N-Alkoxyimidoyl Bromides as a New and Efficient Coupling Partner in Pd-Catalyzed Stille Reaction

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Abstract: *N*-Alkoxyimidoyl bromides have been successfully employed as an efficient organic partner in the Pd-catalyzed Stille coupling reaction with various organotin compounds, and the corresponding *O*-alkyloximes were obtained in good to excellent yields.

Key Words: catalysis, cross-coupling, palladium, Stille reaction, tin

Stille cross-coupling reaction of organotin compounds with aryl halides and triflates is a powerful and widely used method for carbon-carbon bond formation.¹ Due to its prominent aspects such as excellent tolerance to various functional groups, ready availability of organotin compounds, retention of geometry during the reaction pathway, and high product yields, extensive studies have been carried out in order to find more efficient types of organic donors.² During the course of studies on the synthetic utility of certain oximyl ether derivatives,³ we surmised that N-alkoxyimidoyl halides could be utilized as an efficient organic donor in transition metal-catalyzed coupling reactions. Since the produced O-alkyloximes can be further utilized either as a valuable intermediate in organic synthesis⁴ or as a carbonyl equivalent in chemical transforamtions, easy and preparative methods for O-alkyloximes would be highly desirable.⁵ Although there have been some related examples of Pd-catalyzed coupling reactions with trifluoroacetimidoyl iodides^{6a} and imidoyl chlorides,^{6b} some limitations such as long reaction times (up to 63 h) or low to moderate product yields are apparently found. We have discovered that N-alkoxyimines can be produced with extremely high efficiency by the Pd-catalyzed coupling reaction of N-alkoxyimidoyl bromides with organotin compounds (Scheme), which will be described in this letter.⁷



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In our initial studies, N-benzyloxybenzimidoyl chloride⁸ was examined as a test substrate in the Pd-catalyzed coupling reaction with tributyl(vinyl)tin (2 equiv to imidoyl chloride) under various conditions. While the coupling was sluggish in the absence of additives in toluene under reflux, improved conversion and better yields for the desired product were observed by the addition of certain inorganic bases with the use of $Pd(PPh_3)_4$ as a catalyst. Among several bases examined, potassium fluoride (2 equiv to the halide) turned out to be the most efficient additive on the coupling reaction although the desired product, phenyl vinyl (O-benzyl)oxime, was still isolated in a rather unsatisfactory yield (1 h, 58%). Change of halide in substrate from chloride to bromide resulted in much cleaner reaction, and the coupled product was isolated in 90% yield from the reaction of N-benzyloxybenzimidoyl bromide in the presence of 2.0 equiv of KF (30 min). Other Pd catalysts such as Pd(OAc)₂/PR₃ (R=Ph, 2-Me-Ph, cyclohexyl) or $Pd_2(dba)_3$ effected the coupling reaction with much lower efficiency compared to $Pd(PPh_3)_4$. The coupling reaction proceeded slowly at temperatures lower than 110 °C (for example, 59% yield after 12 h at 80 °C) under otherwise identical conditions.

The Pd-catalyzed coupling reaction turned out to be general with respect to both organotin compounds and Nalkoxyimidoyl bromides (Table). N-Alkoxyimidoyl bromides used in this study were prepared in good yields (60-85%) from the reaction of the corresponding N-alkoxyamides with CBr₄/PPh₃ in acetonitrile (85 °C, 3–5 h).⁹ Not only olefinic groups could be readily transferred from tributyl(alkenyl)stannanes but also alkynyl (entry 3), allylic (entry 4), and aryl group (entry 5) were all smoothly coupled with the imidoyl bromides affording the corresponding *O*-alkyloximes in good to excellent yields.¹⁰ Electronic variation on the imidoyl bromide gave little effect on the efficiency of the coupling (entries 6-9). Cinnamylimidoyl bromide was also successfully employed as an efficient coupling partner in the Pd-catalyzed Stille reaction (entries 10-12). Methyl- (entry 13) and formyl imidoyl bromide (entry 14) also reacted with organotin compounds under the same conditions to provide coupled products in high yields.¹¹ Substrates having a different Nalkoxy group were similarly prepared⁹ and coupling reaction using those were examined to see the feasibility of the present coupling reaction. We were pleased to observe that N-methoxyimidoyl bromides were also efficiently coupled with various organotin compounds, and that the

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desired *O*-methyloxime compounds were obtained in good yields (entries 15–17). It is known that both *O*-benzyloximes³ and *O*-methyloximes¹² can be readily hydrolyzed to generate corresponding carbonyl compounds in high yields by aqueous HCl solution and a titanium reagent, respectively.

 Table
 Pd-Catalyzed Cross-Coupling Reaction of N-Alkoxyimidoyl

 Bromide with Organotin Compounds^a

N H $+ R_2$ $- S_2$		Pd(PPh ₃) ₄ (5 mol%) KF (2.0 equiv)		N OR ₂	
R ₁	Br (2.0 equiv)		toluene 110 °C	R ₁ R ₂	3
Entry	R ₁	\mathbf{R}_2	R ₃	Time	Yield (%) ^b
1	C_6H_5	Bn	н₂с=сн	30 min	90
2	C_6H_5	Bn	Me	30 min	71
3	C_6H_5	Bn	HC≡C	20 min	95
4	C ₆ H ₅	Bn		2 h	92
5	C_6H_5	Bn	C_6H_5	1 h	82
6	$(p-MeO)C_6H_4$	Bn	н₂с≕сн	1 h	97
7	$(p-MeO)C_6H_4$	Bn	MeC≡C	20 min	86
8	(p-MeO)C ₆ H ₄	Bn	Me	2 h	98
9	$(p-Cl)C_6H_4$	Bn	н₂С=СН	1 h	98
10	C ₆ H ₅	Bn	н₂с≕сн	1 h	97
11	C ₆ H ₅	Bn	Me	20 min	77
12	C ₆ H ₅	Bn	нс≡с	20 min	95
13	Me	Bn	H₂C≡СН	1 h	82
14	Н	Bn	н₂С=СН	3 h	62
15	$(p-Cl)C_6H_4$	Me	н₂С=СН	2 h	74
16	$(p-MeO)C_6H_4$	Me	н₂С=СН	1 h	99
17	(p-MeO)C ₆ H ₄	Me	Me	3 h	92

^a All reactions were carried out in 0.1 M concentration.

^b Isolated yields after purification by silica gel column chromatography.

In conclusion, it has been demonstrated that a series of *N*-alkoxyimidoyl bromides can be added as a new type of efficient coupling partner in the Pd-catalyzed Stille reaction, and various *O*-alkyloximes with unsaturated functional groups could be readily obtained in good to excellent yields from the coupling reactions.

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