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Palladium-Catalyzed Cross Coupling Reaction of *N*-Alkoxyimidoyl Bromides and Its Application to One-Pot Synthesis of *N*-Arylamines

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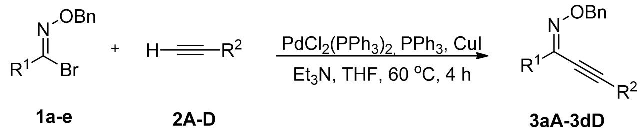
The synthetic utility of *N*-alkoxyimidoyl halides is demonstrated using the palladium-catalyzed cross-coupling reaction. The Sonogashira and Suzuki–Miyaura coupling reactions of *N*-alkoxyimidoyl bromides produced versatile ketoxime ethers in good to excellent yields. A one-pot reaction of the imidoyl bromides with arylboronic acid and allylmagnesium bromide to produce *N*-arylamines *via* Suzuki–Miyaura coupling followed by domino reaction involving sequential addition-eliminative rearrangement-addition reactions was developed.

Key words imidoyl bromide; Suzuki–Miyaura coupling; Sonogashira coupling; one-pot reaction; *N*-arylamine

Imidoyl halides are often used as a versatile scaffold in organic synthesis.[1,2] In particular, *N*-alkyl or *N*-arylimidoyl halides are utilized in transition metal-catalyzed cross-coupling reactions.[3—8] In contrast, although the substitution reactions of *N*-alkoxyimidoyl halides with nucleophiles such as carbanion,[9] alkoxide,[10,11] amine,[12,13] azide[14] and halogen[15,16] have been developed, the catalytic cross-coupling reaction is less studied, despite the fact that the oxime ethers produced are useful intermediates for the syntheses of amines and heterocycles.[17—20] Kim and Chang's group reported that *N*-alkoxyimidoyl halides are efficient coupling partners in the Stille reaction.[21] Weinreb and co-workers also reported the palladium-catalyzed coupling reaction of *N*-methoxyimidoyl bromide bearing imidazole with vinylstannane proceeded with relatively lower yield, however no desired coupling product was obtained in the reaction with boronic acid or organozinc halide due to the undesirable formation of nitrile by elimination.[22] Although a few examples exist where Suzuki–Miyaura coupling has been employed for the synthesis of biologically active compounds by pharmaceutical companies,[23—25] systematic research focused on the reactivity of *N*-alkoxyimidoyl halides has not been reported. Moreover, one-pot transformation of the coupling product, which would demonstrate the potential utility of this reaction, has never been reported. Furthermore, the Sonogashira coupling reactions of *N*-alkoxyimidoyl halides have not yet been described in the literature.[26,27] Herein, we report Sonogashira[28,29] and Suzuki–Miyaura[30,31] coupling reactions of *N*-alkoxyimidoyl bromide and their application to one-pot reactions of the resulting oxime ether with allylmagnesium bromide in connection with our recent efforts to synthesize *N*-alkyl arylamines by domino reaction with organometallic reagents.[32—34]

Table 1. Sonogashira Coupling of *N*-Alkoxyimidoyl Bromide **1**[a)]



Entry	R^1	R^2	Product	Yield (%)[b)]
1	Ph (**1a**)	TMS (**2A**)	**3aA**	79
2	Ph (**1a**)	Ph (**2B**)	**3aB**	71
3	Ph (**1a**)	*n*-Bu (**2C**)	**3aC**	79
4	Ph (**1a**)	$\mathrm{CH_2OTBS}$ (**2D**)	**3aD**	73
5	2-Furyl (**1b**)	TMS (**2A**)	**3bA**	67
6	4-$\mathrm{CF_3C_6H_4}$ (**1c**)	TMS (**2A**)	**3cA**	91
7	2-Furyl (**1b**)	$\mathrm{CH_2OTBS}$ (**2D**)	**3bD**	66
8	4-$\mathrm{CF_3C_6H_4}$ (**1c**)	$\mathrm{CH_2OTBS}$ (**2D**)	**3cD**	90
9	4-$\mathrm{MeOC_6H_4}$ (**1d**)	$\mathrm{CH_2OTBS}$ (**2D**)	**3dD**	Quant.
10	c-Hexyl (**1e**)	$\mathrm{CH_2OTBS}$ (**2D**)	—	Complex mixture

a) Reactions were carried out with acetylene (2.0 eq), $\mathrm{PdCl_2(PPh_3)_2}$ (4 mol%), $\mathrm{PPh_3}$ (8 mol%) and CuI (8 mol%) and $\mathrm{Et_3N}$ in THF. *b*) Isolated yields.

We initially studied palladium-catalyzed reactions with alkynes (Table 1). Treatment of (*Z*)-*N*-benzyloxyimidoyl bromide **1a**[35] with (trimethylsilyl)acetylene (**2A**), $\mathrm{PdCl_2(PPh_3)_2}$ (4 mol%), $\mathrm{PPh_3}$ (8 mol%), CuI (8 mol%) and $\mathrm{Et_3N}$ in tetrahydrofuran (THF) at 60 °C led to efficient Sonogashira coupling to give (*Z*)-alkynyl oxime ether **3aA**[36] in 79% yield (entry 1). The reaction not only occurs with (trimethylsilyl)acetylene (**2A**) but also with phenylacetylene (**2B**) (entry 2) as well as with alkynes substituted by aliphatic groups **2C** and **2D** (entries 3 and 4), producing the corresponding (*Z*)-alkynyl oxime ethers **3aB**—**3aD** in good yields. Variation of the substituent for R^1 was then examined. We were pleased to observe that electron-rich and electron-poor aryl groups were readily accommodated (entries 5—9), while imidoyl bromide **1e**, which contains the cyclohexyl group as R^1, did not undergo detectable coupling reaction and thus led to an unidentified complex mixture probably due to decomposition of **1e** (entry 10). It is noteworthy that excellent chemical yield was observed in the reaction of substrate **1d** bearing a *p*-methoxylphenyl group (entry 9). The alkynyl oxime ethers produced can be used for both synthesis of isoxazoles and radical reactions.[18,37,38]

We next focused our attention on the Suzuki–Miyaura reaction of imidoyl bromide. After simple screening of catalysts, ligands, bases, solvents and reaction temperature, the optimal reaction conditions were found to be boronic acid (2.0 eq), $\mathrm{Pd(OAc)_2}$ (10 mol%), $\mathrm{PPh_3}$ (20 mol%) and $\mathrm{Cs_2CO_3}$ (5.0 eq) in refluxing toluene (Table 2). The coupling reaction of (*Z*)-*N*-benzyloxyimidoyl bromide **1a** with phenylboronic acid (**4A**) proceeded smoothly to afford the desired oxime ether **5aA** in 74% yield with retention in the double-bond geometry (entry 1).[36] Interestingly, replacement of the benzyl group with a methyl group improved the chemical yield, thus *O*-methyl oxime **5fA** was obtained in 82% yield (entry 2). The electronic and steric effects were then evaluated by using various arylboronic acids. Phenylboronic acids carrying electronic donating (methoxy, methyl) and withdrawing groups (trifluoromethyl, chloro) at the *para* or *meta* positions gave good to excellent yields of coupling products **5fB**—**5fD** and **5fG—5fI**, respectively (entries 3—5 and 8—10). It is not clear why employing electron poor boronic acid bearing

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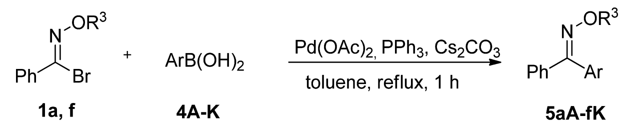
Table 2. Suzuki–Miyaura Coupling of *N*-Alkoxyimidoyl Bromide **1**[a)]



Entry	Substrate	R^3	Ar	Product	Yield (%)[b)]
1	**1a**	Bn	Ph (**4A**)	**5aA**	74
2	**1f**	Me	Ph (**4A**)	**5fA**	82
3	**1f**	Me	4-$MeOC_6H_4$ (**4B**)	**5fB**	91
4	**1f**	Me	4-MeC_6H_4 (**4C**)	**5fC**	85
5	**1f**	Me	4-$CF_3C_6H_4$ (**4D**)	**5fD**	77
6[c)]	**1f**	Me	4-CNC_6H_4 (**4E**)	**5fE**	14
7[d)]	**1f**	Me	4-$CO_2MeC_6H_4$ (**4F**)	**5fF**	4
8	**1f**	Me	4-ClC_6H_4 (**4G**)	**5fG**	77
9	**1f**	Me	3-$MeOC_6H_4$ (**4H**)	**5fH**	87
10	**1f**	Me	3-$CF_3C_6H_4$ (**4I**)	**5fI**	96
11[d)]	**1f**	Me	2-MeC_6H_4 (**4J**)	**5fJ**	21
12	**1f**	Me	2-Naphthyl (**4K**)	**5fK**	82

a) Reactions were carried out with boronic acid (2.0 eq), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 (5.0 eq). *b*) Isolated yields. *c*) Reaction time was 6 h. *d*) Reaction time was 3 h.

p-cyanophenyl (**4E**) or *p*-methoxycarbonylphenyl groups (**4F**) resulted in a marked drop in yields (entries 6 and 7). The sterically demanding 2-methylphenylboronic acid (**4J**) proved to be a difficult substrate (entry 11). 2-Naphthylboronic acid was also employed in this reaction (entry 12), affording oxime ether **5fK** in 82% yield.

To demonstrate the synthetic utility of *N*-alkoxyimidoyl bromides as highly versatile building blocks, we investigated their one-pot transformation *via* Suzuki–Miyaura coupling reaction and domino reaction involving sequential addition-eliminative rearrangement-addition into *N*-alkyl arylamines containing a quaternary carbon (Table 3). After completion of Suzuki–Miyaura coupling of **1f** with phenylboronic acid **4A** as described in Table 2, allylmagnesium bromide (4 eq) was added to the reaction vessel and the reaction mixture was stirred in refluxing toluene. The simple procedure provided (diallyl)methyl amine **6A** in 85% yield (entry 1). The one-pot reaction with 4-methoxyphenylboronic acid (**4B**) produced **7B** in good yield *via* rearrangement of the 4-methoxyphenyl group onto the nitrogen atom (entry 2). In contrast, when 4-trifluoromethylphenylboronic acid (**4D**), an electron-deficient coupling partner, was employed, selective migration of the phenyl group was observed to afford **6D**, albeit in lower yield (entry 3). The chloro group did not affect the course of the reaction, thus chemoselective migrative allylation gave **6G** in 59% yield.

In summary, we have shown the synthetic utility of *N*-alkoxyimidoyl halides using the palladium-catalyzed cross coupling reaction. The Sonogashira and Suzuki–Miyaura coupling of *N*-alkoxyimidoyl bromides produced ketoxime ethers, which are versatile synthetically. The Suzuki–Miyaura coupling reaction was successfully applied to the one-pot synthesis of *N*-alkyl arylamines containing a quaternary carbon *via* domino reaction with allylmagnesium bromide.

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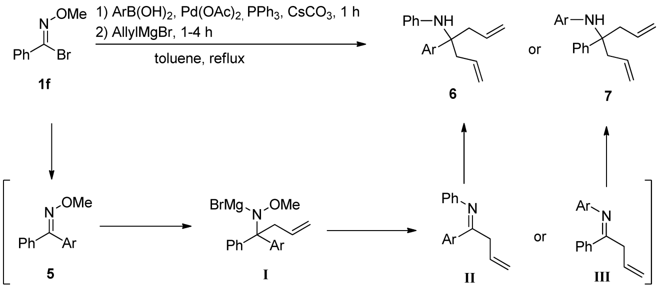
Table 3. One-Pot Synthesis of *N*-Arylamines from *N*-Methoxyimidoyl Bromide **1f**[a)]



Entry	Ar	Product	Yield (%)[b)]
1	Ph (**4A**)	**6A**	85
2	4-$MeOC_6H_4$ (**4B**)	**7B**	68
3	4-$CF_3C_6H_4$ (**4D**)	**6D**	31
4	4-ClC_6H_4 (**4G**)	**6G**	59

a) Reactions were carried out with boronic acid (2.0 eq), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), $CsCO_3$ (5.0 eq) and then allylMgBr (4.0 eq). *b*) Isolated yields.

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