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Sonogashira Cross-Coupling of Aryltrimethylammonium Salts

Qianwei Chen,[†] Fengchen Gao,[†] Huiling Tang,[†] Miao Yao,[†] Qian Zhao, [†] Yanhui Shi,^{*,†} Yanfeng Dang^{*,‡} and Changsheng Cao^{*,†}

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ABSTRACT: A protocol for C(sp)–C(sp²) bond formation via the Sonogashira coupling reaction involving C–N bond cleavage with aryltrimethylammonium triflate as an electrophilic coupling partner was described in this work. The reactions proceeded well under mild conditions with stoichiometric ratio of alkyl, aryl, or heteroaryl acetylenes and provided yields of up to 93%. Numerous useful functional groups were tolerated under the reaction conditions. Direct amine alkynylation can be achieved through a one-pot process without the isolation of ammonium salt. The protocol can be performed on the gram scale. Density functional theory calculations were performed to investigate the reaction mechanism that involved oxidative addition, alkyne coordination, deprotonation, and reductive elimination, which yielded the cross-coupling product.

Keywords: C-N bond activation, Sonogashira, Cross-coupling, Pd-NHC complex, DFT

INTRODUCTION

Transition-metal catalyzed cross-coupling reactions have been widely applied in organic synthesis as a powerful tool for C-C bond construction.¹ Most of these cross-coupling reactions, for example, the Suzuki-Miyaura,² Kumada,³ Negishi,⁴ Mizoroki-Heck⁵, and Stille⁶ reactions, focus on the formation of C(sp²)-C(sp²) bonds. The Sonogashira crosscoupling reaction plays an irreplaceable role as a unique method for $C(sp)-C(sp^2)$ bond formation in the preparation of aryl alkynes or enynes, which are often encountered in natural products, pharmaceuticals, biologically important molecules, and molecular organic materials.7 Aryl halides, triflates, and tosylates are the most commonly used electrophilic coupling partners in the Sonogashira reaction.8 Recently, the development of new coupling partners has received widespread attention, the cross-coupling reactions involving the activation of C-O,9 C-S,10 C-P11 and C-N12 bonds have been investigated. Given the abundance of C-N bonds in biomacromolecules, drugs, and materials,¹³ the transition-metal-catalyzed C-N bond activation reaction has considerable potential for application in organic synthesis. Despite the synthetic challenge posed by the high dissociation energy of the C–N bond, many cross-coupling reactions that occur via the cleavage of inert C-N bonds have been discovered in the last 20 years.¹⁴⁻¹⁵ One of the attractive approaches for these cross-coupling reactions is the activation of an inert C-N bond to an activated C-N bond, e.g. the transformation of amines into their corresponding diazonium salts¹⁶ or pyridinium salts.¹⁷ Unlike pyridinium salts, arenediazonium salts have been successfully employed as arylation reagents in numerous cross-coupling reactions. including the Sonogashira reaction (Scheme 1).18 These compounds, however, are unstable and can only be converted from primary amines. Quaternary ammonium salts are attractive alternatives to arenediazonium salts because of their sufficient stability; long shelf life; and

Scheme 1. Songashira Cross-coupling Reactions via Activation of a C-N Bond



availability from various inexpensive amines, including primary, secondary, and tertiary amines.¹⁹

Since Wenkert first used aryltrimethylammonium iodides as an electrophilic coupling partner in the Ni-catalyzed Kumada reaction,20 various Ni or Pd-catalyzed reactions involving quaternary ammonium salts have been reported for the construction of $C(sp^2)-C(sp^2)$ or $C(sp^3)-C(sp^2)$ bonds. These reactions include the Kumada,²¹ Suzuki,²² Negishi,²³ Buchwald-Hartwig,²⁴ and Stille reactions,²⁵ as well as various other reactions.²⁶ Nevertheless, $C(sp)-C(sp^2)$ bond formation via the Sonogashira cross-coupling reaction with quaternary ammonium salts as reactants remains challenging. Herein, we report the first example of the use of aryltrimethylammonium salts in Sonogashira cross-coupling reactions catalyzed by the stable Pd-NHC complex. Our approach provides a potential protocol for the activation of the C-N bonds of primary, secondary, and tertiary amines. Furthermore, we investigated the reaction

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Table 1. Optimization of the Reaction Conditions

+N, + =-√		<u>}</u> -	cat. (10 mol%), ligand (10 mol%) base(2.0 equiv.), N ₂		-	- =-4	
1a	2	2	solve	nt, 45 °C		3	
Entry	cat.	ligand		base	solvent	time (h)	yield (%) ^b
1	Ni(PPh ₃) ₂ Cl ₂			t-BuONa	THF	10	0
2	Pd(PPh ₃) ₂ Cl ₂			t-BuONa	THF	10	2
3	Pd(OAc) ₂	XPhos		t-BuONa	THF	10	trace
4	$Pd(OAc)_2$	PCy ₃		t-BuONa	THF	10	18
5	$Pd(OAc)_2$	IPr∙HO	Cl	t-BuONa	THF	10	15
6	$Pd(OAc)_2$	SIPr·H	ICl	t-BuONa	THF	10	29
7	PdCl ₂	SIPr·H	ICl	t-BuONa	THF	10	20
8	IMes-PdCl ₂ -Py			<i>t</i> -BuONa	THF	10	41
9	IPr-PdCl ₂ -Py			t-BuONa	THF	10	57
10	SIPr-PdCl ₂ -Py			t-BuONa	THF	10	74
11	SIPr-PdCl ₂ -Py			<i>t</i> -BuONa	THF	2	72
12	SIPr-PdCl ₂ -Py			t-BuONa	THF	4	78
13	SIPr-PdCl ₂ -Py			t-BuONa	THF	6	75
14	SIPr-PdCl ₂ -Py			<i>t</i> -BuONa	THF	8	76
15	SIPr-PdCl ₂ -Py			<i>t</i> -BuOLi	THF	4	trace
16	SIPr-PdCl ₂ -Py			t-BuOK	THF	4	53
17	SIPr-PdCl ₂ -Py			Cs_2CO_3	THF	4	0
18	SIPr-PdCl ₂ -Py			t-BuONa	EtOH	4	trace
19	SIPr-PdCl ₂ -Py			t-BuONa	DMF	4	trace
20	SIPr-PdCl ₂ -Py			t-BuONa	MeCN	4	trace
21	SIPr-PdCl ₂ -Py			t-BuONa	dioxane	4	12
22	SIPr-PdCl ₂ -Py			t-BuONa	toluene	4	19

^a 0.2 mmol scale reactions. ^b HPLC yield with biphenyl as the internal standard.



mechanism of our approach through density functional theory (DFT) calculations.

RESULTS AND DISCUSSION

The successful employment of Ni and Pd catalysts in many coupling reactions of quaternary ammonium salts suggests that Ni(0) or Pd(0) could insert into the C-N bond of an aryl ammonium. We began our studies by attempting to alkynylate phenyltrimethylammonium triflate (1a) by using 4ethynyltoluene (2) with different Pd or Ni catalysts (Table 1). Initially, we examined the feasibility of using moisture- and airstable Ni(PPh₃)₂Cl₂ and Pd(PPh₃)₂Cl₂ (10 mol%) as the catalyst precursor. The reactions were performed with t-BuONa (2 eq.) as the base and THF as the solvent at 45 °C for 10 h. However, $Ni(PPh_3)_2Cl_2$ was completely ineffective, and $Pd(PPh_3)_2Cl_2$ provided a 1-methyl-4-(phenylethynyl)benzene (3) yield of 2% (Table 1, entries 1–2). Therefore, we examined the effects of increasing the amount of Pd precatalyst (Table 1, entries 3-10). The reactions catalyzed by Pd(OAc)₂ with the phosphine ligand PCy₃ and XPhos (Table 1, entries 3-4) and with the Nheterocycle carbene (NHC) ligands SIPr and IPr (Table 1,

entries 5-6) provided **3** at yields of less than 30%.

Table 2. The Effect of the Counterion of Ammonium Salts



^a0.2 mmol scale reactions. ^bHPLC yield with biphenyl as the internal standard.

Yield decreased when PdCl₂ was used as a precursor instead of Pd(OAc)₂ (Table 1, entries 6–7). Furthermore, we tested the catalytic performances of three well-defined Pd-NHC complexes. Moderate product yields were generated when IMes-PdCl₂-Py (41%) and IPr-PdCl₂-Py (57%) were utilized (Table 1, entries 8–9). The SIPr–PdCl₂–Py complex showed the best catalytic activity among all tested catalysts and generated a good yield of 74% (Table 1, entry 10). In contrast to IMes-PdCl₂-Py, IPr-PdCl₂-Py provided good yields. This result implies that the presence of a ligand with steric hindrance facilitates the reaction.²⁷ The negligible effects on the reaction when the reaction time was shortened from 10 h to 4 h suggests that the reaction reached completion within 4 h (Table 1, entries 10-14). Our following results indicate that the base and solvent played a crucial role in the success of the reaction. t-BuOK provided only modest yields of the desired product (53%), and t-BuOLi and Cs₂CO₃ severely inhibited the reaction (Table 1, entries 14-17). Although THF provided good product yields, dioxane and toluene only provided 12%-19% product yields (Table 1, entry 21-22). In addition, only trace amounts of the product were obtained with N,N-dimethylformamide (DMF), acetonitrile (MeCN) and ethanol (EtOH).

The counterion effect of the ammonium salts on the reactivity of Sonogashira reaction was examined in the reaction of phenyltrimethylammonium salts (1a-g) with 4-ethynyltoluene (2) under the optimized reaction conditions. As shown in Table 2, the tested counterions have slightly effect on the yield of 3 except for I ion. The good reactivity of very soluble triflate salt 1a (78% yield) and poor soluble tetrafluoroborate salt 1e (76% yield) in THF were observed, suggesting that the solubility of the salts has insignificantly effect on the reaction. Over 60% yield of 3 was detected with the halide salts (1b and 1c) and around 54% yield was observed with the sulfonate salts (1f and 1g). However, the iodide salt 1d reacted much more slowly under the same conditions, leading to low yield of 3 (20%) with a large amount of recovered 1d.

Furthermore, the scope and generality of the protocol was explored. First, a variety of terminal alkynes were reacted with ammonium salt **1a** under the optimized reaction conditions (Table 3, **3-18**). The results showed that various substituted phenylacetylenes could be successfully converted to the corresponding diaryl acetylenes in moderate to excellent yields. Either electron-rich or electron-deficient aryl acetylenes were suitable for the reaction. Generally, good yields were obtained

Table 3. The Sonogashira Cross-coupling of Terminal Alkyne with Aryltrimethylamonium Triflate



^a Unless specified indication in brackets, SIPr-PdCl₂-Py (0.05 mmol), alkyne (0.50 mmol), aryltrimethylammonium triflate (0.50 mmol) and t-BuONa (1 mmol) were employed in 2.5 mL of THF at 45 °C for 4 h under N2 atmosphere; ^b Isolated yields.

Scheme 2. Alkynylation of Dimethylaniline in One-pot Process





Scheme 4. Competition Reaction



with phenylacetylenes that bear an electron-donating group. Meanwhile, the reaction time must be prolonged to achieve satisfactory yields of aryl acetylenes with a withdrawing group. For example, 8 was isolated with a yield of 92% within 4 h when *p*-methoxyphenylacetylene was used in the reaction,

Scheme 5. Proposed Catalytic Cycle for the Palladium-Catalyzed C-C Coupling



whereas 10 was isolated with a yield of 53% within 12 h when *p*-fluorophenylacetylene was applied in the reaction. Notably, 11 was generated with a yield of 72% when para-chloro phenylacetylene was used. This result indicates that the potentially labile Cl was inert in the reaction and thus facilitated further transformation. The C-N bond of ammonium could be selectively functionalized given that amine and amide groups remained intact during the reaction (Table 3, 9 and 12). Hetero



Figure 1. DFT-computed free energy profiles for the Pd-catalyzed C-C coupling reaction. Energies are relative to the active catalyst IN1, and are mass balanced.

cycles, such as thiophene, can be tolerated under the optimized reaction conditions (Table 3, 13–14). Interestingly, terminal alkyl alkynes were also applicable in this reaction and can be successfully converted to the corresponding alkynes in moderate yields (Table 3, 15–16 and 18). However, Cl substitution on the alkyl group interfered with the reaction and resulted in the low yield of the desired product 17.

Furthermore, the use of various aryltrimethylammonium triflates in the ammonium Sonogashira coupling reaction with 4-ethynylanisole was examined (Table 3, 19–29). The results showed that reactions performed with active electron-poor aryltrimethylammonium triflates occurred smoothly and provided the corresponding diphenyl alkynes in moderate to good yields (Table 3, 19-23). By contrast, reactions conducted with electron-rich aryltrimethylammonium triflates were sluggish and generated the desired products at low yields (Table 3, 24–25). For example, 19 was obtained at the yield of 73% when 4-fluorophenyltrimethylamonium triflate was used, whereas 24 was obtained at the yield of 25% when 4methylphenyltrimethylamonium triflate was utilized. The low yield in the case of 4-ethoxycarbonyl-phenyltrimethylamonium triflate was attributed to the decomposition of ester groups under the employed conditions (Table 3, 28).²⁸ Some interesting tolerances of functional groups, including fluoro, chloro, ether, amine, amide, cyano, pyridinyl and thiophene groups, were noted.

Interestingly, amines can be directly alkynylated through a two-step one-pot process. For example, dimethylaniline can be converted to **3** with a 73% overall yield via methylation by methyl triflate followed by the Pd-catalyzed Sonogashira reaction with 4-ethynyltoluene (Scheme 2).

Furthermore, 0.7 g of **3** was obtained (yield: 75%) when the reaction scale of the alkynylation of **1a** with **2** was enlarged 10 times. This yield is comparable with the yield of the small-scale reaction (Scheme 3).

We also performed the competition experiments of the Sonogashira reaction with the Heck and Hiyama reaction (Scheme 4). Competition between vinyl and ethynyl group showed that only the arylation of ethynyl occurred in the reaction of 1-ethynyl-4-vinylbenzene with **1a**. Likewise, in the reaction of (4-ethynylphenyl)trimethylsilane with **1a**, the TMS group remained intact, whereas acetylene underwent arylation.

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Figure 2. DFT-optimized structures of selected intermediates and transition states for the Pd-catalyzed C-C coupling reaction. All the H atoms are hidden for simplicity.

To gain insight into the reaction mechanism, we performed DFT studies with Gaussian 09 package.²⁹ The reaction shown in Scheme 5 was chosen as a representative for the mechanistic investigation. BP86³⁰ and a mixed basis set of SDD for Pd and 6-31G(d,p) for other atoms were used in geometry optimizations and frequency calculations. Single-point energies were calculated with M06³¹ and a mixed basis set of SDD for Pd and 6-31++G(d,p) for other atoms. Solvation energy corrections were calculated using the SMD³² model with THF as the solvent. Note that the catalytic precursor (SIPr)(Py)Pd(II)(Cl)₂ can be easily reduced to Pd(0) species under the experimental condition (*t*-BuONa). Accordingly, (SIPr)Pd(0)(Py) was employed as the active catalyst in the following computational studies.

Scheme 5 illustrates our proposed catalytic cycle, which can be characterized by four steps, namely, oxidative addition (step 1), substrate coordination (step 2), deprotonation (step 3), and C-C reductive elimination to provide the final coupling product (step 4). The free energy profiles for steps 1-4 are presented in Figure 1.

39 As shown in Figure 1, the 14e Pd(0) catalyst IN1 initially 40 undergoes substrate coordination leading to the 16e π -bound 41 complex IN2 [(SIPr)Pd(Py)(η^2 -PhNMe₃)⁺]. Relative to the 42 active catalyst IN1, the coordination is thermodynamically 43 unfavorable by 6.6 kcal/mol. Then, the oxidative addition of 44 quaternary ammonium (Ph-NMe₃)⁺ takes place via transition 45 state **TS1** ($\Delta G^{\neq} = 23.8$ kcal/mol) giving the T-shaped Pd(II) 46 intermediate IN3 and releasing NMe3. The oxidative addition 47 occurs through an S_N2 back-side attack type transition state, where the optimized structures of TS1 and its precursor IN2 are 48 shown in Figure 2. This is different from the general mechanism 49 in Pd-catalyzed oxidative addition of R-X (X = Cl, Br, or I), for 50 which this-type transition state (i.e., TS1' in Figure 1) is 9.1 51 kcal/mol higher than that of TS1. The higher energy barrier of 52 TS1' may attribute to the steric influence arising from the bulky 53 NMe₃ group. Complex **IN3** could isomerize to its more stable 54 isomer IN4 or IN5. The coordination of the PhC=CH substrate 55 to Pd(II) center transforms IN4 to IN6 to facilitate the 56 succeeding deprotonation and C-C coupling. Control reactions 57 shown in Table 2 (Entry 1 and 5) indicate that the sodium tertbutoxide acts as base to deprotonate the C-H bond. However, the transition state for the deprotonated $H-C(\equiv CPh)$ step assisted by t-BuO⁻ in IN6 appears nonexistent, as the attempted optimizations all converged to IN8 + t-BuOH. This is probably due to an extremely flat potential energy surface arising from that the activation of alkyne C-H bond by the strong base t-BuO- is too easy to occur, and tracking the C-H bond deprotonation process by means of scan coordinates analysis demonstrates this point (see Figure S1 in Supporting Information for detail). The deprotonated step is highly exergonic by 49.2 kcal/mol. Although IN5 is more stable than Pd(II) intermediates IN4 and IN6, it will not have an important effect on the energy profile, because the deprotonated product (IN9) derived from IN5 must isomerize to IN8 to promote C-C coupling. Finally, IN8 undertakes feasible reductive elimination at the Pd(II) center (TS2, $\Delta G^{\neq} = 10.3$ kcal/mol) to form a new carbon-carbon bond (Figures 1 and 2), providing the cross-coupling product and regenerating the active catalyst IN1.

Taken the complete reaction pathway into consideration (Figure 1), the C–N oxidative addition of substrate Ph-NMe₃⁺ (**TS1**) is found to be the turnover-limiting step, which is 23.8 kcal/mol. This energy barrier would be achievable at the experimental condition (45 °C), thereby accounting for the good yield of the reactions shown in Table 3 (up to 93 % yield). In addition, the transformation shown in Figure 1 is highly exergonic (–77.7 kcal/mol), driving the reaction into next catalytic cycle.

CONCLUSION

In conclusion, the Pd–NHC-catalyzed cross-coupling of terminal alkynes with aryltrimethylammonium triflate was established. To the best of our knowledge, this transformation is the first example of the alkynylation of quaternary ammonium salts. The reaction occurred under mild conditions with stoichiometric ratios of reactants and provided moderate to good product yields. A variety of alkyl, aryl, and heteroaryl substituents on the alkyne substrate can be used, and many useful functional groups can be tolerated. Amines can be directly alkynylated through a one-pot process without the isolation of ammonium salts. The protocol is compatible on a gram scale. Computational mechanistic studies indicated that the reaction occurred through oxidative addition, alkyne coordination, deprotonation, and C–C reductive elimination, which yielded the final cross-coupling product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, $^1\,\mathrm{H}$ and $^{13}\mathrm{C}$ NMR spectra, and DFT results.

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Notes

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The authors declare no competing financial interest.

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TOC graphic

 $R^{1} \xrightarrow{Z} \stackrel{H}{\longrightarrow} OTf + H \longrightarrow R^{2}$ 1 ea. 1 eq.

SIPr-PdCl₂-Py (10 mol%) t-BuONa (2-3 eq.), THF, N₂ 45-70 °C, 4-24 h (Z = CH, N; R¹ = H, F, Cl, CH₃, CF₃, CN, COOEt,; R² = aryl or alkyl)

33 examples up to 93% yield