Organic LETTERS

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Palladium-Catalyzed C−H Arylation of (Benzo)oxazoles or (Benzo)thiazoles with Aryltrimethylammonium Triflates

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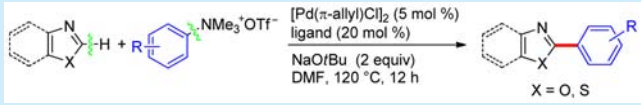
Supporting Information

ABSTRACT: The C−H arylation of (benzo)oxazoles or (benzo)thiazoles with aryltrimethylammonium triflates was carried out via Pd-catalyzed C−H/C−N cleavage. Oxazoles, thiazoles, benzoxazole, and benzothiazole were arylated using activated and deactivated aryltrimethylammonium triflates to give 2-aryl(benzo)oxazoles or 2-aryl(benzo)thiazoles in reasonable to excellent yields.



Studies on synthetic methods of 2-aryl(benzo)oxazoles or (benzo)thiazoles have attracted considerable attention because the compounds are important structural units in natural products, functional materials, agrochemicals, and pharmaceutically active compounds.[1] Among the synthetic approaches explored, cross-coupling is one of the most powerful and reliable methods. Compared with traditional cross-couplings, the C−H arylation of (benzo)oxazoles or (benzo)thiazoles avoids the need to prepare stoichiometric amounts of aryl-metal reagent.[2] On the other hand, it was reported that C2-lithiated benzothiazole is very unstable even at −50 °C.[3] This leads to difficult to prepare 2-arylated benzothiazole derivatives through cross-coupling of 2-metalated benzothiazoles such as benzothiazolato magnesium reagents and benzothiazolato zinc reagents with an aryl electrophilic reagent. Hence, the C−H arylation of (benzo)oxazoles or (benzo)thiazoles is receiving increasing attention. A variety of electrophilic reagents including aryl halides, sulfides, and phenol derivatives such as triflates, tosylates, mesylates, sulfamates, esters, and carbamates have been employed for the transformation.[4−9] However, developing new arylating reagents for the coupling reaction is still an active research subject.

Aryltrimethylammonium salts are easily prepared from arylamines, and the latter are widely available in nature and industry. Compared with corresponding arylamines, the ammonium salts show much higher C−N reactivity due to strong C−N bond polarity and release of electronically neutral amine in the process of reaction. Hence, aryltrimethylammonium salts are promising arylation reagents in organic transformations. A disadvantage of using this arylation reagent is the presence of competing reactions of C_{sp3}−N and C_{sp2}−N cleavages. However, the choice of suitable catalysts and optimization of reaction conditions can overcome the drawbacks. Several transition-metal-catalyzed cross-coupling reactions using aryltrimethylammonium salts as the electrophiles, such as Suzuki, Kumada, and Negishi couplings, have been carried out.[10] It is of interest to explore the possibility of using aryltrimethylammonium salts as arylating reagents in the direct C−H arylation of (benzo)oxazoles and (benzo)thiazoles.

The reaction of 1-naphthyltrimethylammonium triflate with benzoxazole was used to screen catalysts and reaction conditions, and the results are listed in Table S1 (Supporting Information). The combination of $Ni(COD)_2$ and dcype, PCy_3, or IPr·HCl was, respectively, tested in DMF at 120 °C in the presence of NaO-*t*-Bu as base, and the results showed that the above catalyst systems were not very effective for this reaction (Table S1, entries 1−3). By contrast, a combination of $Pd(OAc)_2$ and dcype gave higher yield under the same conditions (Table S1, entry 4). This improvement encouraged us to test combinations of $Pd(OAc)_2$ and other didentate phosphine ligands, including dppm, dppe, dppb, dppp, Xantphos, and DPEphos (Table S1, entries 5−10). However, application of these didentate phosphines did not further improve the reaction in comparison with $Pd(OAc)_2$/dcype system. This made us switch to monodentate phosphine and *N*-heterocyclic carbene ligands such as Xphos, P(*t*-Bu)$_3$, PCy_3, IPr, and IMes (Table S1, entries 11−15). Both PCy_3 and IPr were demonstrated to be excellent ligands in the palladium-catalyzed reaction, whereas Xphos, P(*t*-Bu)$_3$, and IMes were less effective. Different palladium compounds also affected the reaction to some extent. $PdCl_2$ was less active than $Pd(OAc)_2$, but the activities of $Pd_2(dba)_3$ and $[Pd(\pi\text{-allyl})Cl]_2$ were comparable with that of $Pd(OAc)_2$ when PCy_3 was employed as the ligand (Table S1, entries 16−18). We also screened bases and solvents using $[Pd(\pi\text{-allyl})Cl]_2/PCy_3$ as catalyst (Table S1, entries 19−23). NaO-*t*-Bu was superior to other bases such as LiO-*t*-Bu, Cs_2CO_3, and K_3PO_4. Toluene and dioxane proved to be less effective solvents than DMF. It was also noted that the amount of the catalyst could be decreased. A combination of 2.5 mol % of $[Pd(\pi\text{-allyl})Cl]_2$ and 10 mol % of PCy_3 resulted in the

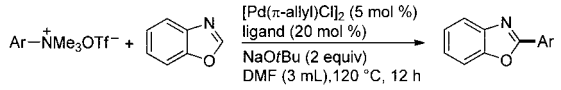
Received: September 10, 2015
Published: September 23, 2015

DOI: 10.1021/acs.orglett.5b02458
Org. Lett. 2015, 17, 4926−4929

desired product in 92% yield. The combination of 2.5 mol % of $[Pd(\pi\text{-allyl})Cl]_2$ and 10 mol % of IPr·HCl gave a slightly lower yield (Table S1, entries 24 and 25). In addition, we noted that a small amount of homocoupling species of 1-naphthyltrimethylammonium triflate were often obtained in the reactions. Hence, we tried to carry out the reaction using excess 1-naphthyltrimethylammonium triflate. The result showed that the yield of the desired product could be increased to 97% (Table S1, entry 26). We also tested the counterion effect using 1-naphthyltrimethylammonium salts with I^- and BF_4^- as the counterions under the optimized conditions (Table S1, entries 27 and 28). The results clearly showed that the iodide and tetrafluoroborate salts were less reactive than the triflate salt. Finally, we examined the reaction in the absence of catalyst. The result showed that only a trace amount of coupling product was observed (Table S1, entry 29), accompanied by formation of *N*,*N*-dimethylnaphthalen-1-amine.

With the optimized reaction conditions in hand, the scope of the aryltrimethylammonium triflates was tested using benzoxazole as the nucleophilic precursor, and the results are listed in Table 1. Compared with 1-naphthyltrimethylammonium triflate, more electron-rich (4-methoxynaphthyl)trimethylammonium triflate exhibited somewhat lower reactivity. This is reasonable because (1) more electron-rich (4-methoxynaphthyl)trimethylammonium triflate has a stronger C−N bond which is more difficult to cleave in the oxidative addition step and (2) the C−Pd bond between more electron-rich 4-methoxynaphthyl group and palladium is stronger, which is disadvantageous to the reductive elimination in the catalytic cycle. Surprisingly, 2-naphthyltrimethylammonium triflate and 2-anthryltrimethylammonium triflate showed lower reactivity than both (4-methoxy-1-naphthyl)trimethylammonium triflate and 1-naphthyltrimethylammonium triflate (Table 1, entries 1−3). Further, phenyltrimethylammonium triflate and (4-methylphenyl)trimethylammonium triflate were discovered to have lower reactivity than (2-methylphenyl)trimethylammonium triflate (Table 1, entries 4−6). The former required higher catalyst loadings and led to lower product yield. In these examples, it seems that the ammonium salts with more sterically hindered aryl groups have higher reactivity. The same phenomenon was also observed by other researchers.[7e,11] We deduced that in these reactions the reductive elimination step is the rate-determining step and a bulky aryl group can promote the reductive elimination due to steric repulsion. However, the methoxy-substituted phenyltrimethylammonium triflates exhibited different reactivity trends. Both (*p*-methoxyphenyl)- and (*m*-methoxyphenyl)trimethylammonium triflates exhibited higher reactivity than (*o*-methoxyphenyl)trimethylammonium triflate under the same conditions (Table 1, entries 7−9). The *o*-methoxy-substituted substrate may form a C,O-chelate intermediate through coordination of the oxygen atom to the central palladium atom in the process of catalysis. The chelation plays a leading role in the reductive elimination step and makes the reductive elimination of the *o*-methoxyphenyl-substituted intermediate more difficult compared with *meta*- and *para*-substituted ones. [*p*-(Dimethylamino)phenyl]trimethylammonium triflate exhibited reactivity similar to that of (*p*-methoxyphenyl)trimethylammonium triflate. Its reaction with benzoxazole under the same conditions gave 40% product yield (Table 1, entry 10). For installing the phenyl groups with electron-withdrawing substituents onto benzoxazole, we found that IPr is a more suitable ligand than PCy_3. All electron-deficient aryltrimethylammonium triflates gave moderate to high product yields (Table 1, entries 11−14). Meanwhile, the functional groups on the aromatic rings such as CF_3, CN, COPh, and $CONEt_2$ were well tolerated. However, reaction of $p\text{-}EtO_2CC_6H_4NMe_3^+OTf^-$ with benzoxazole under the standard conditions could not give the desired product. In addition, (2-pyridyltrimethyl)ammonium triflate was proved to be a good reaction partner. Its reaction with benzoxazole resulted in desired product in 82% isolated yield (Table 1, entry 15).

Table 1. Reaction of Aryltrimethylammonium Triflates with Benzoxazole[a]



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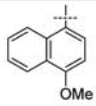
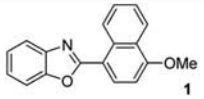
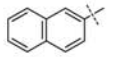
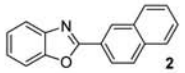
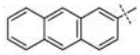
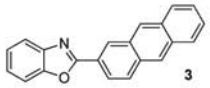
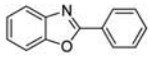
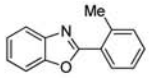
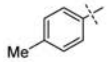
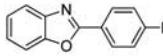
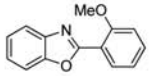
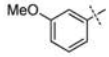
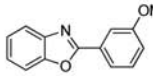
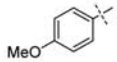
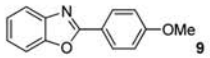
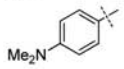
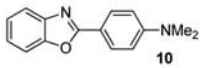
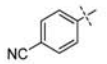
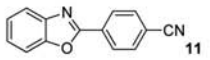
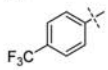
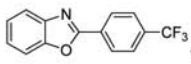
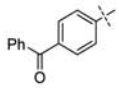
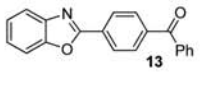
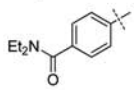
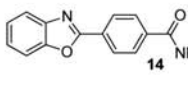
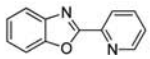
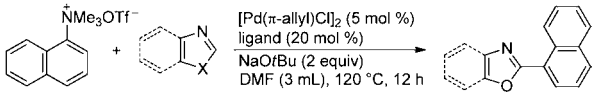
1		PCy_3		82
2		PCy_3		65
3		PCy_3		60
4[c]		PCy_3		43
5		PCy_3		81
6[c]		PCy_3		43
7[c]		PCy_3		23
8[c]		PCy_3		33
9[c]		PCy_3		35
10[c]		PCy_3		40
11		IPr·HCl		62
12		IPr·HCl		73
13		IPr·HCl		80
14		IPr·HCl		86
15		IPr·HCl		82

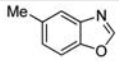
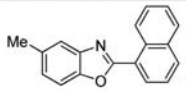
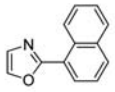
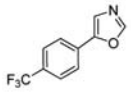
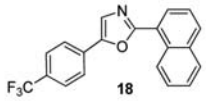
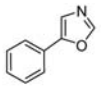
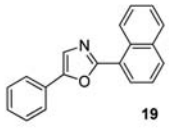
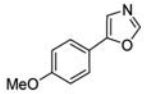
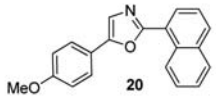
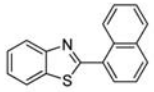
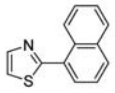
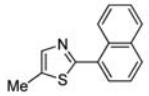
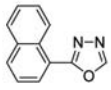
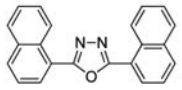
[a]Unless otherwise specified, the reactions were carried out according to the conditions indicated by the above equation; 0.5 mmol of benzoxazole and 0.75 mmol of aryltrimethylammonium triflate were employed. [b]Isolated yield. [c]10 mol % of $[Pd(\pi\text{-allyl})Cl]_2$ and 40 mol % of PCy_3 were employed.

DOI: 10.1021/acs.orglett.5b02458
Org. Lett. 2015, 17, 4926−4929

We next examined the range of azoles using 1-naphthyltrimethylammonium triflate as the electrophile. As can be seen from Table 2, various azoles including oxazoles, thioazoles, 5-methylbenzoxazole, and benzothiazole could be used for the reaction and gave the arylated products in reasonable to excellent yields. Compared with benzoxazole, 5-methylbenzoxazole exhibited lower reactivity (Table 2, entry 1). Oxazole reacted smoothly with 1-naphthyltrimethylammonium triflate under the same conditions to give corresponding product in 89% yield (Table 2, entry 2). Reaction of 5-aryloxazoles was demonstrated to proceed smoothly using $[Pd(\pi\text{-allyl})Cl]_2$/IPr as the catalyst, leading to the desired products in modest yields regardless of the electron-deficient or electron-rich properties of the aryl groups on the oxazole rings (Table 2, entries 3–5).

Table 2. Reaction of Azoles with 1-Naphthyltrimethylammonium Triflate[a]



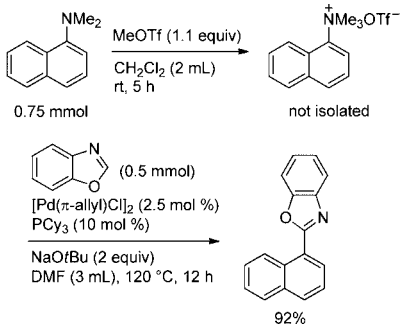
entry	oxazole or thiazole	ligand	product	yield (%)[b]
1		PCy_3	 16	61
2		PCy_3	 17	89
3[c]		IPr·HCl	 18	62
4[c]		IPr·HCl	 19	65
5[c]		IPr·HCl	 20	64
6		PCy_3	 21	97
7[c]		PCy_3	 22	53
8[c]		PCy_3	 23	43
9		PCy_3	 24	42

[a]Unless otherwise specified, the reactions were carried out according to the conditions indicated by the above equation; 0.5 mmol of oxazole or thiazole and 0.75 mmol of aryltrimethylammonium triflate were employed. [b]Isolated yield. [c]0.5 mmol of 1-naphthyltrimethylammonium triflate and 0.75 mmol of oxazole or thiazole were employed.

Benzothiazole displayed excellent reactivity under the optimized conditions, and its reaction resulted in the cross-coupling product in 97% yield (Table 2, entry 6). Both thiazole and 5-methylthiazole showed much lower reactivity compared with benzothiazole. Reaction of the former gave the corresponding products in 53% and 43% yields, respectivity (Table 2, entries 7 and 8). Meanwhile, some demethylation products of 1-naphthyltrimethylammonium triflates, 1-(*N*,*N*-dimethylamino)-naphthalene, were observed. Finally, we found that 2-(naphthalen-1-yl)-1,3,4-oxadiazole could also be arylated using 1-naphthyltrimethylammonium triflate, but the product yield was lower than those using oxazoles (Table 2, entry 9).

To further demonstrate the utility of this method for organic synthesis, we examined the reaction of benzoxazole with 1-naphthyltrimethylammonium triflate on a 10 mmol scale under the conditions as shown in Table S1, entry 26. The corresponding product was isolated in 95% yield. In addition, the direct C–H bond arylation can also be performed in a convenient one-pot procedure. Thus, *N*,*N*-dimethylnaphthalen-1-amine was treated with MeOTf in CH_2Cl_2 at room temperature. After removal of CH_2Cl_2, the resultant ammonium salt was reacted directly with benzoxazole under the optimized conditions to afford the arylated product in 92% overall yield (Scheme 1). This result showed that the one-pot reaction is as effective as the reaction between an aryltrimethylammonium salt and benzoxazole under identical conditions.

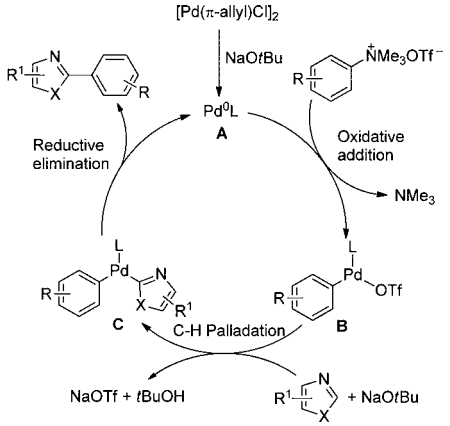
Scheme 1. One-Pot Reaction for the C–H Arylation of Benzoxazole



To gain preliminary mechanistic information about this transformation, several control experiments were carried out under the standard conditions. When an equimolar amount of free-radical inhibitor 1,1-diphenylethylene or TEMPO was added to the reaction mixture of benzoxazole and 1-naphthyltrimethylammonium triflate, the product yields were not affected. The experimental facts ruled out the possibility of a free-radical reaction. As shown in Table S1, entry 17, the $Pd_2(dba)_3/PCy_3$ system exhibited comparable catalytic activity with the combination of $[Pd(\pi\text{-allyl})Cl]_2$ or $Pd(OAc)_2$ and PCy_3. Hence, the active catalyst in the catalytic cycle may be a Pd(0) species. On the basis of the above observations and the previous reports,[2h,11] a plausible catalystic cycle is outlined in Scheme 2. It is believed that this process is initiated from a Pd(0) species (**A**) generated under the reaction conditions. The Pd(0) species reacts with $ArNMe_3^+OTf^-$ to form an oxidative addition species LPd(OTf)Ar (**B**) and release NMe_3, which was monitored by GC–MS. Next, the C–H palladation of azoles with LPd(OTf)Ar (**B**) in the presence of a base gives aryl(heteroaryl) palladium intermediate (**C**), which undergoes

DOI: 10.1021/acs.orglett.5b02458
Org. Lett. 2015, 17, 4926–4929

Scheme 2. Proposed Catalytic Cycle



reductive elimination to form the cross-coupling product along with regeneration of the Pd(0) complex (**A**).

In summary, we report the first example of palladium-catalyzed direct C−H arylation of oxazoles and thiozaoles using aryltrimethylammonium triflates as the arylating reagents. This methodology displays a broad substrate scope. Various aryltrimethylammonium triflates including electron-rich and -poor ones can be used as arylating reagents. A variety of azoles or thiazoles can be arylated with aryltrimethylammonium triflates under the optimal reaction conditions. The reaction gives reasonable to excellent yields in most cases and shows good compatibility of functional groups. We believe that this methodology would provide a valuable complement to the direct C−H arylation of azoles and thiozaoles and enrich the utilization of aromatic amines in organic synthesis chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02458.

Experimental details of the coupling reaction, characterization data, and NMR spectra of the cross-coupling products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Grant No. 21372212) and the National Basic Research Program of China (Grant No. 2015CB856600) is greatly acknowledged. Ms. Fang He of the Department of Chemistry, University of Science and Technology of China, is thanked for her help with sample purification.

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DOI: 10.1021/acs.orglett.5b02458
Org. Lett. 2015, 17, 4926−4929