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Digest paper

Transition-metal-catalyzed cyclization reactions using vinyl and ethynyl benzoxazinones as dipole precursors

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ABSTRACT

Vinyl and ethynyl benzoxazinones have recently received increasing attention from organic chemists because they are powerful tools for the construction of structurally diverse *aza*-heterocycles. A number of catalytic cyclization reactions have been developed that used these two reagents and required the presence of a transition-metal catalyst (i.e., palladium, iron, and copper). This review highlights the design and synthesis of these versatile reagents, and their applications as precursors for transition-metal-containing 1,4-dipoles in dipolar cyclizations and related cascade reactions. The general mechanisms and asymmetric inductions are briefly discussed as well.

Contents

Introduction

Nitrogen-containing heterocycles are a class of fundamentally important organic molecules. They are widespread in biologically active natural products, synthetic agrochemicals and pharmaceutical agents as well as many functional materials.[1] For this reason, the development of efficient synthetic methods to prepare these molecules, including new techniques, new reagents and new reactions, is one of the most important goals of organic chemists. In the field of transition-metal catalysis,[2,3] the catalytic formation of transition-metal-containing dipolar intermediates and their subsequent cycloaddition reactions with different acceptors have been established as a powerful strategy for this purpose.[4,5] Beginning in the 1980s, Trost and Tsuji independently developed Pd-catalyzed [3+2] dipolar cycloadditions of 2-(trimethylsilyl)methyl-2-propenyl acetates and vinyl cyclopropanes with electron-deficient alkenes through Pd-containing dipolar intermediates.[6,7] Following these two pioneering works, many other related dipole precursors and dipolar cycloadditions, especially for catalytic asymmetric processes, have been efficiently exploited in recent years.[8–13] For example, a Pd-containing C4-dipole precursor, γ-methylidene-δ-valerolactone, and its [4+n] reactions were thoroughly investigated by Hayashi and Shintani starting in

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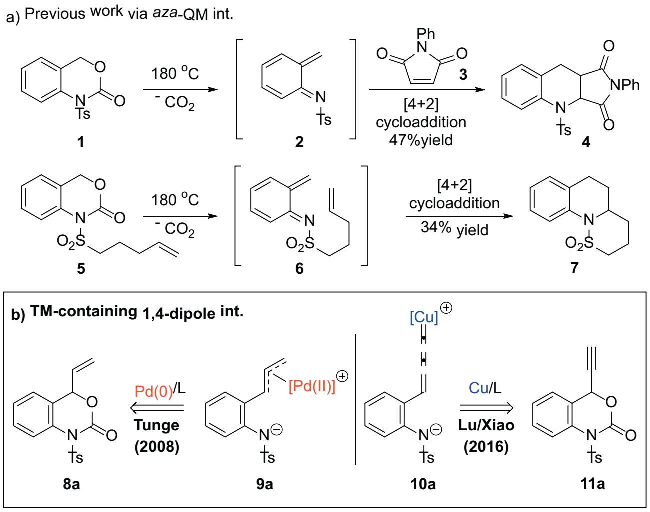
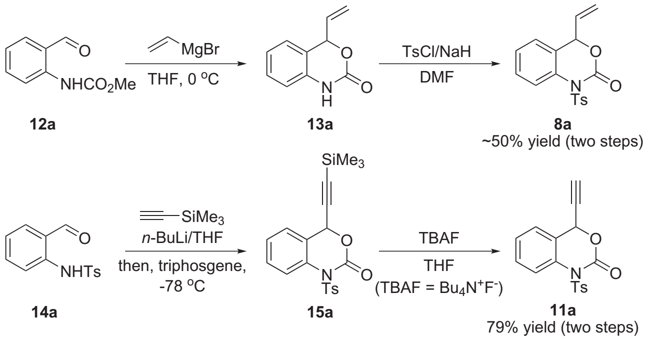
2007.[9,14] Similar to these reagents, a vinyl benzoxazinone was designed and synthesized by Tunge in 2008.[15] This reagent can be used for the *in situ* generation of the π-allyl-Pd zwitterionic intermediate, a formal Pd-containing 1,4-dipole, in the presence of Pd(0) catalysts. In the following ten years, this reactive species was widely used for [4+n] cycloadditions (n = 1–3), which substantially enriched the synthetic methods for preparing nitrogen-containing heterocycles.[15–27] In 2016, Lu and Xiao further developed an ethynyl benzoxazinone reagent that can form Cu-allenylidene species, a formal copper-containing 1,4-dipole, under mild conditions by reacting with Cu catalysts.[28] Then, this reagent was promptly applied to Cu-catalyzed dipolar cyclizations and related cascade processes.[28–34] In this review, we summarize the development of these two reagents and their applications in *aza*-heterocycle synthesis.

Design and synthesis of vinyl and ethynyl benzoxazinones

Benzoxazinone is a useful nitrogen-containing synthon that has been widely used for thermal cycloaddition reactions through a key *aza*-quinone methide (*aza*-QM) intermediate (Scheme 1a).[35,36] Although it is efficient and useful, the limitations of this reagent are obvious and include poor functional group tolerance and difficult asymmetric induction. The application of transition-metal catalysts for generating reactive intermediates and promoting transformations is a powerful strategy for cyclization reactions.[2,3] As shown in Scheme 1b, Pd-containing 1,4-dipolar intermediate **9a**, which bears a nucleophilic sulfonamide anion and an electrophilic π-allyl-Pd component can be formed from the reaction of vinyl benzoxazinone **8a** with a Pd(0) catalyst.[15] In addition, Cu-containing dipolar intermediate **10a**, with both a Cu-allenylidene and a sulfonamide component, can the generated from ethynyl benzoxazinone **11a** in the presence of a Cu catalyst (Scheme 1b).[28] These methods elegantly avoid the high temperature required by traditional thermal decarboxylation processes, which increases the chance for good functional group tolerance and asymmetric transformations with the help of chiral ligands.



Scheme 1. Design of Pd/Cu-containing 1,4-dipoles and their precursors.



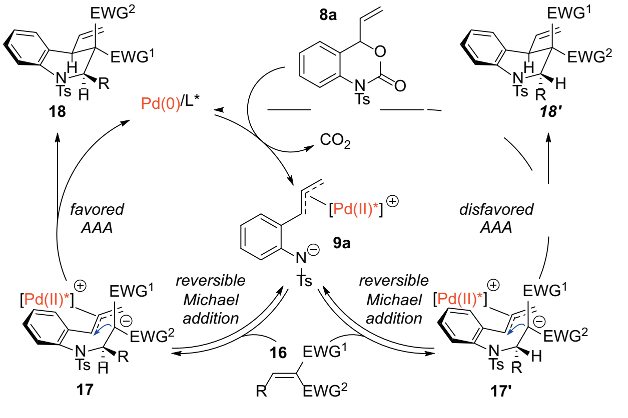
Scheme 2. Synthetic routes to vinyl and ethynyl benzoxazinones.

As shown in Scheme 2, vinyl/ethynyl benzoxazinones **8a** and **11a** can be facilely synthesized from known chemicals, namely protected 2-aminobenzaldehydes **12a** and **14a**, through two-step procedures.[15,17,28,29] *N*-free vinyl benzoxazinone **13a** was prepared from methyl (2-formylphenyl)carbamate **12a** and vinyl magnesium bromide through a Grignard reaction, and the protection of this compound with tosyl chloride gave vinyl benzoxazinone **8a**. To obtain its ethynyl analogue **11a**, *N*-tosyl aminobenzaldehyde **14a** was employed as the starting material, and the ethynyl group was installed with lithiated trimethylsilylacetylene. Then, the reaction was directly quenched with triphosgene to furnish TMS-substituted carbamate intermediate **15a**. Lastly, target compound **11a** was furnished via a desiliconization reaction by TBAF.

Cycloaddition reactions of vinyl benzoxazinones with electrophiles

The general reaction mechanism of vinyl benzoxazinone **8** with electron-deficient alkenes is illustrated in Scheme 3.[15,16] Initially, decarboxylation of vinyl benzoxazinone **8a** in the presence of a Pd(0) catalyst generates Pd-containing 1,4-dipole **9a**, which can be trapped by a range of Michael accepters **16**. Then, thermodynamically favored isomer **17** undergoes an intramolecular asymmetric allylic alkylation (AAA) to furnish the main product, **18**; isomer **17′** can decompose into dipole **9a** and **16** through a reversible Michael addition due to the relative pH values of the tosyl amide and the CH(EWG^1)(EWG^2) (EWG: electron-withdrawing group). Notably, the intermolecular dimerization and intramolecular cyclization of **9a** are two competitive processes that accompany the desired reaction pathway. Additionally, the stereo-control of the multiple stereocenters, especially the chiral quaternary stereocenter, is another formidable challenge.

In 2008, Tunge first reported a Pd-catalyzed, asymmetric decarboxylative [4+2] cycloaddition reaction of vinyl benzoxazinones **8** with benzylidene malononitriles **16-I** (Scheme 4).[15] When Trost's ligand **L1** was employed as the chiral ligand,[37] this reaction was found to proceed well, and enantioenriched tetrahydroquinolines **18-I** were provided in generally high yields with high *enantio-*



Scheme 3. A general mechanism for the cycloaddition of vinyl benzoxazinones with electron-deficient alkenes.