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Palladium-Catalyzed Construction of Amidines from Arylsilanes in the absence of Ligand under Oxidative Conditions

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Abstract: An interesting palladium-catalyzed procedure on the synthesis of amidines from arylsilanes, isocyanides and amines has been developed. Moderate to good yields of the desired amidines were produced in the absence of phosphine ligand under oxidative conditions.

Amidine is a class of important chemicals which have been widely used as antibiotics, diuretics, antiphlogistic drugs, anthelmintics and acaricides.[1] Amidines have also been applied as valuable synthons for the preparation of azacyclic compounds in organic synthesis as well.[2] Considering their importance, various synthetic procedures have been established for their preparation. Traditionally, amidines can be synthesized by the addition of amines to nitriles or imido ester intermediates or by the condensation of amides with amines.[3] However some disadvantages such as limited substrates scope, relatively harsh reaction conditions and etc. limited their applications in nowadays.

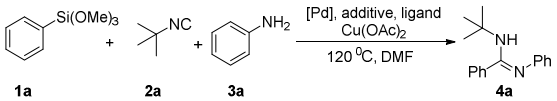
On the other hand, palladium known as the metal of the 21st century, its catalysts have been widely applied in cross-coupling chemistry and also many other topics.[4] In general, there are three types of reaction pathways for the palladium-catalyzed reactions. They are: 1) Pd(0)→Pd(II)→Pd(0); 2) Pd(II)→Pd(0)→Pd(II); 3) Pd(II)→Pd(IV)→Pd(II). The first type of Pd(0) initiated chemistry usually requires inert gas protection, addition of expensive ligands and under basic reaction conditions. These conditions which will surely increase the manipulation complexity and prevent the usage of base sensitive functional group substituted substrates. The third type of transformation pathway requires strong oxidant to oxidize Pd(II) to Pd(IV). This pathway is quite useful for certain type of reaction, such as C-F bond formation, as the reductive elimination from Pd(IV) is much easier. However, its limitations are obvious as well. The second type of pathway is an interesting option, as the oxidant needed is milder and no inert gas protection or ligand addition is required.

Not surprisingly, methodologies for amidines synthesis using palladium-catalyzed isocyanides insertion were developed. As early as in 1986, the cross-coupling of bromobenzene, *tert*-butyl isocyanide and organotin reagents was reported and 22 % of the desired amidine was formed.[5] In 2000, Whitby and co-workers developed a procedure with aryl bromides, isocyanides and amines as the starting materials.[6] Good yields of the desired amidines can be obtained. Later on, they also succeed to extend the substrates of their methodology to alkenyl bromides to produce *α,β*-unsaturated amidines and cyclic amidines. In 2016, we developed a palladium-catalyzed procedure based on the cross-coupling of arylboronic acids, isocyanides and anilines.[7] Under air and with copper salt as the terminal oxidant, various amidines were isolated in good yields.

In order to further extend the toolbox for amidines synthesis, we become interested to explore the possibility on using arylsilanes as the substrates. In general, organosilicon compounds have several unique advantages in the respect of stability, solubility, nontoxicity, and easy-handling.[8] In this communication, we wishes to report our new results on palladium-catalyzed cross-coupling of arylsilanes, isocyanides and amines for the synthesis of amidines. In this system, no addition of phosphine ligand or inert gas protection is required.

Initially, we choose trimethoxyphenylsilane, *tert*-butyl isocyanide and aniline as the model substrates to establish this catalytic system. With $Pd(OAc)_2$ and DPPF as the catalyst, different fluoride sources were tested and the desired amidine can be obtained with KF as the activator (Table 1, entries 1-3). Then different phosphine ligands were tested in order to improve the catalytic activity, however, no significant variation on the yields can be detected (Table 1, entries 4-7). To our surprise, no product could be detected by replacing $Cu(OAc)_2$ with $Cu(acac)_2$ or $CuCl_2$ (Table 1, entries 8 and 9). And if increasing the loading of DPPF from 5 mol% to 10 mol%, the reaction was totally inhibited (Table 1, entry 10). This result implies that phosphine ligand may have no effect or even negative effect on this transformation. Hence, a reaction in the absence of phosphine ligand was carried out and 41% of the desired amidine was formed (Table 1, entry 11). Then different palladium precursors were checked (Table 1, entries 12-16) and 69% of the corresponding product can be produced with $PdCl_2$ as the catalyst (Table 1, entry 12). Concerning the amount of isocyanide, one and two equivalents of it were tested respectively; the yields were decreased in both cases.

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a 4a

Entry	[Pd]/Ligand	Additive	Yield (%)[b]
1	$Pd(OAc)_2$/dppf	TBAF	-
2	$Pd(OAc)_2$/dppf	AgF	-
3	$Pd(OAc)_2$/dppf	KF	38
4	$Pd(OAc)_2$/DPEPhos	KF	37
5	$Pd(OAc)_2$/XantPhos	KF	35
6[c]	$Pd(OAc)_2$/PPh_3	KF	35
7	$Pd(OAc)_2$/DPPE	KF	26
8[d]	$Pd(OAc)_2$/dppf	KF	-

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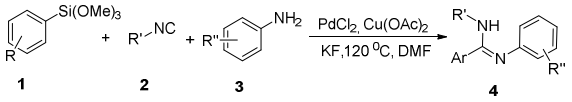
9[e]	$Pd(OAc)_2$/dppf	KF	-
10[f]	$Pd(OAc)_2$/dppf	KF	-
11	$Pd(OAc)_2$	KF	41
12	$PdCl_2$	KF	69
13	$Pd(TFA)_2$	KF	-
14	$Pd(CH_3CN)_2Cl_2$	KF	42
15	$Pd(COD)Cl_2$	KF	48
16[g]	[(Cinnamyl)PdCl]$_2$	KF	56

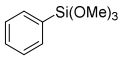
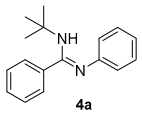
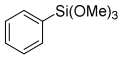
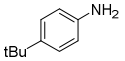
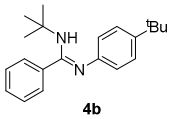
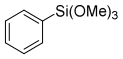
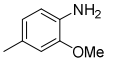
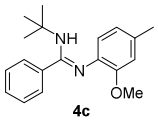
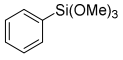
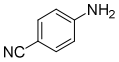
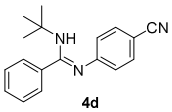
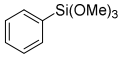
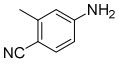
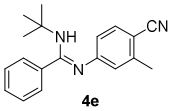
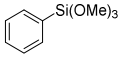
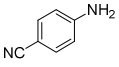
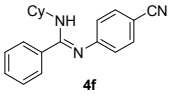
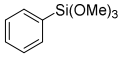
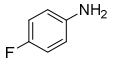
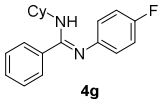
[a] **1a** (0.2 mmol), **2a** (0.3 mmol), **2a** (0.3 mmol), [Pd] (5 mol%), ligand (5 mol%), $Cu(OAc)_2$ (0.4 mmol), DMF (2 mL), additive (0.4 mmol), 24 h. [b] GC yields using hexadecane as internal standard. [c] PPh_3 (10 mol%). [d] $Cu(acac)_2$ (0.4 mmol). [e] $CuCl_2$ (0.4 mmol). [f] dppf (10 mol%). [g] [Pd] (2.5 mol%). dppf: 1,1′-bis(diphenylphosphino)ferrocen. DPEPhos: bis(2-diphenylphosphinophenyl)ether. XantPhos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. DPPE: 1,2-bis(diphenylphosphino)ethan.

With the best reaction conditions in hand, the testing of substrates was performed (Table 2). The testing of amines was carried out firstly. Basically, all the tested anilines can give the desired amidines with various functional groups (Table 2, entries 1-10). In the case of aliphatic amines, no desired product could be detested with cyclohexylamine. However, around 30% of the desired product can be formed with piperidine as the reaction partner (Table 2, entry 11). But the product is too sensitive to be isolated. In addition to *tert*-butyl isocyanide, cyclohexyl isocyanide can be used as well (Table 2, entries 6-10, 18). Then, the testing of various arylsilanes was performed (Table 2, entries 12-18). Moderate to good yields can be achieved in all the tested cases.

Table 2. Pd-catalyzed amidines synthesis from arylsilanes.[a]



1 2 3 4

Entry	Arylsilanes	isocyanides	Amines	Products	Isolated yield
1		*t*BuNC	$PhNH_2$	 **4a**	67%
2		*t*BuNC		 **4b**	61%
3		*t*BuNC		 **4c**	55%
4		*t*BuNC		 **4d**	68%
5		*t*BuNC		 **4e**	66%
6		CyNC		 **4f**	61%
7		CyNC		 **4g**	63%

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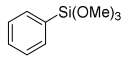
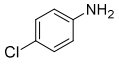
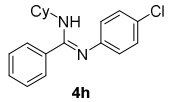
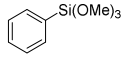
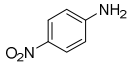
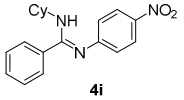
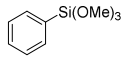
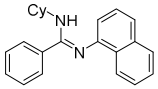
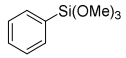
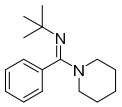
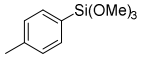
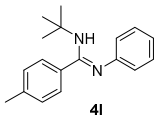
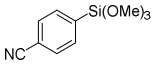
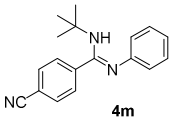
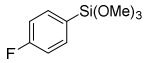
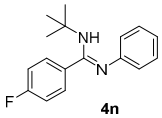
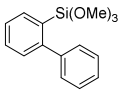
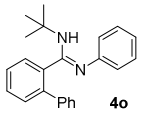
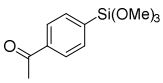
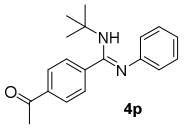
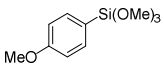
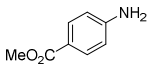
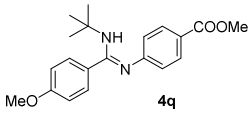
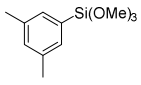
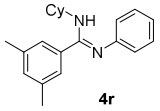
8		CyNC		 **4h**	64%
9		CyNC		 **4i**	47%
10		CyNC		 **4j**	57%
11		*t*BuNC		 **4k**	<30%[b]
12		*t*BuNC	$PhNH_2$	 **4l**	67%
13		*t*BuNC	$PhNH_2$	 **4m**	64%
14		*t*BuNC	$PhNH_2$	 **4n**	58%
15		*t*BuNC	$PhNH_2$	 **4o**	53%
16		*t*BuNC	$PhNH_2$	 **4p**	58%
17		*t*BuNC		 **4q**	58%
18		CyNC	$PhNH_2$	 **4r**	57%

[a] **1** (0.2 mmol), **2** (0.3 mmol), **2** (0.3 mmol), $PdCl_2$ (5 mol%), $Cu(OAc)_2$ (0.4 mmol), DMF (2 mL), KF (0.4 mmol), 24 h, isolated yield. [b] NMR yield using mesitylene as internal standard.

Concerning the reaction pathway, a possible reaction mechanism is proposed in Scheme 1.[9] The reaction starts with Pd(II), then transmetalation with fluoride activated arylsilane to

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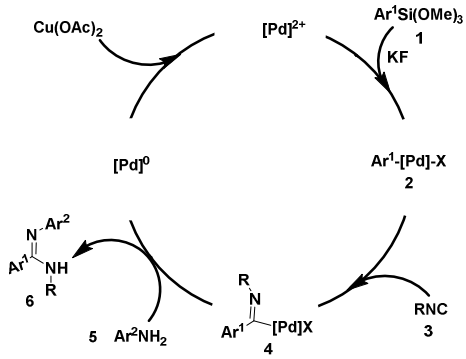
give the corresponding aryl-palladium intermediate. After the insertion of isocyanide, nucleophilic attract of anilines take place which will provide the terminal product after rearrangement. The Pd(0) will be oxidized back to Pd(II) for the next catalyst cycle.



Scheme 1. Proposed reaction mechanism.

In conclusion, an interesting palladium-catalyzed procedure for the synthesis of amidines from arylsilanes, isocyanides and amines has been developed. Moderate to good yields of the desired amidines were produced in the absence of phosphine ligand under oxidative conditions.

Acknowledgements

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General procedure: In a 5 mL pressure tube equipped with a stirring bar, trimethoxyphenylsilane (0.2 mmol), $Cu(OAc)_2$ (0.4 mmol), $PdCl_2$ (5 mol%), KF (0.4 mmol), isocyanide (0.3 mmol), aniline (0.3 mmol) and DMF (2 mL) were added. Then close the tube and heat it up to 120 ℃ for 1 day. Cool the reaction mixture to room temperature when the reaction completed. The reaction solution was quenched with distilled water and extracted with ethyl acetate three times. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. The crude product was purified by column chromatography (ethyl acetate/pentante = 1:10) to give the pure product.

Keywords: Palladium catalyst • Domino reaction • Amidines synthesis • Isocyanide • CO surrogate

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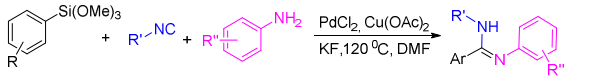
Graphic Abstract



An interesting palladium-catalyzed procedure for the synthesis of amidines from arylsilanes, isocyanides and amines has been developed.

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