

Lewis Acid Acceleration of C–N Bond-Forming Reductive Elimination from Heteroaryl Palladium Complexes and Catalytic Amidation of Heteroaryl Bromides

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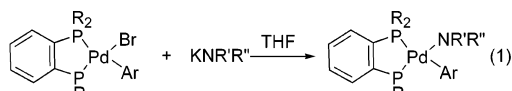
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Catalytic reactions of basic heteroaromatic reagents can be challenging because the ligating ability of the heteroatom can lead to catalyst deactivation and because the electronic properties of certain ring positions can be unfavorable for the elementary reactions required for the catalytic processes. These factors have particularly complicated the palladium-catalyzed coupling of amines¹ with heteroaryl halides.² We report a strategy to address these challenges. We show that the coordination of Lewis acids to the nitrogen of pyridylpalladium complexes leads to an acceleration of the rate of reductive elimination by more than 3 orders of magnitude and that this coordination can facilitate palladium-catalyzed coupling of amides with unactivated heteroaryl halides.³

We and others have observed that the coupling of heteroaryl halides with zinc and alkali metal reagents can be different.⁴ This observation led us to probe the potential effect of Lewis acids on the reactivity of isolated heteroaryl palladium amido complexes and on the catalytic coupling of heteroaryl halides with nitrogen nucleophiles. To do so, we compared the rates and yields of reductive elimination from pyridylpalladium amido complexes in the presence and absence of added Lewis acids.

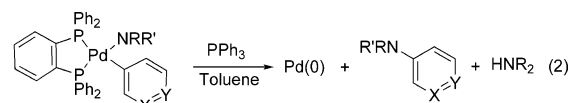
Equation 1 summarizes the synthesis of pyridylpalladium complexes in this study. Addition of KN(*p*-*t*-BuC₆H₄)₂ to DPPBz-ligated pyridyl- and *p*-tolylpalladium complexes **1**–**5** formed the diarylamido complexes **6**–**9**.⁵ Likewise, addition of KNMe(SO₂-Ar) formed the sulfonamides **10** and **11**. Complexes **6**–**11** were stable at room temperature and were characterized by conventional spectroscopic and microanalytical methods.



R = Ph, Ar = 4-Py, 1	R' = R'' = <i>p</i> - <i>t</i> -BuC ₆ H ₄	NR'R'' = N(Me)(SO ₂ Ph)
R = Ph, Ar = 3-Py, 2	R = Ph, Ar = 4-Py, 6	R = <i>p</i> -Tol, Ar = 4-Py, 10
R = Ph, Ar = 2-Py, 3	R = Ph, Ar = 3-Py, 7	NR'R'' = N(Me)(SO ₂ - <i>p</i> -Tol)
R = Ph, Ar = <i>p</i> -Tol, 4	R = Ph, Ar = 2-Py, 8	R = <i>p</i> -Tol, Ar = 4-Py, 11
R = <i>p</i> -Tol, Ar = 4-Py, 5	R = Ph, Ar = <i>p</i> -Tol, 9	

Reductive eliminations of the pyridyl- and arylpalladium amido complexes are summarized in eq 2. In the absence of Lewis acids, reductive elimination from 3-pyridyl- and 4-pyridylpalladium diarylamido complexes occurred in lower yields than from arylpalladium diarylamido complexes. Warming 4-pyridyl complex **6** at 90 °C in toluene for 10 h with added PPh₃ did not form the pyridyl diarylamine. Instead, free amine and biaryl products derived from the palladium-bound pyridyl and the phosphine phenyl groups formed. Likewise, reaction of the 3-pyridyl complex **7** required heating in toluene at 110 °C for 5 h and formed the triarylamine in a low 38% yield. Although reductive elimination from the DPPBz-ligated arylpalladium amido complexes is less favorable than that from complexes containing other phosphines,^{6,7} heating of *p*-tolylpalladium complex **9** in the presence of PPh₃ did form triarylamine in 50% yield after 8 h at 90 °C.

In contrast to the slow rates and low yields for formation of heteroaryl amines from reactions of **6** and **7** with phosphine alone,



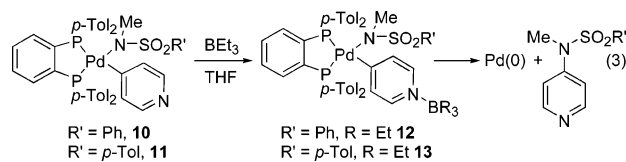
R=R' = <i>p</i> - <i>t</i> -BuC ₆ H ₄				
X=CH, Y=N (6)	without ZnCl ₂ , 90 °C, 10 h	0%	100%	
	with ZnCl ₂ (1.0 equiv), 90 °C, 10 min	90%	0%	
	with BEt ₃ (1.0 equiv), RT, 30 min	>90%	<5%	
X=N, Y=CH (7)	without BPh ₃ , 110 °C, 5 h	38%	62%	
	with BPh ₃ (1.0 equiv), 110 °C, 2 h	70%	30%	
R=Me, R'=SO ₂ Ph				
X=CH, Y=N (10)	without BEt ₃ , 110 °C, 24 h	<10%	90%	
	with BEt ₃ , (1.0 equiv), 110 °C, 1 h	80%	20%	
R=Me, R'=SO ₂ - <i>p</i> -Tol				
X=CH, Y=N (11)	without BEt ₃ , 110 °C, 24 h	<10%	90%	
	with BEt ₃ , (1.0 equiv), 110 °C, 1 h	81%	19%	

heating of **6** with PPh₃ and suspended ZnCl₂ in toluene solvent formed over 90% yield of 4-*N,N*-diarylaminopyridine after 10 min at 90 °C (eq 2). Because of the lack of solubility of ZnCl₂, we could not study the effect of this Lewis acid quantitatively. Thus, to obtain more quantitative data, we studied the reductive elimination of 4-pyridyl complex **6** in the presence of soluble boron Lewis acids.

Like ZnCl₂, BEt₃ accelerated the reductive elimination of heteroaryl amines from 4-pyridyl complex **6** (eq 2). Mixing of **6** with 1 equiv of BEt₃, followed by addition of PPh₃, led to reductive elimination at room temperature within 30 min to give the pyridyl di(*tert*-butylphenyl)amine in >90% yield. A similar effect of the Lewis acid on reductive elimination from the pyridylpalladium amidate complexes **10** and **11** was observed. Heating of **10** or **11** with BEt₃ at 110 °C for 30–60 min formed the *N*-pyridyl sulfonamide in 80 and 81% yields. In the absence of Lewis acid, little reaction occurred after 1 h; after 24 h at 110 °C, the complex was consumed but <10% yield of coupled product was observed.

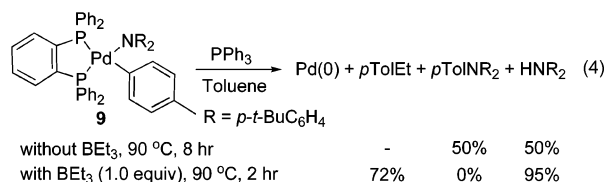
Boron Lewis acids also accelerated reductive elimination from 3-pyridylpalladium amide **7**, but the magnitude of this effect was smaller than that for reductive elimination from 4-pyridyl complex **6**. Heating a toluene solution of **7** with 1 equiv of BPh₃ and excess PPh₃ at 90 °C for 2 h formed the corresponding triarylamine in 70% yield instead of the 38% yield that was observed after 5 h in the absence of Lewis acid (eq 2).

To define the origin of the effect of the Lewis acid more explicitly, the product from interaction of BEt₃ with a heteroaryl palladium complex was isolated. Because the amide complexes are unstable after coordination of the Lewis acid, we were unable to isolate the BEt₃ adduct of the 4-pyridylpalladium amide complex. However, addition of BEt₃ to a THF solution of sulfonamidate **10** formed a stable complex **12** containing borane coordinated at the nitrogen of the pyridyl group (eq 3). Complex **12** was characterized by ¹H NMR, ³¹P NMR, and ¹¹B NMR spectroscopy. The ¹¹B NMR resonance at δ 1.0, which lies in the range of chemical shifts that are characteristic of R₃B·Py complexes,⁸ indicated that the boron was bound to nitrogen. This assignment was confirmed by X-ray diffraction, although the quality of the data was not high enough to obtain detailed structural information. Heating of this adduct in



toluene for 2 h at 90 °C formed the *N*-methyl-*N*-4-pyridyl sulfonamide in 80% yield.

Although the most stable adduct contains the Lewis acid at the pyridyl nitrogen, reductive elimination need not occur through this species. To distinguish an effect of the Lewis acid by coordination to the pyridyl nitrogen from an effect from coordination to the amido nitrogen or the metal center, we heated the *p*-tolylpalladium complex **9** in the presence of the Lewis acid. Acceleration of C–N reductive elimination by the Lewis acid was not observed. Warming of **9** with 1 equiv of BEt₃ in the presence of PPh₃ at 90 °C for 2 h formed 4-ethyltoluene in 72% yield from exchange of the amido and Lewis acid groups (eq 4). Warming of **9** with 1 equiv of BEt₃ in the absence of PPh₃ at 110 °C for 2 h formed 4-ethyltoluene in 57% yield. Thus, the accelerating effect of the Lewis acid on the reductive eliminations from the 4-pyridyl complex **6** appears to result from coordination of the Lewis acid to the pyridyl nitrogen.



The Lewis acids did not affect the rate or yield of reductive elimination of 2-pyridylpalladium amides. Reductive elimination from the 2-pyridylpalladium complex **8** is relatively fast in the absence of Lewis acids (heating of **8** at 70 °C for 5 h gave the 2-pyridyl diarylamine in 95% yield), and the nitrogen is sterically hindered. Further, the Pd–C–N bond angle in the solid-state structure of **8** is only 115.3°, which suggests the presence of a weak interaction of the pyridyl nitrogen with the palladium.

The rate of reductive elimination increased with increasing strength of the Lewis acids. Table 1 summarizes rates of reaction of the heteroaryl palladium amidate **11** in the presence of BEt₃, BPh₃, and B(C₆F₅)₃. The complex containing BPh₃ reacted nearly 12 times faster than the complex containing BEt₃, and the complex containing B(C₆F₅)₃ reacted even faster.

To probe whether this acceleration of reductive elimination could affect catalytic processes, we studied the effect of Lewis acids on the amidation of aryl halides. In principle, this effect could be used to improve these reactions conducted with any ligand. Data on couplings in the presence and absence of added BEt₃ for reactions conducted with the Xantphos ligand commonly used for the amidation of haloarenes⁹ are shown in Table 2. The reactions of heteroaryl bromides with amides in the presence of K₃PO₄ as base and Pd(dba)₂/Xantphos as catalyst in toluene solvent occurred to full conversion. The reactions formed the coupled product in 57–91% yields in the presence of 1.0 equiv of BEt₃ and in similar yields with substoichiometric BEt₃ in the example tested. Reactions under the same conditions but without Lewis acid occurred to lower conversions and formed the products in 5–63% yield.¹⁰ Products from ethyl group transfer were formed in less than 10% yield when BEt₃ was used. Further investigation of the scope of C–N coupling in the presence of Lewis acids will be part of future studies.

In summary, we report the promotion of reductive elimination from several heteroaryl palladium amido complexes by Lewis acids. This effect is most similar to the Lewis acid acceleration of the reductive elimination of nitriles during catalytic hydrocyanation by

Table 1. Rate Constants for Reductive Eliminations from Pyridylpalladium Sulfonamide **11** in the Presence of Different Lewis Acids

entry	Lewis acid	temp (°C)	<i>k</i> (s ⁻¹ × 10 ⁻⁴)	<i>t</i> _{1/2} (min)
1	BEt ₃	90	7.7 (0.8)	15
2	BEt ₃	70		~170
3	BPh ₃	70	8.3 (0.2)	14
4	B(C ₆ F ₅) ₃	40	6.8 (0.5)	17

Table 2. Palladium-Catalyzed Amidation of Heteroaryl Halides in the Presence of Lewis Acids

Product	Yield ^a with added BEt ₃ (%)	Yield ^b without added BEt ₃ (%)
84%	83% ^d (17%)	
74%, 99% ^b	63%	
91%	41%	
88%	17%	
57% ^c	<5%	

^a Isolated yield from an average of at least two runs; the borane is removed during chromatography. ^b Yield by GC with an internal standard. ^c 48 h. ^d BEt₃ (20 mol %) was used.

binding to the cyanide ligand.¹¹ The origin of the effect of Lewis acids on the C–N reductive elimination is likely to result from the creation of an electron-poor aryl group by Lewis acid binding; reductive elimination of arylamines is known to be faster from arylpalladium complexes containing more electron-poor aryl groups.⁶ Studies to define the origin and scope of this effect are ongoing.

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Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) The rate of the catalytic reactions was affected by whether the catalyst or reagents were added first. Further study is needed to optimize conditions, but the Lewis acid accelerated reactions conducted with either order.
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