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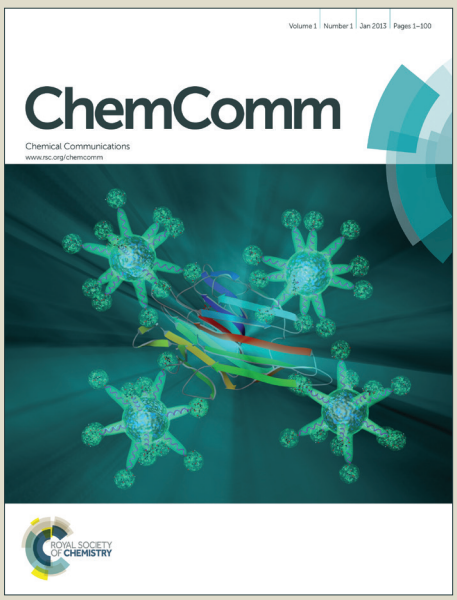

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ARTICLE TYPE

Synthesis of 3-Bromosubstituted Pyrroles *via* Palladium-Catalyzed Intermolecular Oxidative Cyclization of Bromoalkynes with *N*-Allylamines

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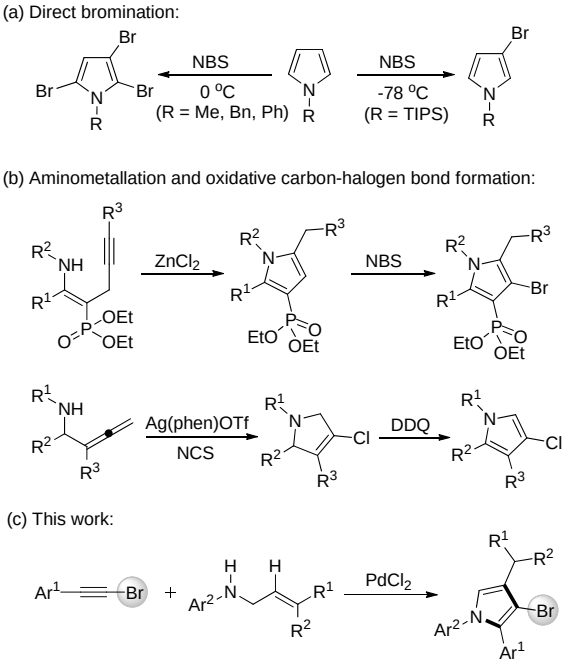
This paper describes a novel palladium-catalyzed oxidative cyclization of bromoalkynes with *N*-allylamines *via* cascade formation of C–N and C–C bonds. During this process, the bromine atom was retained to form 3-bromo-pyrroles, which can undergo the subsequent structural modifications.

Pyrroles represent an interesting class of nitrogen-containing heterocycles that exhibit diverse biological and therapeutic activities.[1] Over the past few decades, a number of methods to access pyrrole derivatives have been reported.[2] Meanwhile, 3-halo-subsituted pyrroles provide a facile way to the derivatization at 3-position of pyrroles since there are only limited reports about the selective functionalization of C-3 position of pyrroles.[3-4] However, the examples of the synthesis of 3-halo-subsituted pyrroles are still very rare.[5] Generally, 3-halo-subsituted pyrroles can be obtained by direct C-H bromination of pyrroles which require low temperature and specific substituents (Scheme 1, a).[5a] Another route to these structures is initiated by aminometallation, followed by the oxidative carbon-halogen bond formation (Scheme 1, b).[5b, 5c] Herein, we report a Pd-catalyzed intermolecular oxidative cyclization of bromoalkynes with *N*-allylamines, which offers a novel and convenient strategy for the synthesis of 3-bromo-pyrrole derivatives (Scheme 1, c).

In recent years, as powerful and versatile building blocks, haloalkynes have attracted increasing attention and been used widely in organic synthesis.[6] However, the halide atoms are usually removed in these reactions, especially in Pd-catalyzed tranfromations.[7] Therefore, to retain the halide moiety in the reaction of haloalkynes is still a challenge, which makes these protocols more atom economic.[8] As our continuous interest in developing novel and practical synthetic methods based on haloalkyne reagents,[6a, 9] herein, we report a Pd-catalyzed oxidative cyclization to afford various 3-bromopyrroles in a single operation. This strategy demonstrates the atom economy nature of the reaction since only two hydrogen atoms are removed. Moreover, the bromine atom retained in the reaction processes makes further functionalizations possible at the 3-position of pyrroles.

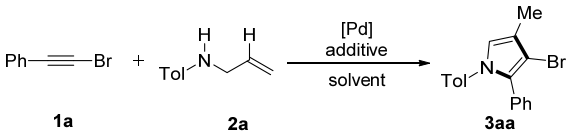


Scheme 1. Synthesis of 3-halo-substituted pyrroles.

We commenced our investigation by selecting 1-bromo-2-phenylacetylene (**1a**) and *N*-allyl-4-methylaniline (**2a**) as the model substrates (Table 1). In the presence of 10 mol % $PdCl_2$ in MeCN, we found that BQ (1,4-benzoquinone) was the best oxidant for this transformation, in comparison with O_2, $Cu(OAc)_2$, $K_2S_2O_8$, TBHP etc. (Table 1, entries 1-8). Subsequently, different solvents were tested and 48% yield of the desired product **3aa** was obtained in toluene (Table 1, entries 9-12). Then we discovered that a mixed solvent system of toluene-DMF (5:1) promoted this reaction to afford **3aa** in 65% yield (Table 1, entry 15). The screening of catalysts showed that $Pd(OAc)_2$ gave a lower yield, while $Pd(PPh_3)_2Cl_2$ and $Pd(CH_3CN)_2Cl_2$ exhibited considerable reactivity as $PdCl_2$ (Table 1, entries 17-19). To further enhance the yield, we tried to add different additives. When PivOH was used, there was a decline of yield (Table 1, entry 20). No reaction occurred when using bpy and an obvious decrease in yield was found when using $P(Cy)_3$ (Table 1, entries 21-22). Other additives such as KI and $Cu(OTf)_2$ showed

negative effects as well (Table 1, entries 23-24). Finally, an improved yield of 77% was obtained when we raised the reaction temperature to reflux (Table 1, entry 25). No reaction occurred when this reaction was carried out without Pd catalyst (Table 1, entry 26).

Table 1. Survey of reaction conditions.[a]



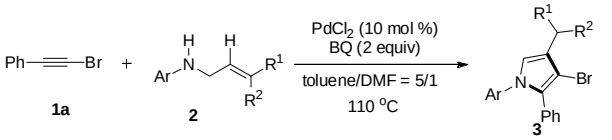
1a **2a** **3aa**

entry	catalyst	additive	solvent	yields (%)[b]
1	$PdCl_2$	O_2	MeCN	trace
2	$PdCl_2$	$Cu(OAc)_2$	MeCN	8
3	$PdCl_2$	AgOAc	MeCN	N.D.
4	$PdCl_2$	DDQ	MeCN	N.D.
5	$PdCl_2$	BQ	MeCN	25
6	$PdCl_2$	$K_2S_2O_8$	MeCN	12
7	$PdCl_2$	TBHP	MeCN	trace
8	$PdCl_2$	MnO_2	MeCN	trace
9	$PdCl_2$	BQ	DMSO	N.D.
10	$PdCl_2$	BQ	DMF	N.D.
11	$PdCl_2$	BQ	dioxane	trace
12	$PdCl_2$	BQ	toluene	48
13	$PdCl_2$	BQ	toluene/MeCN = 5/1	31
14	$PdCl_2$	BQ	toluene/DMF = 5/1	65
15	$PdCl_2$	BQ	toluene/DMF = 10/1	51
16	$PdCl_2$	BQ	toluene/DMF = 3/1	42
17	$Pd(OAc)_2$	BQ	toluene/DMF = 5/1	42
18	$Pd(PPh_3)_2Cl_2$	BQ	toluene/DMF = 3/1	64
19	$Pd(CH_3CN)_2Cl_2$	BQ	toluene/DMF = 5/1	60
20[c]	$PdCl_2$	BQ/PivOH	toluene/DMF = 5/1	42
21[d]	$PdCl_2$	BQ/BPy	toluene/DMF = 5/1	N.R.
22[e]	$PdCl_2$	BQ/$P(Cy)_3$	toluene/DMF = 5/1	15
23[f]	$PdCl_2$	BQ/KI	toluene/DMF = 5/1	trace
24[g]	$PdCl_2$	BQ/$Cu(OTf)_2$	toluene/DMF = 5/1	trace
25[h]	$PdCl_2$	BQ	toluene/DMF = 5/1	83 (77)[i]
26	-	BQ	toluene/DMF = 5/1	N.R.

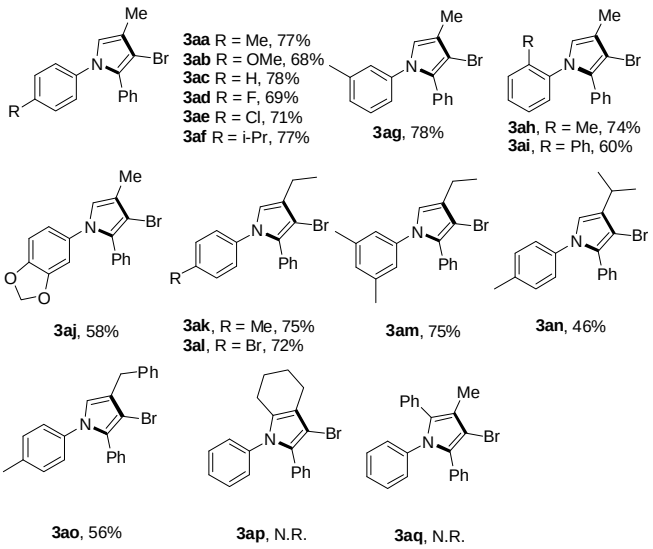
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $PdCl_2$ (10 mol %) and additive (2 equiv) in 2 mL solvent at 80 °C for 1 h. [b] Determined by GC. [c] 20 mol % PivOH. [d] 10 mol % bpy. [e] 20 mol % $P(Cy)_3$. [f] 20 mol % KI. [g] 20 mol % $Cu(OTf)_2$. [h] at 110 °C. [i] Isolated yield.

With the optimized conditions, a variety of *N*-allylamines were examined. Substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring worked well under the optimal conditions and the desired 3-bromo-pyrroles were formed in moderate to good yields (Table 2, **3aa-af**). *Meta*- and *ortho*-substituents on the phenyl ring were tolerated (Table 2, **3ag-ai**). Di-substituted substrates also proceeded well with **1a** (Table 2, **3aj**, **3am**). To our delight, allylamines bearing different R^1 and R^2 were compatible, providing a facile access to 4-Et-, ^{i}Pr- or Bn-substituted pyrroles in moderate to good yields (Table 2, **3ak-al**, **3an-ao**). However, branched allylamines failed to provide the desired products under our optimized reaction conditions (Table 2, **3ap** and **3aq**).

Table 2. The reaction of **1a** with different *N*-allylamines **2**. [a, b]



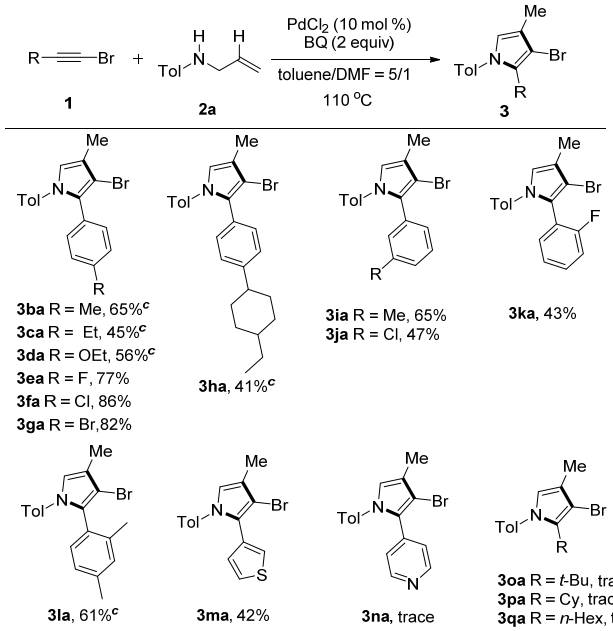
1a **2** **3**



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $PdCl_2$ (10 mol %) and BQ (2 equiv) in 2 mL toluene/DMF = 5/1 at 110 °C for 1 h. [b] Isolated yield.

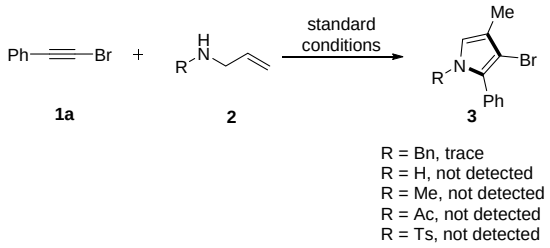
After successfully investigating the substrate scope of *N*-allylamines, we next evaluated the scope of bromoalkynes. For the *para*-position of phenyl ring, pyrrole products with electron-withdrawing groups like halogen (Table 3, **3ea-ga**) were obtained in relatively higher yields than electron-donating groups including alkyl and alkoxy (Table 3, **3ba-da**, **3ha**). *Meta*- and *ortho*-subsituted bromoalkynes can be also tolerated, albeit in moderate yields (Table 3, **3ia-ka**). 2,4-Dimethyl-subsituted aryl bromoalkyne worked well as *para*-substituent (Table 3, **3la**). It is noteworthy to mention that thiophene-containing aryl bromoalkyne was also tolerated in this protocol, which gave the corresponding product **3ma** in 42% yield. Unfortunately, pyridine-substituted and aliphatic bromoalkynes only gave a trace amount of products in this reaction (Table 3, **3na-qa**). Besides, iodoalkyne and chloroalkyne were not tolerated in this transformation (see ESI for details).

Table 3. The reaction of different bromoalkynes **1** with **2a**.[a, b]



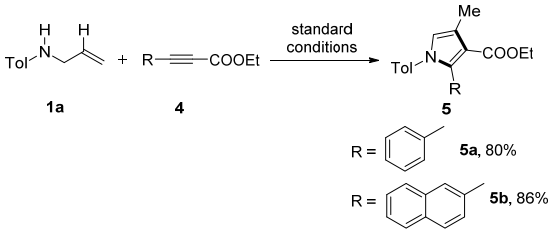
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), $PdCl_2$ (10 mol %) and BQ (2 equiv) in 2 mL toluene/DMF = 5/1 at 110 °C for 1 h. [b] Isolated yield. [c] 1.5 equiv of **1** was added in 3 times.

Finally, some *N*-protected allylamines were investigated (Scheme 2). However, *N*-benzyl allylamine only gave a trace amount of the desired product. For allylamines, *N*-methyl allylamines, Ac- or Ts-protected allylamines, no target molecule was detected. Thus, the *N*-phenyl substitution on allylamines was crucial to this transformation.



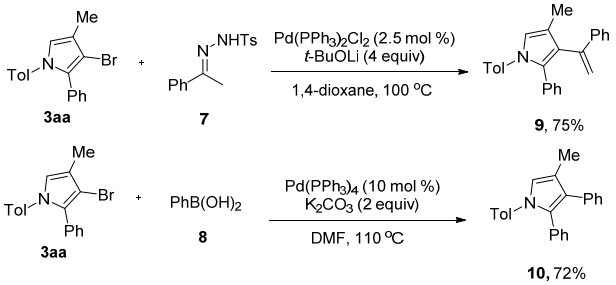
Scheme 2. Reaction with different *N*-protected allylamines.

In addition, this strategy was also applicable to aryl alkynyl esters (Scheme 3). Both phenyl- and naphthyl-substituted alkynyl esters reacted well with **1a** under the standard conditions to afford the 3-ester-substituted pyrroles **5** in high yields. Unfortunately, aliphatic alkynyl esters, such as methyl oct-2-ynoate and ethyl but-2-ynoate failed to afford the corresponding products.



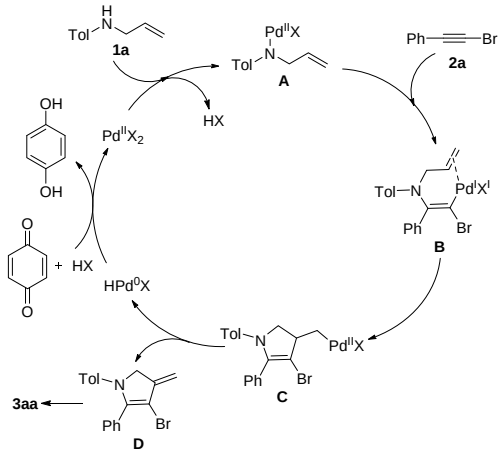
Scheme 3. Reaction with propargyl esters.

The synthetic utility of this protocol was illustrated in Scheme 4. Alkenylation of **3aa** smoothly proceeded, providing the desired product **9** in 75% yield (see ESI for X-ray crystallographic analysis).[10] The Suzuki coupling reaction between **3aa** and phenylboronic acid **8** also gave C-3 arylated pyrrole in good yield.



Scheme 4. Further transformations of 3-bromo-substituted pyrroles.

On the basis of experimental data and previous reports, a tentative mechanism for this transformation is proposed in Scheme 5. Initially, the intermediate **A** is formed by the reaction of palladium(II) and *N*-allylamine (**1a**). Subsequently, an intermolecular *cis*-insertion of bromoalkyne (**2a**) into N─Pd bond gives rise to the intermediate **B**,[11] which undergoes 1,2-migratory insertion, affording the intermediate **C**. A sequence of *β*-hydride elimination and isomerization provides the desired product **3aa**. Palladium(0) species is reoxidized to palladium(II) species by BQ.



Scheme 5. A proposed reaction mechanism.

In conclusion, a convenient Pd(II)-catalyzed intermolecular oxidative annulation between bromoalkynes and *N*-allylamines has been developed to provide 3-bromopyrroles in moderate to excellent yields. The retained bromine atom in 3-bromopyrrole products also offers a facile functionalization of pyrroles at 3-position.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

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