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Palladium-Catalyzed Formal (3 + 2) Cycloaddition Reactions of 2-Nitro-1,3-enynes with Vinylaziridines, -epoxides, and -cyclopropanes

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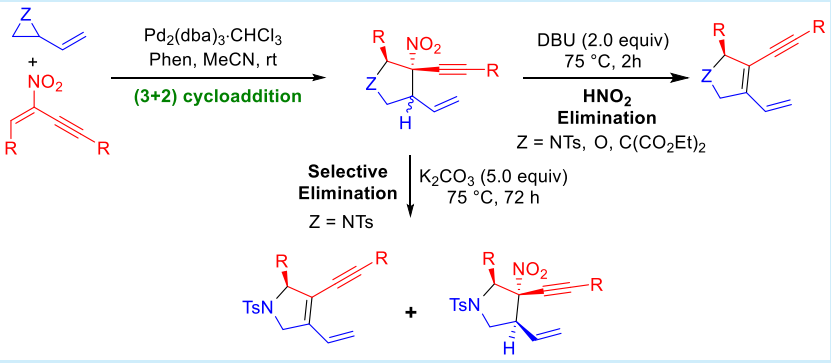

ABSTRACT: A two-step Pd-catalyzed (3 + 2) cycloaddition/HNO_2 elimination reaction sequence has been developed to give novel cyclic 1,3-dien-5-yne systems from Pd-stabilized zwitterionic 1,3-dipoles and 2-nitro-1,3-enyne substrates. The process is highly atom-efficient and tolerates the reaction of 2-vinyloxirane, 1-tosyl-2-vinylaziridine, and diethyl 2-vinylcyclopropane-1,1-dicarboxylate derived 1,3-dipoles with a variety of 2-nitro-1,3-enyne substrates. The stereochemistry of the intermediate (3 + 2) cycloadducts was determined by single crystal X-ray analysis. Furthermore, a selective kinetic elimination of the cycloadduct with an antiperiplanar relationship between the NO_2 group and the participating hydrogen was demonstrated, allowing for efficient isolation of a single diastereoisomer of the cycloadduct.

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The use of palladium-stabilized zwitterionic dipoles in (3 + 2) cycloaddition reactions constitutes a potent methodology for the construction of five-membered ring systems.[1] The three-membered dipole precursors vinylaziridines, vinylepoxides, and vinylcyclopropanes have proven to be very versatile reactants that undergo stepwise formal cycloaddition to activated alkenes,[2−7] activated indoles,[8−17] benzofurans,[17] isocyanates,[18] carbodiimides,[19] or aldehydes[20] to give the corresponding cycloadducts. Despite recent activity using nitro-indoles and nitro-benzofurans in cycloadditions with Pd-stabilized zwitterionic dipoles **A** derived from these three-membered precursors, simple nitroalkenes **2** have yet to be fully explored (Scheme 1a). This is despite the ready availability of these systems and their ability to undergo reductions to amines (**4**).

Stoltz and coworkers reported the use of a Pd-catalyzed (3 + 2) cycloaddition between a *β*-nitrostyrene and a vinylcyclopropane to construct the cyclopentane ring of Melodinus alkaloids.[21] While inconsequential to the target, the key reaction proceeded to give an inseparable mixture of the cycloadducts in low diastereomeric ratio (dr). Liu and coworkers subsequently developed an enantioselective (3 + 2) cycloaddition of vinylcyclopropanes with nitroalkenes.[22] Despite the high enantioselectivity observed, several substrates again displayed low diastereoselectivity. The cycloaddition of 2-vinyl-2-methyloxirane to nitroalkenes has provided heavily substituted tetrahydrofurans with high dr but only moderate enantiomeric excess (ee).[5] It was also found that the methyl substituent on the epoxide was essential for a diastereoselective reaction. To the best of our knowledge, however, there have been no reports of vinylaziridines undergoing (3 + 2) cycloaddition reactions with nitroalkenes.

Related to nitroalkenes, 2-nitro-1,3-enyne substrates **5** are a valuable class of electron-deficient unsaturated reactants that have proven to be excellent Michael acceptors.[23−34] To date,

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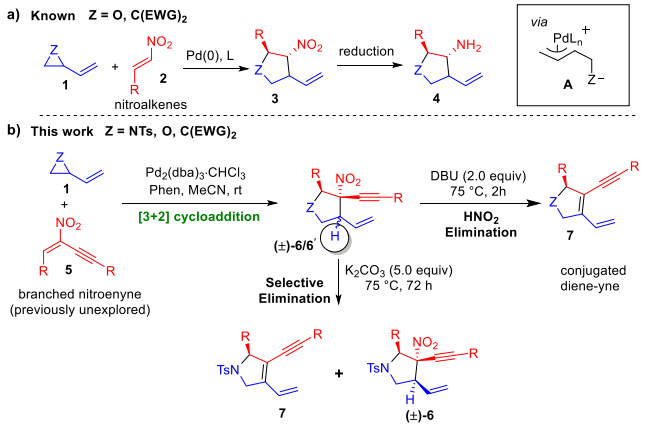
Scheme 1. (a) Known Pd-Catalyzed Cycloadditions to Nitroalkenes and (b) This Work on Pd-Catalyzed Cycloadditions to 2-Nitro-1,3-enyne Substrates Followed by HNO_2 Elimination

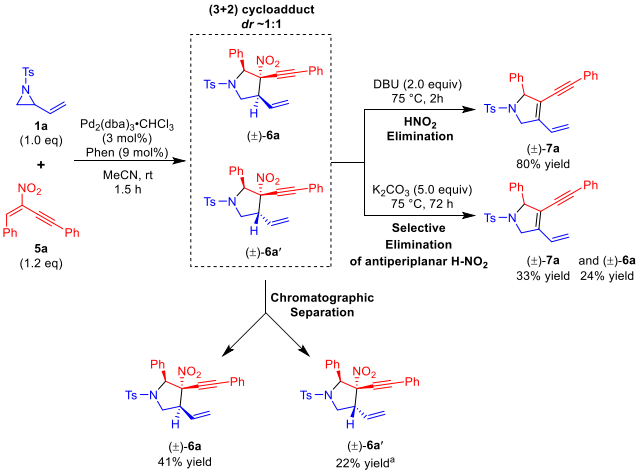


they have not been shown to undergo (3 + 2) cycloaddition reactions with Pd-stabilized zwitterionic dipoles. It was speculated that they could act as partners in Pd-catalyzed (3 + 2) cycloadditions with vinylaziridines, vinylepoxides, and vinylcyclopropanes, given that these processes proceed via an initial Michael-type attack by a Pd-stabilized zwitterionic dipole. One benefit of this approach is that the resulting cycloadduct **6** should be very amenable to elimination of HNO_2 to form conjugated diene-yne **7** by virtue of the additional alkyne substituent vs the nitroalkene cycloadducts **3** (Scheme 1). Interestingly, while HNO_2 eliminations have been explored by ourselves and others in azomethine ylide cycloadditions to nitroaromatics,[35−38] this approach has not been used with the cycloadducts derived from Pd-catalyzed (3 + 2) cycloadditions with vinylaziridines, -epoxides, or -cyclopropanes. In the current case, such an approach negates the issue of diastereoselectivity, which is problematic for some (3 + 2) cycloaddition reactions to nitroalkenes and provides routes to synthetically valuable 1,3-dien-5-yne systems.[39−41] Despite their synthetic potential for the preparation of privileged heterocyclic moieties for medicinal chemistry applications (e.g., isoindolines/isoindoles[42] and isobenzofurans), the synthesis of the requisite 1,3-dien-5-yne precursors is not trivial.

Herein, we report the two-step Pd-catalyzed (3 + 2) cycloaddition/HNO_2 elimination reaction sequence to give novel cyclic 1,3-dien-5-yne systems from Pd-stabilized zwitterionic 1,3-dipoles and 2-nitro-1,3-enyne substrates. The process is highly atom-efficient and tolerates the reactions of 2-vinyloxirane, 1-tosyl-2-vinylaziridine, and diethyl 2-vinylcyclopropane-1,1-dicarboxylate. Furthermore, a selective E2 elimination of one diastereoisomer of the vinylaziridine-derived cycloadduct was demonstrated.

Our starting investigations involved the reaction of 1-tosyl-2-vinylaziridine **1a** (1.0 equiv) with the NO_2-activated enyne **5a** under slightly modified conditions from those previously described by Hyland and coworkers (see Supporting Information).[8] These Pd-catalyzed conditions gave the 3-nitropyrrolidine (3 + 2) cycloadducts as a 1:1 mixture of two diastereomers (**6a**/**6a′**) (Scheme 2). Pleasingly, the two diastereoisomers could be separated by chromatography, and the relative stereochemistry was determined unambiguously by X-ray crystallography (Supporting Information). Furthermore, a one-pot cycloaddition−elimination reaction could be realized

Scheme 2. Overview of (3 + 2) Cycloaddition−Elimination Sequence between Vinylaziridine 1a and Nitroenyne 5a



[a]Cycloadduct **6a′** had a purity of ~93% (33% yield) due to dba ligand contamination. The dba ligand was removed by reduction with $NaBH_4$ followed by chromatography; therefore, the yield is reported over two steps.

by running the cycloaddition reaction, followed by addition of the sterically hindered amine base DBU and heating to give the 1,3-dien-5-yne **7a** in an excellent two-step yield of 80% (Scheme 2).

Replacing the DBU with K_2CO_3 in this one-pot process allowed for a selective elimination of cycloadduct **6a′** to provide diastereomerically pure **6a** and the elimination product **7a**. Presumably, **6a′** underwent more rapid E2 elimination of HNO_2 in the presence of K_2CO_3 due to the favorable antiperiplanar relationship of the relevant hydrogen and nitro groups. With the optimized set of conditions in hand, efforts were directed toward investigating the versatility of the one-pot cycloaddition/HNO_2 elimination reaction (Table 1). Pleasingly, when reacted with 1-tosyl-2-vinylaziridine **1a** (Method A), nitroenynes with either an electron-rich or electron-poor aryl group at R^1 successfully underwent reaction to give the corresponding products **7b** and **7c** in 68% and 83% yields, respectively. The presence of an aromatic thien-2-yl group in the R^1 position and an aliphatic hexyl chain in the R^2 position also gave the desired 1,3-dien-5-yne **7d** in moderate yield. A TBS group in the R^2 position gave the corresponding 1,3-dien-5-yne **7e** in good yield; however, use of the 2-nitro-1,3-enyne substrate **5f** with a terminal alkyne (R^2 = H) in the reaction failed to produce the corresponding 1,3-dien-5-yne (**7f**). Various attempts to synthesize an alkylnitroenyne (i.e., R^1 = alkyl) substrate from the corresponding bromonitroalkene for further reaction scope investigation proved unsuccessful. As far as we know, no examples of any such alkylnitroenynes exist in the literature. Furthermore, Ganesh and Namboothiri[43] reported substrate decomposition when attempting to synthesize a similar alkylnitroenyne (R^1 = isobutyl).

The Pd-catalyzed (3 + 2) cycloaddition/HNO_2 elimination reaction sequence was also successfully performed with vinylepoxide **1b**. Method B (Table 1) was used for these reactions as the epoxide was highly volatile, and utilizing the nitroenyne as the limiting reagent allowed for facile reaction monitoring. As with the vinylaziridine substrate **1a**, reactions with the vinylepoxide **1b** tolerated a phenyl ring or an electron-donating 2-MeO-phenyl ring in the R^1 position, giving the

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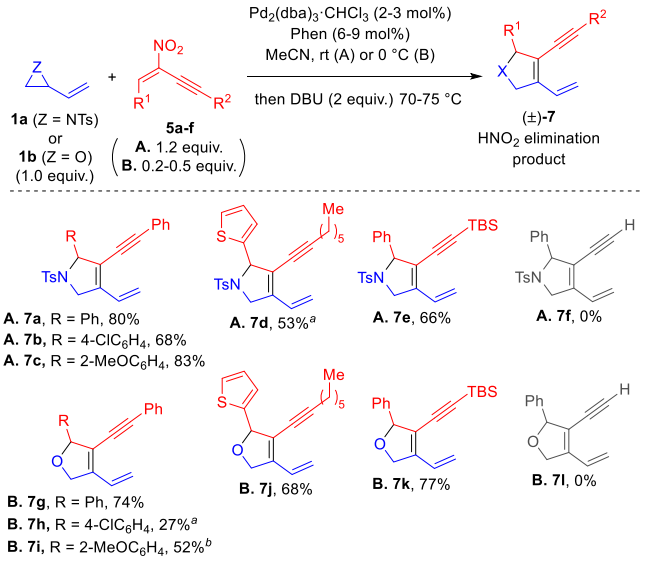
Table 1. Reactions of Nitroenynes with 1-Tosyl-2-vinylaziridine (1a) and 2-Vinyloxirane (1b) Using Method A or B



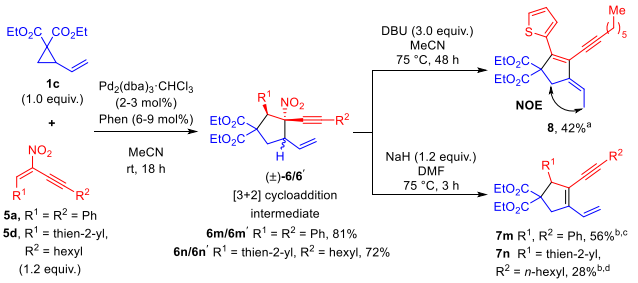
[a]The (3 + 2) cycloaddition intermediate **6**/**6′** was isolated to remove dba ligand; therefore, the yield is reported for two steps. [b]1,3-Dien-5-yne **7i** had a purity of ∼89% (87% yield) due to dba ligand contamination. The dba ligand was removed by reduction with $NaBH_4$; therefore, the yield is reported for two steps.

corresponding 1,3-dien-5-ynes **7g** and **7i** in 74% and 52% yields, respectively. A larger 1 mmol scale reaction to produce **7g** was also carried out and gave the product in comparable yield (76%). However, having a *para*-chloro group on the aryl ring in the R^1 position resulted in a low yield of 1,3-dien-5-yne **7h** due to incomplete cycloaddition. Reaction of the vinyl epoxide **1b** with a nitroenyne bearing a thien-2-yl ring in the R^1 position and a hexyl chain in the R^2 position gave **7j** in 68% yield. The nitroenyne containing a TBS group in the R^2 position of the triple bond (**5e**) reacted smoothly with the vinyl epoxide to give compound **7k** (77%). However, reaction of vinylepoxide **1b** with the terminal nitroenyne **5f** (R^2 = H) did not produce any desired product, paralleling the result for the vinylaziridine substrate **1a**.

While the cycloaddition reaction between the activated vinylcyclopropane substrate **1c** and nitroenynes **5** proceeded efficiently, the DBU-promoted elimination was substantially slower for the less reactive diastereoisomer **6** (requiring days to effect complete elimination). Furthermore, the DBU-promoted HNO_2 elimination conditions resulted in base-catalyzed isomerization of the intended 1,3-dien-5-yne product (**7**) to the conjugated exocyclic alkene (e.g., compound **8**). Therefore, the base-promoted HNO_2 elimination reaction conditions were reoptimized for these carbocyclic analogues. The intermediate (3 + 2) cycloadducts were purified by silica gel column chromatography prior to NaH (1.2 equiv) promoted HNO_2 elimination in DMF at 75 °C for 3 h; this methodology gave compounds **7m** and **7n** in 55% and 28% yields, respectively (Scheme 3).

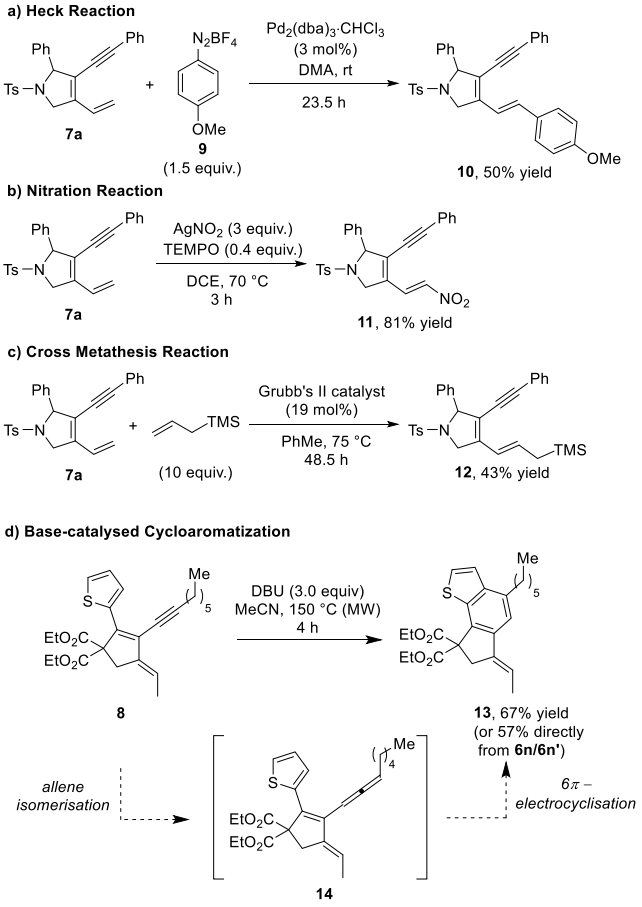
Chemical transformations were also performed with the 1,3-dien-5-yne **7a**, compounds **6n**/**6n′**, and compound **8**, as shown in Scheme 4. Using a literature procedure reported by Werner and Sigman,[44] **7a** was reacted with the diazonium salt **9** under Heck-type conditions to obtain the desired product (*E*)-**10** in

Scheme 3. Reactions of Nitroenynes with Diethyl 2-Vinylcyclopropane-1,1-dicarboxylate (1c)



[a]Reaction was performed sequentially in one pot, yield is reported over two steps. [b]The (3 + 2) cycloaddition intermediate **6**/**6′** was isolated by silica gel chromatography to remove unreacted nitroenyne, catalyst and dba ligand prior to NaH-promoted HNO_2 elimination; therefore, the yield is reported directly from the purified cycloadduct (**6**/**6′**). [c]Unreacted starting material was recovered as a single diastereomer (**6m**) in 36% yield. [d]Reaction was heated for 6 h. Further product (**7n**), isomerized product **8**, and unreacted starting material (single diastereomer, **6n**) were also recovered as a mixture (∼1:2:2 ratio, respectively, 40%).

Scheme 4. Chemical Transformations of Cycloadducts



50% yield (Scheme 4a). A nitration reaction using conditions reported by Maity and coworkers successfully produced product (*E*)-**11** in 81% yield (Scheme 4b).[45] An X-ray crystal structure of (*E*)-**11** was obtained, which unambiguously confirmed the structure (Supporting Information).

A cross-metathesis reaction was also successful between 1,3-dien-5-yne **7a** and allyltrimethylsilane, providing the desired

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product **12** in 43% yield (Scheme 4c). The 1,3-dien-5-yne **8** was found to undergo an interesting base-promoted cycloaromatization reaction when heated in a microwave reactor at 150 °C with DBU,[46] presumably via the allene intermediate **14**, to give the tricyclic benzothiophene compound **13** in 67% yield (Scheme 4d). Compound **13** was also obtained directly from the diastereoisomeric mixture of **6n**/**6n′** in 57% yield under the same basic reaction conditions.

In conclusion, a novel methodology for the synthesis of heterocyclic and carbocyclic 1,3-dien-5-yne systems was developed and investigated. Pd-catalyzed (3 + 2) cycloaddition of vinylaziridine, -epoxide and -cyclopropane-derived 1,3-dipoles with NO_2-activated enynes allows for construction of the target cyclic scaffold in excellent yields. This is the first use of 2-nitro-1,3-enyne substrates as dipolarophiles for (3 + 2) cycloaddition reactions with Pd-stabilized zwitterionic 1,3-dipoles. The resulting cycloadducts undergo facile base-promoted HNO_2 elimination in a one-pot reaction to yield complex cyclic 1,3-dien-5-ynes in a short synthetic sequence. These products were shown to be amenable to further synthetic modifications, as the pendant vinyl and alkyne handles serve as easily manipulated functionalities. Further investigation into cycloaddition reactions of 2-nitro-1,3-enyne substrates, including stereoselective variants, is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01364.

General synthetic information (S2); preparation of precursor materials (S3), synthesis and characterization of all novel compounds (S8); postsynthetic chemical transformations (S17); ^{1}H and ^{13}C NMR spectra of all novel compounds (S20); X-ray crystallography structures and data tables for compounds **6a**, **6a′**, and **11** (S43) (PDF)

FAIR data, including the primary NMR FID files, for compounds **5e**, **5f**, **6a**, **6a′**, **6m**/**6m′**, **6n**/**6n′**, **7a**−**e**, **7g**−**k**, **7m**, **7n**, **8**, and **9**−**13** (ZIP)

Accession Codes

CCDC 2073395−2073397 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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