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

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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 amines<sup>1</sup> with heteroaryl halides.<sup>2</sup> We report a strategy to address these challenges. We show that the coordination of Lewis acids to the nitrogen of pyridylplatinum 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.<sup>3</sup>

We and others have observed that the coupling of heteroaryl halides with zinc and alkali metal reagents can be different.<sup>4</sup> This observation led us to probe the potential effect of Lewis acids on the reactivity of isolated heteroarylplatinum 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 pyridylplatinum amido complexes in the presence and absence of added Lewis acids.

Equation 1 summarizes the synthesis of pyridylplatinum complexes in this study. Addition of KN(*p*-*t*-BuC<sub>6</sub>H<sub>4</sub>)<sub>2</sub> to DPPBz-ligated pyridyl- and *p*-tolylplatinum complexes **1–5** formed the diarylamido complexes **6–9**.<sup>5</sup> Likewise, addition of KNMe(SO<sub>2</sub>-Ar) formed the sulfonamidates **10** and **11**. Complexes **6–11** were stable at room temperature and were characterized by conventional spectroscopic and microanalytical methods.

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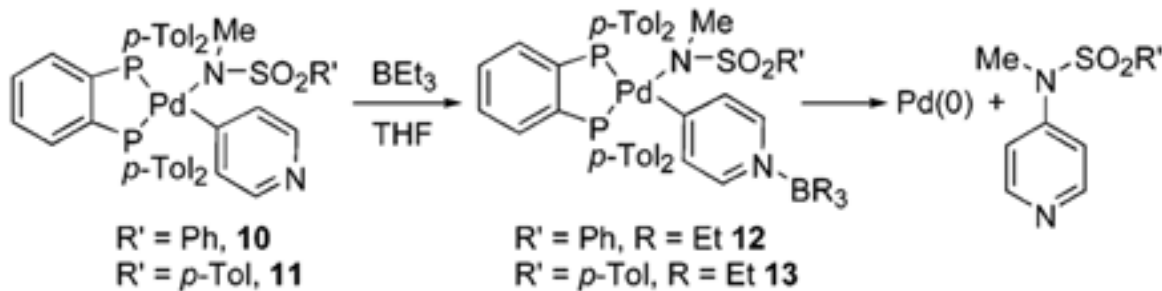
Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.



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 BEt<sub>3</sub> 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.

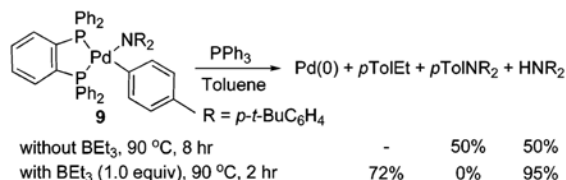
Boron Lewis acids also accelerated reductive elimination from 3-pyridylpalladium amide **7**, but the magnitude of this effect was smaller than that for reductive elimination from 4-pyridyl complex **6**. Heating a toluene solution of **7** with 1 equiv of BPh<sub>3</sub> and excess PPh<sub>3</sub> at 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 BEt<sub>3</sub> 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 BEt<sub>3</sub> adduct of the 4-pyridylpalladium amide complex. However, addition of BEt<sub>3</sub> 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 <sup>1</sup>H NMR, <sup>31</sup>P NMR, and <sup>11</sup>B NMR spectroscopy. The <sup>11</sup>B NMR resonance at δ 1.0, which lies in the range of chemical shifts that are characteristic of R<sub>3</sub>B·Py complexes,<sup>8</sup> 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.



(3)

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 BEt<sub>3</sub> in the presence of PPh<sub>3</sub> 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 BEt<sub>3</sub> in the absence of PPh<sub>3</sub> 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.



(4)

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 amide **11** in the presence of BEt<sub>3</sub>, BPh<sub>3</sub>, and B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>. The complex containing BPh<sub>3</sub> reacted nearly 12 times faster than the complex containing BEt<sub>3</sub>, and the complex containing B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> 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 BEt<sub>3</sub> for reactions conducted with the Xantphos ligand commonly used for the amidation of haloarenes<sup>9</sup> are shown in Table 2. The reactions of heteroaryl bromides with amides in the presence of K<sub>3</sub>PO<sub>4</sub> as base and Pd(dba)<sub>2</sub>/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 BEt<sub>3</sub> and in similar yields with substoichiometric BEt<sub>3</sub> 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.<sup>10</sup> Products from ethyl group transfer were formed in less than 10% yield when BEt<sub>3</sub> 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 binding to the cyanide ligand.<sup>11</sup> 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.<sup>6</sup> Studies to define the origin and scope of this effect are ongoing.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## References

1. (a) Hartwig, JF. In *Handbook of Organopalladium Chemistry for Organic Synthesis*. Negishi, EI., editor. Vol. 1. Wiley-Interscience; New York: 2002. p. 1051 (b) Hartwig, JF. In *Modern Arene Chemistry*. Astruc, C., editor. Wiley-VCH; Weinheim, Germany: 2002. p. 107 (c) Hartwig, JF. In *Modern Amination Methods*. Ricci, A., editor. Wiley-VCH; Weinheim, Germany: 2000. p. 195 (d) Yang BH, Buchwald SL. *J Organomet Chem* 1999;576:125. (e) Muci AR, Buchwald SL. *Top Curr Chem* 2002;219:131.
2. (a) Shen Q, Shekhar S, Stambuli JP, Hartwig JF. *Angew Chem, Int Ed* 2004;44:1371. (b) Anderson KW, Tundel RE, Ikawa T, Altman RA, Buchwald SL. *Angew Chem, Int Ed* 2006;45:6523.
3. (a) Burton G, Cao P, Li G, Rivero R. *Org Lett* 2003;5:4373. [PubMed: 14602003] (b) Alcaraz L, Bennion C, Morris J, Meghani P, Thom SM. *Org Lett* 2004;6:2705. [PubMed: 15281749] (c) Ji J, Li T, Bunnelle WH. *Org Lett* 2003;5:4611. [PubMed: 14627396] (d) Klapars A, Huang X, Buchwald SL. *J Am Chem Soc* 2002;124:7421. [PubMed: 12071751]
4. (a) Hama T, Culkin DA, Hartwig JF. *J Am Chem Soc* 2006;128:4976. [PubMed: 16608331] (b) Liebeskind LS, Srogl J. *Org Lett* 2002;4:979. [PubMed: 11893201] (c) Ghosh I, Jacobi PA. *J Org Chem* 2002;67:9304. [PubMed: 12492332]
5. (a) Hartwig JF. *Acc Chem Res* 1998;31:852. (b) Hooper MW, Hartwig JF. *Organometallics* 2003;22:3394.
6. Driver MS, Hartwig JF. *J Am Chem Soc* 1997;119:8232.
7. Yamashita M, Hartwig JF. *J Am Chem Soc* 2004;126:5344. [PubMed: 15113190]
8. (a) Noth H, Wrackmeyer B. *Chem Ber* 1974;107:3070. (b) Weisman A, Gozin M, Kraatz H, Milstein D. *Inorg Chem* 1996;35:1792.
9. (a) Yin J, Buchwald SL. *J Am Chem Soc* 2002;124:6043. [PubMed: 12022838] (b) Yin J, Buchwald SL. *Org Lett* 2000;2:1101. [PubMed: 10804564] (c) Yin J, Zhao MM, Huffman MA, McNamara JM. *Org Lett* 2002;4:3481. [PubMed: 12323049]
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.
11. (a) Tolman CA, Seidel WC, Druliner JD, Domaille PJ. *Organometallics* 1984;3:33. (b) Huang JK, Haar CM, Nolan SP, Marccone JE, Moloy KG. *Organometallics* 1999;18:297.

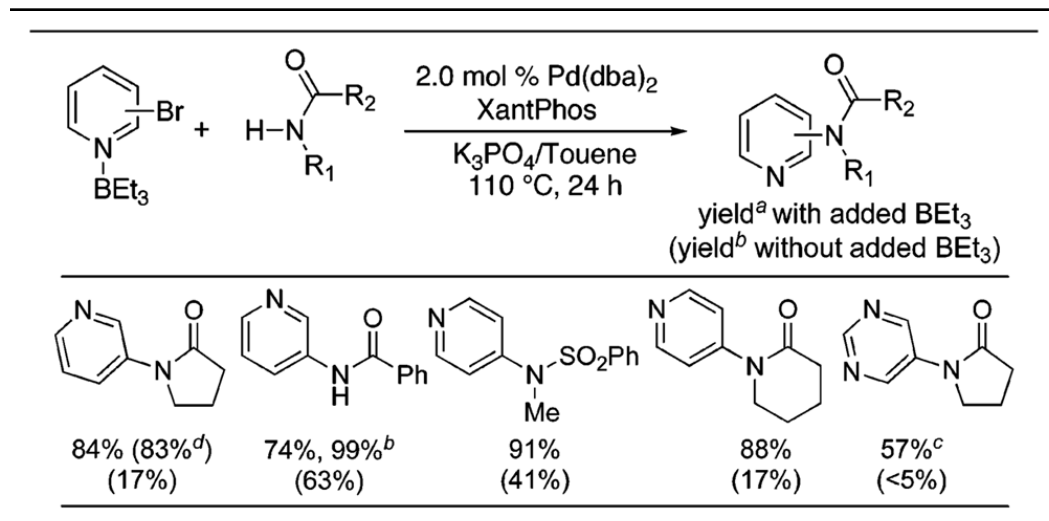
**Table 1**

Rate Constants for Reductive Eliminations from Pyridylpalladium Sulfonamidate **11** in the Presence of Different Lewis Acids

entry	Lewis acid	temp (°C)	$k$ ( $\text{s}^{-1} \times 10^{-4}$ )	$t_{1/2}$ (min)
1	BEt <sub>3</sub>	90	7.7 (0.8)	15
2	BEt <sub>3</sub>	70		~170
3	BPh <sub>3</sub>	70	8.3 (0.2)	14
4	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub>	40	6.8 (0.5)	17

Table 2

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

<sup>a</sup> Isolated yield from an average of at least two runs; the borane is removed during chromatography.<sup>b</sup> Yield by GC with an internal standard.<sup>c</sup> 48 h.<sup>d</sup> BEt<sub>3</sub> (20 mol %) was used.