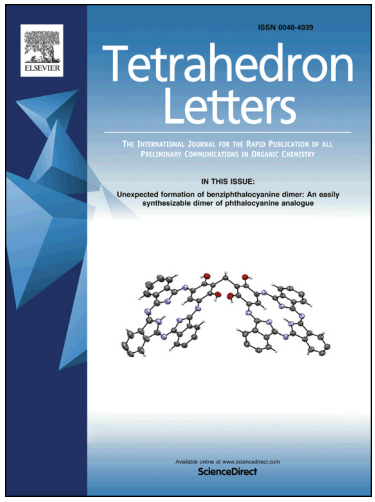

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Graphical Abstract

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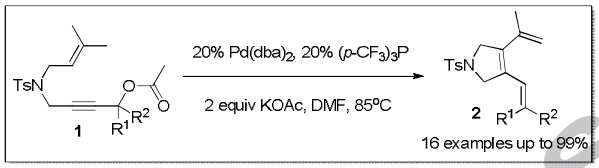

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Palladium-catalyzed cycloisomerisation reaction of 1, 6-enyne acetic esters to form five-membered nitrogenated heterocyclic conjugated trienes

Ting He [a, *], Pin Gao [b, c], Shan Fang [a], Yaling Chi [a] and Yuantao Chen [a, *]

[a] School of Chemistry and Chemical Engineering, Qinghai Normal University, Xining 810008, China
[b] Department of Chemistry, School of Science, Xi'an Jiaotong University, Xi'an 710049, China
[c] MOE Key Laboratory for Nonequilibrium Synthesis and Modulation of Condensed Matter, Xi'an Jiaotong University, Xi'an 710049, China

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ABSTRACT

A palladium-catalyzed cycloisomerisation reaction of 1,6-enyne acetic esters have been developed. This cyclization reaction shows excellent regioselectivity and good functional group tolerance to obtain five-membered nitrogenated heterocyclic conjugated trienes in moderate to excellent yields. The resulting conjugated trienes could be facilely converted to highly substituted benzenes through Diels-Alder reactions.

1. Introduction

Five-membered nitrogenated heterocycles play an important role in organic chemistry, not only as key motifs in many biologically active natural products and pharmaceuticals such as domoic acid, [1] kainic acid [2] and conessine [3] (Figure 1), but also as useful building blocks in synthetic chemistry. [4] During the past several decades, a plenty of methods based on simple acyclic building blocks to synthesize five-membered nitrogenated heterocycles have been developed. Within this synthetic toolbox, transition metal-catalyzed cyclization of enynes represent extremely attractive processes due to their atom-economy, high efficiency and environmental sustainability. [5]

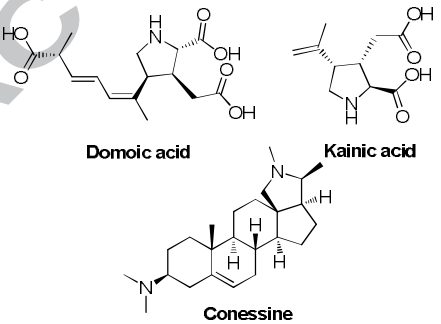


Figure 1. Natural products with five-membered nitrogenated heterocycles motifs.

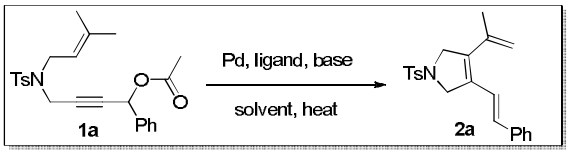
1, 6-enynes, which are well known for their transition metal-catalyzed cycloisomerisation reactions, are a specific class of building blocks to construct cyclic and polycyclic structures. [6] The propargylic structures of 1, 6-enynes could be easily activated by transition-metal and subsequent react with olefin to form carbon-carbon bond. For example, Liang' group has developed a palladium-catalyzed divergent cyclization reactions of 1, 6-enyne carbonates to construct five- or six-membered heterocyclic allenes. [7] Tenaglia and co-works have reported ruthenium-catalyzed 1, 6-enynes cyclization in the presence of terminal alkyne to achieve highly substituted five-membered cyclics with a 1, 5-enyne motif. [8] Tong and co-works have synthesized a series of five- or six-membered heterocyclic compounds bearing sulfonyl group through the cycloaddition reactions of 1, 6-enynes and sulfonyl chlorides by rhodium catalysts. [9] Although many efforts of cycloisomerisation of 1, 6-enynes have been made to synthesize novel cyclic compounds, [10] five-membered nitrogenated heterocycles with a high degree of structural complexity, such as conjugated trienes (useful synthetic building block), have been rarely reported. [11]

Herein, we report a novel and efficient palladium-catalyzed cycloisomerisation of 1, 6-enyne acetic esters to construct five-membered nitrogenated heterocyclic conjugated trienes. To our delight, the resulting conjugated trienes could be converted to highly substituted benzenes by a Diels-Alder process.

∗ Corresponding author.
E-mail: ht15@tju.edu.cn (T. He); ytchen@lzu.edu.cn (Y. Chen).

2. Results and Discussion

Table 1. Optimization of the palladium-catalyzed cyclization of 1, 6-enyne acetic esters **1a** [a]



Entry	Catalyst(mol %)	Base	Ligand (mol %)	Solvent	T(°C)	Yield(%)[d]
1	$Pd(PPh_3)_4$ (10)	KOAc	$(p\text{-}CF_3)_3P$ [b] (10)	DMF	85	16
2	$Pd_2(dba)_3$ (5)	KOAc	$(p\text{-}CF_3)_3P$ (10)	DMF	85	57
3	PdI_2 (5)	KOAc	$(p\text{-}CF_3)_3P$ (10)	DMF	85	61
4	$Pd(dba)_2$ (10)	KOAc	$(p\text{-}CF_3)_3P$ (10)	DMF	85	70
5	$Pd(dba)_2$ (10)	NaOAc	$(p\text{-}CF_3)_3P$ (10)	DMF	85	55
6	$Pd(dba)_2$ (10)	Na_2CO_3	$(p\text{-}CF_3)_3P$ (10)	DMF	85	48
7	$Pd(dba)_2$ (10)	KOH	$(p\text{-}CF_3)_3P$ (10)	DMF	85	—[e]
8	$Pd(dba)_2$ (10)	KOAc	$(3.5\text{-}CF_3)_3P$ [c] (10)	DMF	85	39
9	$Pd(dba)_2$ (10)	KOAc	$(p\text{-}CF_3)_3P$(10)	DMSO	85	60
10	$Pd(dba)_2$ (10)	KOAc	$(p\text{-}CF_3)_3P$(10)	DMF	75	57
11	$Pd(dba)_2$ (10)	KOAc	$(p\text{-}CF_3)_3P$(10)	DMF	95	65
12	**$Pd(dba)_2$(20)**	**KOAc**	**$(p\text{-}CF_3)_3P$(20)**	**DMF**	**85**	**90**

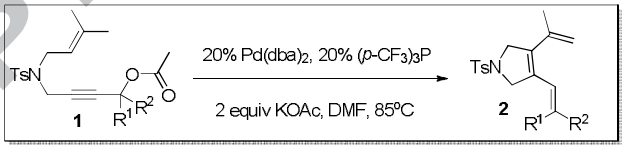
[a] The reaction was carried out with **1a** (0.2 mmol), Pd catalysts, phosphine ligand and 2 equiv of base in solvent (2 mL) at 85°C for 4 h under argon.

[b] tris(4-(trifluoromethyl)phenyl)phosphine. [c] tris(3,5-bis(trifluoromethyl)phenyl)phosphine.

[d] Isolated yields. [e] Decomposed.

We first investigated the cyclization of methyl 5-(4-methyl-*N*-(3-methylbut-2-en-1-yl)phenylsulfonamido)-2-phenylpent-3-ynoate **1a** in the presence of 10 mol % $Pd(PPh_3)_4$, 10 mol % (p-$CF_3)_3P$ [tris(4-(trifluoromethyl)phenyl)phosphine] and 2 equiv of KOAc in DMF at 85°C under an argon atmosphere. (*E*)-3-(prop-1-en-2-yl)-4-styryl-1-tosyl-2, 5-dihydro-1H-pyrrole **2a** was isolated in 16 % yield (Table 1, entry 1). Next, the catalytic activity of palladium catalyst was tested (entries 2-4), $Pd(dba)_2$ was the most effective catalyst of for this reaction and the yield of **2a** increased to 70 %. Other base such as NaOAc and Na_2CO_3 were less efficient and using KOH as the base led to a decomposed (entries 5-7). When (3, 5-$CF_3)_3P$ was used as phosphine ligand, no improvement was found (entry 8). Changing the solvent from DMF to DMSO also did not enhance the yield of **2a** (entry 9). During a survey of the temperature of the reaction, it was determined that 85°C gave the best yield (entries 10, 11). To our delight, significant improvement was achieved by increasing the amount of catalyst to 20 mol %, a good yield of 90 % of **2a** was obtained after 4 h. The optimum reaction conditions for **2a** thus for developed employ 20 mol % $Pd(dba)_2$, 20 mol % (p-$CF_3)_3P$ and 2 equiv of KOAc in DMF at 85°C under argon.

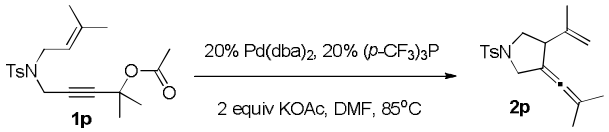
Table 2. Palladium-catalyzed cyclization of 1, 6-enyne acetic esters **1a** [a]



Entry	1	R^1	R^2	2	Yield (%)[b]
1	**1a**	H	Ph-	**2a**	90
2	**1b**	H	p-MeC_6H_4-	**2b**	72
3	**1c**	H	m-MeC_6H_4-	**2c**	80
4	**1d**	H	o-MeC_6H_4-	**2d**	96
5	**1e**	H	p-ClC_6H_4-	**2e**	65
6	**1f**	H	m-ClC_6H_4-	**2f**	69
7	**1g**	H	o-ClC_6H_4-	**2g**	78
8	**1h**	H	p-$MeOC_6H_4$-	**2h**	83
9	**1i**	H	o-$MeOC_6H_4$-	**2i**	99
10	**1j**	H	3,4-dimethylphenyl-	**2j**	82
11	**1k**	H	2,6-dimethoxyphenyl-	**2k**	91
12	**1l**	H	Furyl-	**2l**	50
13	**1m**	H	Thienyl-	**2m**	58
14	**1n**	H	Naphthyl-	**2n**	76
15	**1o**	H	Styryl-	**2o**	42

[a] The reaction was carried out with **1a** (0.2 mmol), 20 mol % $Pd(dba)_2$, 20 mol % (p-$CF_3)_3P$ and 2 equiv of KOAc in DMF (2 mL) at 85°C for 4 h under argon.

[b] Isolated yields.



Scheme 1. Cyclization of **1p** to form five-membered allene **2p**. [7]

With the optimized conditions in hand, various 1, 6-enyne acetic esters **1** were surveyed to clarify the scope of this reaction, as shown in Table 2. A tandem carbon-carbon bond formation of 1, 6-enyne acetic esters **1a-1o** proceeded smoothly to provide corresponding *E*-five-membered nitrogenated heterocyclic conjugated trienes **2a-2o** in moderate to excellent yields. The reaction worked well with a variety of functional groups such as methyl-, chloro-, methoxyl- at the ortho-, meta-, and para-positions of the phenyl moiety in substituted R^2 group (**2b-2i**), whereas ortho-positions give a better yields (**2d** vs **2b, 2c**; **2g** vs **2e**, **2f**; **2i** vs **2h**). Electron-donating aromatic groups showed better results than those with an electron-withdrawing group in this reaction (**2d**, **2i** vs **2h**). The structure of **2f** was confirmed by X-ray crystal structure analysis (Figure 2). [12] The substrate scope can also be extended to naphthyl- and styryl-enyne acetic esters (**2n, 2o**). To our delight, substrate with heteroaromatic R^2 groups can also afford the desired products **2l** and **2m** in 50 % and 58 % yields, respectively. However, the substrate with aliphatic R^1 and R^2 groups cannot afford the desired product, a five-membered allene was obtained in 52 % yield, which had been reported (**2p,** Scheme 1). [7] When propyl group is used at R^2 positon (R^1=H), no product is achieved. It seems that aromatic substituent groups are indispensable for the synthesis of conjugated triene products.

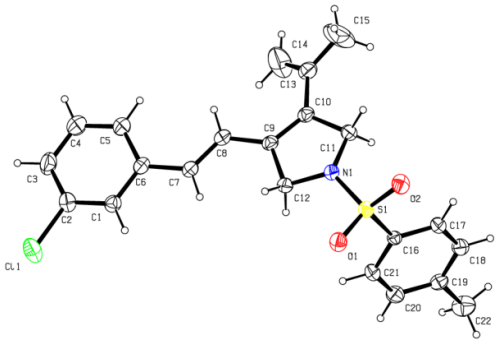
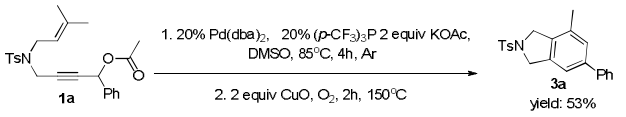
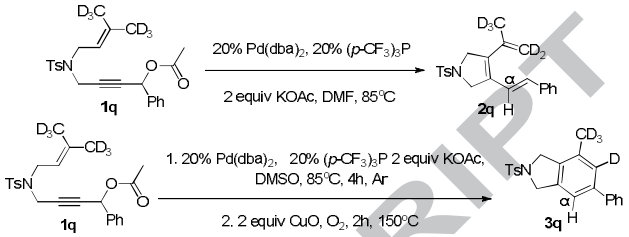


Figure 1. X-Ray Structure of **2f**.

To our surprise, when the substrate **1a** was reacted in the presence of 20 mol % $Pd(dba)_2$, 20 mol % $(p\text{-}CF_3)_3P$ and 2 equiv of KOAc in DMSO (2 mL) at 85°C for 4h under argon, then 2 equiv of CuO was added to the solution and the reaction continued for another 2h at 150°C under oxygen, 4-methyl-6-phenyl-2-tosylisoindoline **3a** was obtained in 53% yield (Scheme 2), this result is beneficial to further researches of five-membered nitrogenated heterocyclic conjugated trienes. To further acquire the information with respect to the mechanism, we conducted some deuterium-labeling studies. As shown in Scheme 3, **1q** was reacted under identical conditions with **1a** to afford desired deuterium-substituted products **2q** and **3q**. These data suggested that the hydrogen in α position of products were obtained from the carbon-carbon double bond of **1p** through a proton migration.

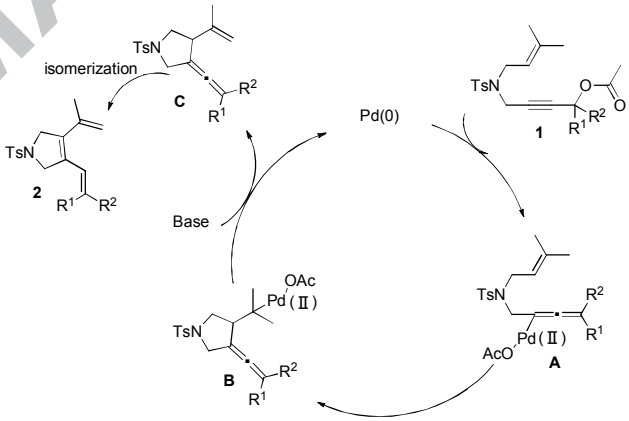


Scheme 2. Cyclization of **1a** and intramolecular Diels-Alder reaction.



Scheme 3. Deuterium-labeling experiments.

Based on the above observations, a plausible mechanism is proposed in Scheme 4. It might be rationalized in terms of the following steps: (a) transformation of 1, 6-enyne acetic ester **1** by Pd(0)-catalyzed generates allenylpalladium intermediate **A**; (b) olefin as a nucleophile attacks the intermediate **A** to form a five-membered palladium complex **B**; (c) reductive elimination of **B** gives a five-membered allene compound **C** and regenerates the Pd(0) catalyst; (d) isomerization of the compound **C** to form the desired product **2**.



Scheme 4. Plausible mechanism.

3. Conclusions

In summary, we have developed a Pd-catalyzed intramolecular cyclization reaction of 1, 6-enyne acetic esters to afford a straightforward approach to (E)-five-membered heterocyclic conjugated trienes. Deuterium-labeling experiments show that intramolecular proton migration is occurred to construct conjugated triene structures. The resulting conjugated trienes could be oxidated to polysubstituted benzene in one-pot.

Acknowledgments

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12. CCDC 1579877 (**2f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at XXXXXXX.

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1. Importance of five-membered nitrogenated heterocyclics as pharmaceutical and bioactive agents.
2. A one-pot to construct five-membered nitrogenated heterocyclics bearing conjugated trienes motif.
3. The reactions show excellent regioselectivity, good functional group tolerance and high yields.
4. The resulting conjugated trienes could be facilely converted to highly substituted benzenes through Diels-Alder reactions.