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Palladium-catalyzed cyclization of vinyl iodide-tethered allensulfonamide

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ABSTRACT

This Letter describes a palladium-catalyzed cyclization of vinyl iodide-tethered allensulfonamide in the presence of alkylol, which provides a facile access to 2-alkoxy-3-methylene-tetrahydropyridine. The asymmetric version of this reaction has also been preliminarily realized with up to 81% enantioselectivity when chiral bisphosphine ligands were used.

Allenamides represent a class of stable allenamine which was firstly reported by Viehe in 1968.[1] In the past decades, along with the substantive emergence of their synthetic methods, allenamides have been identified to be powerful and versatile building blocks.[2] In these contexts, palladium-catalyzed cyclization of allenamides has been proven to be a useful method for the construction of diverse heterocycles.[3] For example, Grigg reported a Pd(0)-catalyzed cyclizative carbopalladation-anion capture cascade process using aryl iodide-tethered allenamide (Scheme 1a).[4] This reaction would involve Pd-π-allyl intermediate **A**, which could be regioselectively attacked at γ-position by amine.[5]

With the combination of Grigg's report and our continuous efforts on the palladium-catalyzed transformation of (*Z*)-vinyl iodides,[6] we envisioned that vinyl iodide-tethered allensulfonamide **1** would also be capable of interacting with Pd(0) catalyst to form similar Pd-π-allyl intermediate **B** (Scheme 1b). Herein, we report a Pd(0)-catalyzed cyclization of **1** with the use of alkylol as nucleophile to capture intermediate **B**. Furthermore, this reaction is found to be different from the Grigg's reports and highly regioselective α-attack was observed, leading to cyclic N,O-acetal **2** as major product (Scheme 1b).

According to the base-induced isomerization of propargyl amide,[7] allenamide **1** can be readily obtained in two steps from (*Z*)-*N*-(3-iodoallyl)-sulfonamide and 3-bromoprop-1-yne (see Supporting Information). With the allenamide **1** in hand, we commenced our research from establishing optimized reaction conditions with the use of **1a** as the model substrate (Table 1). When **1a** was subjected to the reaction systems combined by $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and K_2CO_3 (2 equiv) in refluxing MeOH solvent, it was pleased to isolate the desired α-attack product **2a** albeit in the yield of 12% (Table 1, entry 1). It was disappointed to find that some common bisphosphine ligands, including DPPE, DPPP, DPPB as well as BINAP, only somewhat improved the yield (Table 1, entries 2–5). To our delight, catalyst precursor $Pd(PPh_3)Cl_2$ was proven to be superior, resulting in the isolation of **2a** in 53% yield (Table 1, entry 6). On the base of these results, we then investigated the effect of base additive. We found that base additive imposed strong effect on the reaction with respect to the isolated yield (Table 1, entries 7–12). Et_3N gave the best result, improving the yield to be 85% (Table 1, entry 9). More importantly, the corresponding γ-attack isomer was not detected under these reaction conditions, demonstrating the high regioselectivity of this transformation. It is worth noting that reduction of the amount of MeOH to 1.5 equiv still gave acceptable yields when the reaction was conducted in THF or MeCN solvent (Table 1, entries 13 and 14).

With the optimized conditions (Table 1, entry 9) in hand, we then turned our attention to investigate the reaction scope and the results are summarized in Table 2. In general, this Pd(0)-catalyzed cyclization of (*Z*)-vinyl iodide tethered allenamide **1** could be easily achieved with high regioselectivity, delivering N,O-acetal **2** in moderate to high yields. For the substrates with $R^1 = H$, the nature of R^2 substituent strongly affects the regioselectivity

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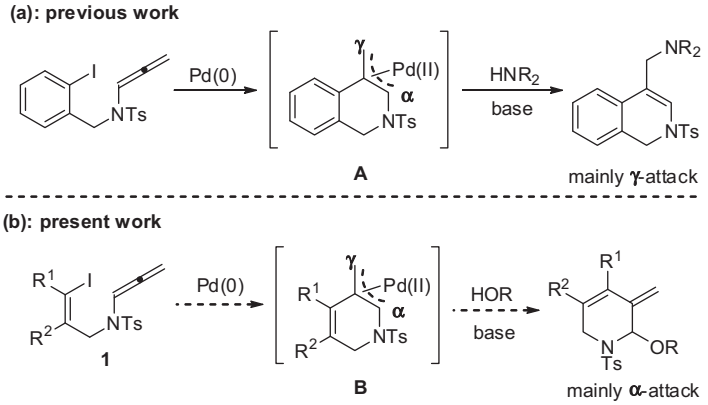
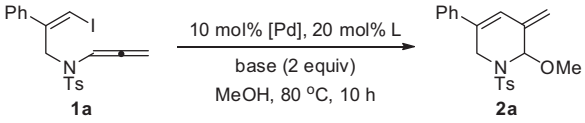


Scheme 1. Design plan for Pd(0)-catalyzed cyclization of allenamides **1**.

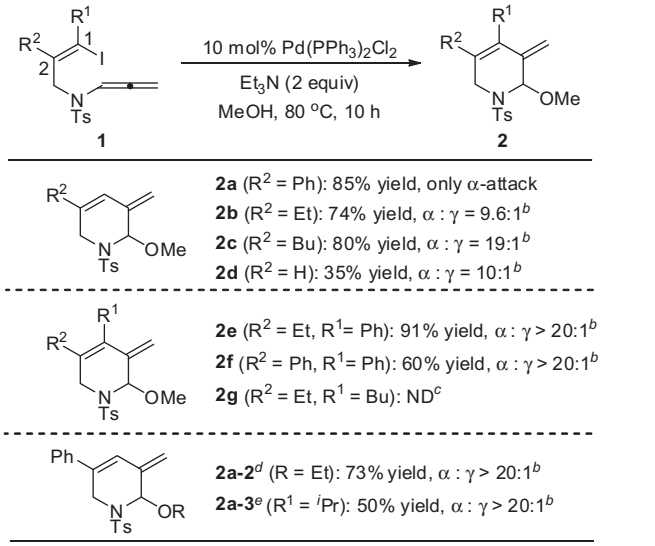
Table 1
Reaction conditions optimization[a]



Entry	[Pd]	L	Base	Yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	12
2	$Pd(OAc)_2$	DPPE[c]	K_2CO_3	5
3	$Pd(OAc)_2$	DPPP[c]	K_2CO_3	34
4	$Pd(OAc)_2$	DPPB[c]	K_2CO_3	24
5	$Pd(OAc)_2$	BINAP[c]	K_2CO_3	40
6	$Pd(PPh_3)_2Cl_2$	—[d]	K_2CO_3	53
7	$Pd(PPh_3)_2Cl_2$	—[d]	Na_2CO_3	65
8	$Pd(PPh_3)_2Cl_2$	—[d]	NaOAc	74
9	$Pd(PPh_3)_2Cl_2$	—[d]	Et_3N	85
10	$Pd(PPh_3)_2Cl_2$	—[d]	DBU	55
11	$Pd(PPh_3)_2Cl_2$	—[d]	DABCO	67
12	$Pd(PPh_3)_2Cl_2$	—[d]	DMAP	79
13	$Pd(PPh_3)_2Cl_2$	—[d]	Et_3N	76[e,f]
14	$Pd(PPh_3)_2Cl_2$	—[d]	Et_3N	69[e,g]

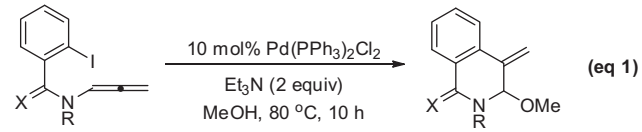
[a] Reaction conditions see Supporting Information.
[b] Isolated yield.
[c] 10 mol % ligand was used.
[d] Without additional ligand.
[e] 1.5 equiv of MeOH was used.
[f] THF was used as solvent.
[g] MeCN was used as solvent.

Table 2
Reaction scope[a]



[a] Reaction conditions see Supporting Information. The isolated yields were presented.
[b] The ratio of α-attack and γ-attack products. The ratio was determined on the basis of ^{1}H NMR analysis. [c]ND = not detection. [d]With the use of EtOH as solvent. [e]With the use of ^{i}PrOH as solvent.

and the yield. Not like the case of **1a**, the reactions of **1b** (R^2 = Et) and **1c** (R^2 = Bu) form both α-attack and γ-attack products with 9.6:1 and 19:1 regioselectivity, respectively. On the other hand, H-atom substituent furnishes the corresponding product **2d** in somewhat lower combined yield and the ratio of α-attack to γ-attack is 10:1. The substituents at C1-position impose stronger effect on the yield. For example, the substrates with phenyl group at C1-position react well to provide products **2e** and **2f** in the isolated yields of 91% and 60%, respectively, while the corresponding product **2g** with butyl group at C1-position cannot be detected at all. The introduction of butyl group into C1-position might increase the steric hindrance, leading to the failure of oxidative addition between vinyl iodide and Pd(0). Furthermore, the Pd(0)-catalyzed cyclization can be conducted in EtOH or ^{i}PrOH solvent, enabling the isolation of N,O-acetals **2a–2** and **2a–3** in the yields of 73% and 50%, respectively. The relative lower yields might arise from steric hindrance of EtOH or ^{i}PrOH which is believed to make the α-attack of nucleophile to Pd-π-allyl intermediate **B** less efficiently.

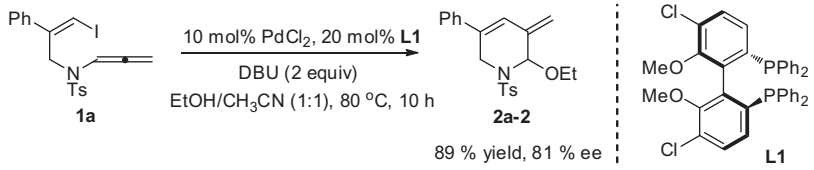


(eq 1)

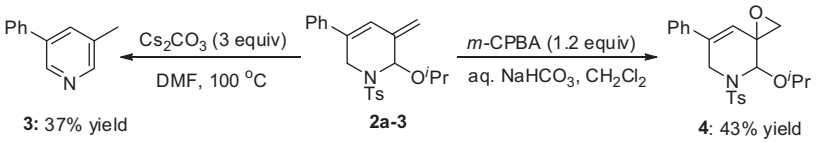
1h: R = Ts, X= H_2
1i: R = NPh, X= O

2h: 55% yield, α:γ > 20:1
2i: 53% yield, α:γ > 20:1

In the Grigg's reports, amine was used as nucleophile and γ-attack products were mainly formed. Complementarily, α-attack products **2a–2g** were obtained with high regioselectivity under our reaction conditions. Furthermore, the catalytic systems can be extended to aryl iodide tethered alleamides **1h** and **1i**. Again, α-attack products **2h** and **2i** were isolated in moderate yields with high regioselectivity (eq. 1).[8]



Scheme 2. Preliminary attempt at asymmetric catalysis.



Scheme 3. Synthetic applications.

It should be noted that product **2a**–**2** was obtained with 53% ee when (R)-BINAP was used as ligand under otherwise identical conditions. The result inspired us to carry out a preliminary attempt at the asymmetric catalysis. Finally, it was found that the highest 81% enantioselectivity could be realized when ligand **L1**[9] was employed under the modified reaction conditions (Scheme 2).

The products of the present Pd(0)-catalyzed cyclization can be converted into other potentially useful compounds. Indeed, pyridine **3** was formed when **2a**–**3** was treated with Cs_2CO_3 in DMF solvent (Scheme 3). Furthermore, selective epoxidation of **2a**–**3** was readily realized, leading to compound **4** in 43% yield (Scheme 3). Compound **4** was isolated as a single diastereoisomer,[10] which demonstrates the potential of stereo-control element of cyclic N,O-acetal.[11]

In summary, we have developed a Pd(0)-catalyzed cyclization of vinyl iodide-tethered allenamides **1**, which provides cyclic N,O-acetals **2** in moderate to good yields. An asymmetric version has also been attempted and the highest 81% enantioselectivity was obtained although only one example was presented. Further investigations are aimed at the development of the asymmetric catalysis and the synthetic applications of products with the use of cyclic N,O-acetal as stereo-control element.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.087.

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