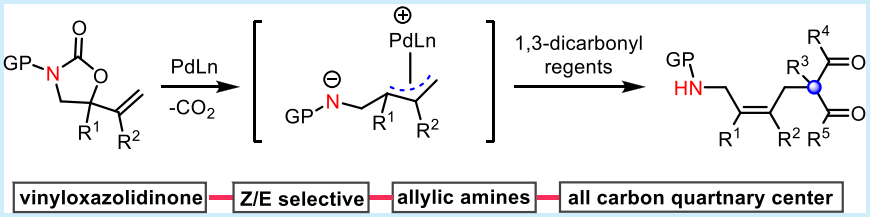
Supporting Information



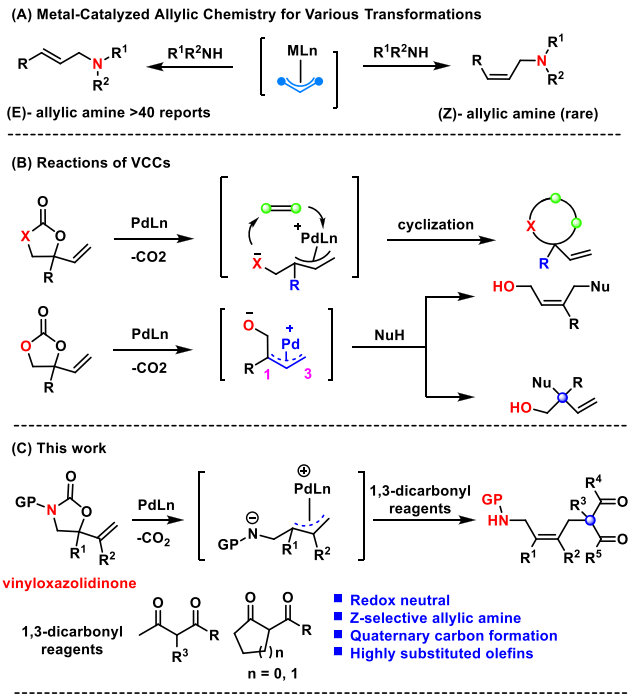
ABSTRACT: Here, we report a practical and reliable methodology to direct construction of tri- and tetrasubstituted olefins bearing an allylic amine, with the concomitant construction of the sterically congested quaternary stereocenter through stereoselective palladium-catalyzed cascade decarboxylation of vinyloxazolidinones.

Highly substituted olefins play a vital role in bioscience, medicine, and chemistry. Stereodefined olefins are important resources in both laboratories and industries.[1−5] Allylic amines, which belong to a class of functional amines, are the basic structural unit in many natural products and pharmaceuticals.[6] However, the syntheses of certain substituted allylic amines with different substituents bearing a quaternary center[7−9] are significantly challenging. In particular, the stereoselective syntheses of highly substituted allylic amines with different substituents remain quite difficult. A convenient synthetic route to these allylic amines involves the direct transformation of the allylic substrates via transition metal catalysis. In this regard, excellent strategies such as classical substitution of allylic compounds,[10] hydroaminations,[11] and metal-catalyzed direct functionalization of the C−H bond (Scheme 1A) have been reported.[12] However, the metal-catalyzed synthesis has limited applications because of the harsh reaction conditions, low yields, undesirable side reactions, and poor stereochemical control.

Vinyl cyclic carbonates (VCCs) are important in modern organic chemistry owing to their multifaceted reactivity and ease of preparation (Scheme 1B).[13] In this context, the palladium-catalyzed cascade decarboxylative transformation, largely developed by Zhang,[14] Kleij,[15] Zhao,[16] and Glorius,[17] is a reliable approach for syntheses of different important allylic manifolds. These reactions involve the release of CO_2 and the formation of a highly reactive Pd-π-allyl intermediate, which can readily undergo nucleophilic addition to form allylic compounds.

Recently, Kleij and co-workers reported an efficient method for the stereocontrolled syntheses of substituted allylic amines by palladium-catalyzed decarboxylation of VCCs, followed by

Scheme 1. Palladium-Catalyzed Cascade Reactions of Cyclic Carbonates



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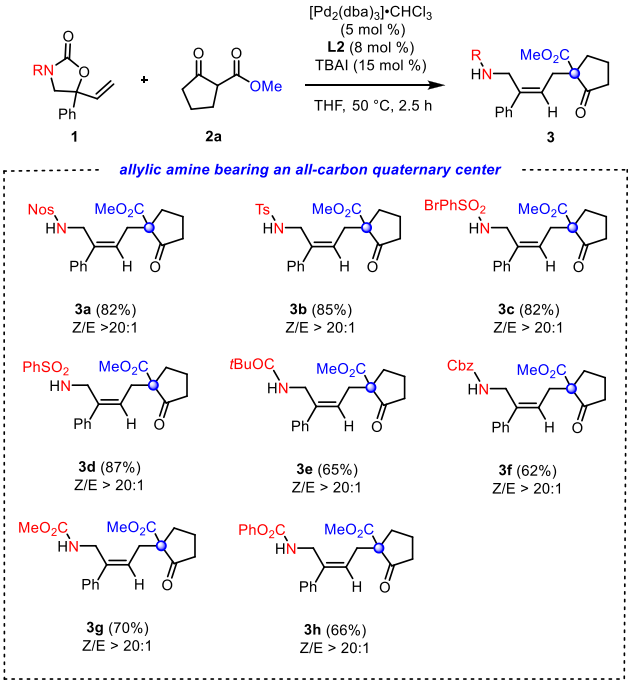
an intermolecular nucleophilic addition of amines.[15d] This is the first example on the stereoselective synthesis of allylic amines based on vinyl cyclic carbonates (Scheme 1B).

Metal catalysts containing halide ligands are ubiquitous because of the stable metal−halide interaction. Recently, the control of halide ligands has been proven to be an important strategy in tuning the reactivity of the transition metal catalysts. Despite the prevalence of this functionality, its widespread application in the development of transition metal catalysts begun only recently.[18] We herein describe an unprecedented stereoselective palladium-catalyzed decarboxylation of vinyloxazolidinones to generate allylic amines (Scheme 1C). This practical and reliable conversion gave good to excellent yields and stereoselectivities, required mild conditions, and had a broad substrate scope and easy accessibility of reagents.

The details related to the optimization of the reaction conditions are provided in the Supporting Information. With the optimized reaction conditions in hand, we investigated various protecting groups for vinyloxazolidinones (Scheme 2)

Scheme 2. Scope of Protecting Groups in Vinyloxazolidinones[a]

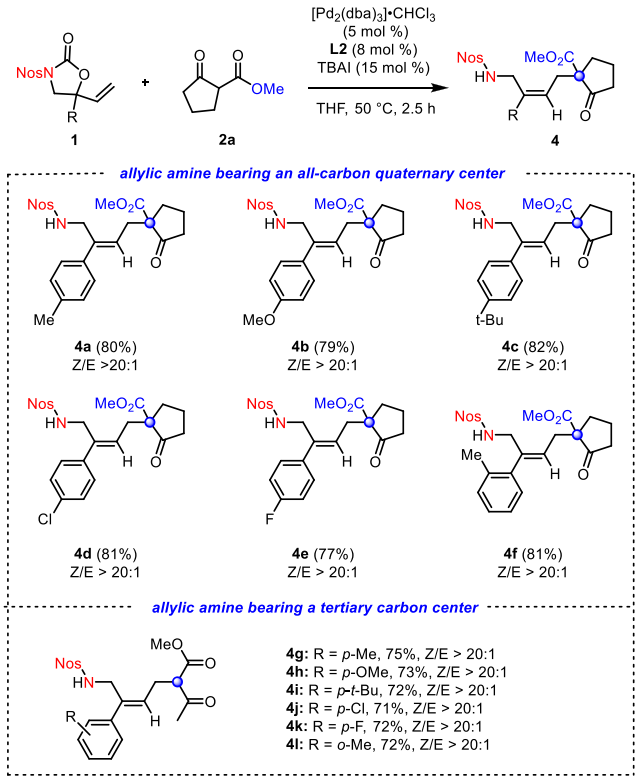


[a]Reaction conditions: A (0.04 mmol), Pd catalyst (5 mol %), **L2** (8 mol %), TBAI (15 mol %) in THF stirred at 50 °C for 2.5 h.

in their palladium-catalyzed decarboxylation to allylic amines. The highly activated sulfonyl group-protected derivatives (**3a**−**d**) gave good stereoselectivities and yields of desired allylic amines. Substrates with other general protecting groups on the nitrogen atom (**3e**−**i**) were also tolerated under the optimized reaction conditions and gave good yields of allylic amines bearing a quaternary center.

The palladium-catalyzed decarboxylative addition of oxazolidinones bearing various substituents was also explored in the presence of ketoesters (Scheme 3). The transformation had good functional group tolerance with both electron-withdrawing (**4d**−**e**) and electron-donating (**4a**−**c**) substituents of the aryl rings, giving the desired allylic amines in good yields and high stereoselectivities. Additionally, a meta substituted

Scheme 3. Scope of Carbonate Partners[a]



[a]Reaction conditions: A (0.04 mmol), Pd catalyst (5 mol %), **L2** (8 mol %), TBAI (15 mol %) in THF stirred at 50 °C for 2.5 h.

substrate (**4f**) on the aromatic rings shows good compatibility. After verifying the general scope of vinyloxazolidinones with **2a**, we proceeded to investigate its feasibility for the formation of allylic amines bearing a tertiary center via the Pd-catalyzed transformation. Interestingly, the same substitution patterns of vinyloxazolidinones were also allowed, affording the desired derivative (**4g**−**l**). Apart from simple aryl groups in the vinyloxazolidinones, more important synthetic functional groups can easily produced into the desired compounds, including 1,3-dicarbonyl reagents.

Furthermore, the range of highly substituted olefins containing allyllic amine was investigated in detail through optimized reaction conditions (Scheme 4). Different functionalized 1,3-dicarbonyl reagents were systematically varied, and a series of highly substituted allylic amines with a tertiary center (**5a**−**c**) or a quaternary center (**3a**, **5d**−**i**) were obtained. In most of the cases, the desired allylic amines were introduced with good yields and selectivities (>20:1).

The stereoselectivities and yields were good with the various esters tested. The use of diketones instead of ketoesters also led to the desired substituted olefins with good stereoselectivities and yields. Furthermore, the steric effect in the methodology was tested. As revealed by the product scope, the presence of hydrogen and the use of methyl or ethyl group (**5h**−**i**) functionalized ketoesters resulted in good reactivity and gave excellent product yields. More complex substrates with fused bulky blocks, such as cyclopentanone 1,3-dicarbonyl reagents and cyclohexenone 1,3-dicarbonyl reagents (**3a**, **5d**−**g**), also showed the same compatibility, giving the desired allylic amines with good yields and stereoselectivities.

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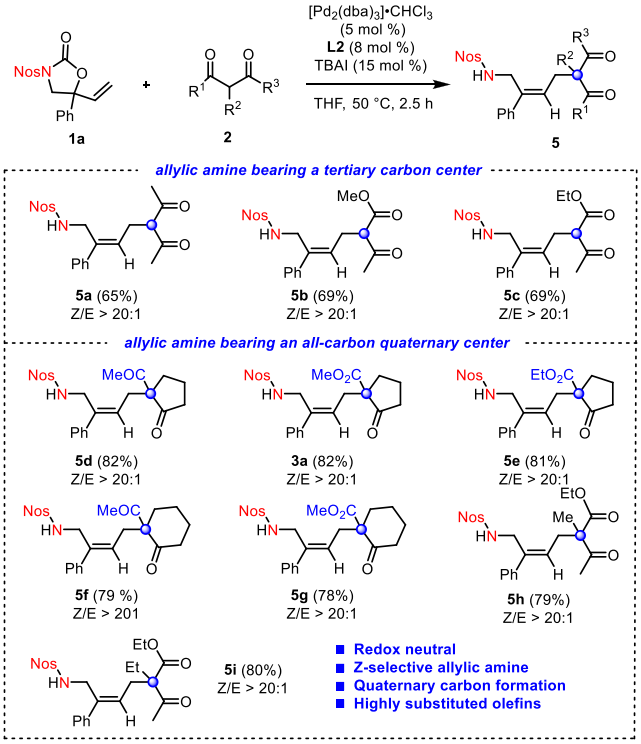
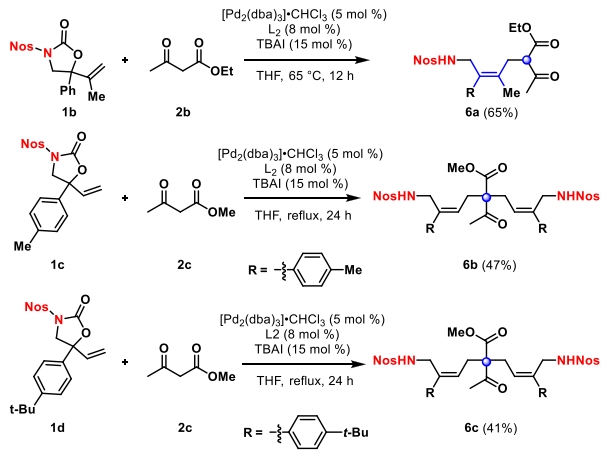
Scheme 4. Scope on the 1,3-Dicarbonyl Reagent Partners[a]



[a]Reaction conditions: A (0.04 mmol), Pd catalyst (5 mol %), **L2** (8 mol %), TBAI (15 mol %) in THF stirred at 50 °C for 2.5 h.

In order to prove the practicability of this methodology, different experiments were conducted based on this Pd-catalyzed decarboxylation transformation (Scheme 5). Com-

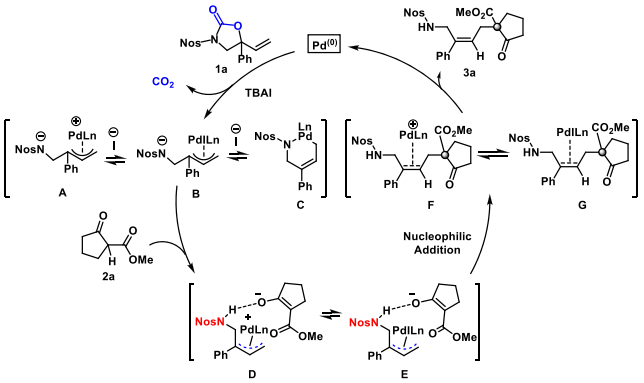
Scheme 5. Stereoselective Synthesis of Tetrasubstituted Olefin Derivatives and Diallylated Compounds



parable yields of tetrasubstituted olefins with an allylic amine group (**6a**) were also observed. The diallylated reactions were also investigated to verify this transformation could maintain the reactivity. It was necessary to increase the temperature and prolong the reaction time for the formation of the tetrasubstituted olefin derivatives (**6a**) and diallylated compounds synthesis (**6b** and **6c**).

We proposed a mechanism for the stereoselective Pd-catalyzed decarboxylative allylation in Scheme 6. The allyl-Pd species **A** and **B** and palladacyclic intermediate **C** are initially

Scheme 6. Proposed Mechanism



formed via the Pd-catalyzed oxidative addition of vinyl-oxazolidinone followed by decarboxylation. It is well-known that halide ions have the ability to affect metal catalytic processes, including the formation of the Pd-catalyzed π-allyl intermediate.[19] Comparison with the calculation and analysis provides useful insight into the origin of stereocontrol of vinyl cyclocarbonate as substrates. In addition, it has been proven that (Z)-palladacyclic intermediate **C**[15h,i] is an important intermediate which exhibits the basic functions of activation of different pronucleophiles. The palladacyclic intermediate **C** could transform itself to afford intermediate **D** or **E** via proton transfer upon reaction with 2-methylacetoacetate **2a**. Nucleophilic addition and ligand dissociation led to the desired allylic amines and regenerated the palladium catalyst.

In conclusion, we developed a practical stereoselective Pd-catalyzed decarboxylative allylation to synthesize highly substituted allylic amines bearing a tertiary or quaternary center. The conversion proceeded under mild reaction conditions, had a broad substrate scope and easy availability of reactants, and gave good to excellent selectivities and yields, thus providing an efficient and concise route to synthesize some important highly substituted allylic amines. We are confident that this protocol would allow the synthesis of many important allylic analogues. This Pd-catalyzed process is undoubtedly a supplementary strategy for the synthesis of new allylic manifolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00673.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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