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Allyl Amines as Ammonia Equivalents in the Preparation of Anilines and Heteroarylamines

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Abstract: A series of anilines and heteroarylamines were synthesized in moderate to excellent yields by palladium catalyzed cross coupling reaction of aryl or heteroaryl halides with allyl- or N,N-diallylamine followed by deallylation.

The conversion of an aryl halide into the corresponding primary amine is a very desirable but sparsely described synthetic transformation.[1] Anilines may be formed by the reaction of halobenzene derivatives with an alkali metal amide in liquid ammonia, but this process is complicated by other products arising from benzyne intermediates.[2] Primary heteroarylamines are also available by the aryne route[3], but are more commonly prepared from the heteroaryl halide and an ammonia solution, a reaction that usually requires high temperature and pressure.[4] Buchwald,[5] Hartwig,[6] and others[7] have recently shown that a wide variety of secondary and tertiary arylamines are easily prepared by the palladium or nickel catalyzed amination of aryl halides or triflates with primary or secondary amines. We reasoned that allylamine and N,N-diallyamine should also participate in palladium catalyzed aminations of aryl halides,[8,9] giving products formally equivalent to primary arylamines. Primary amines could then be generated via noble metal catalyzed isomerization of the allyl groups to the hydrolytically labile enamines.[10] The work herein describes these processes.

As anticipated the palladium catalyzed amination of various aryl halides with allyl- and N,N-diallylamine gave the expected secondary and tertiary amines (Tables 1 and 2), some of which could also be prepared by uncatalyzed direct displacement (Table 1, entry 1; Table 2, entries 5 and 6). The deallylation of these compounds was typically accomplished in good to excellent yield with catalytic amounts of 10% palladium on carbon in boiling ethanol containing an equivalent of methanesulfonic acid. We found, however, that those substrates in which the N,N-diallylamino moiety was adjacent to one or more nuclear nitrogen atoms failed to give the desired product under these conditions (Table 2, entries 1, 3, and 5).[11] Fortunately, the corresponding monoallylamines deallylated smoothly when methanesulfonic acid was replaced with BF_3:Et_2O.

In summary, a new method has been devised to synthesize primary arylamines from aryl halides. The novel features of this process involve a palladium catalyzed amination of the aryl halide[12] with allyl- or N,N-diallylamine and subsequent palladium on carbon catalyzed deallylation[13] of the products in an acidic alcohol solution. Like the complementary method recently disclosed by Buchwald[14] using benzophenone imine as an ammonia equivalent, this process should find widespread application.

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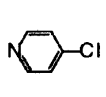
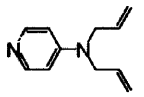
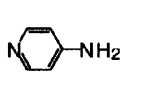
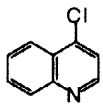
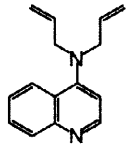
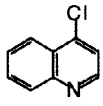
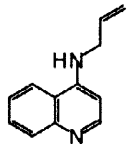
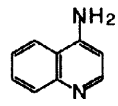
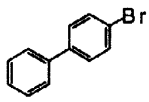
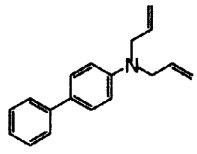
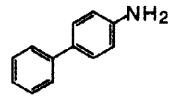
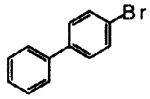
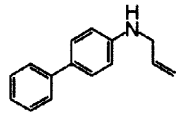
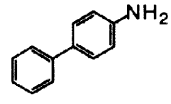
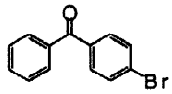
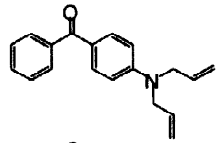
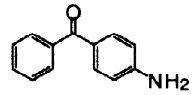
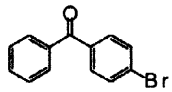
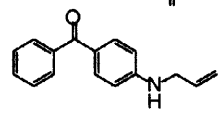
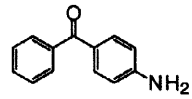
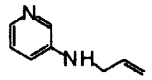
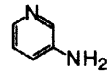
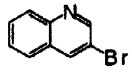
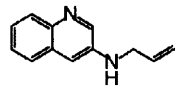
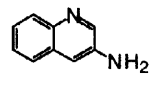
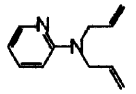
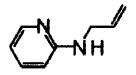
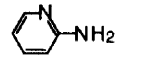
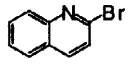
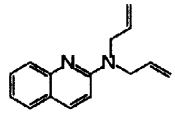
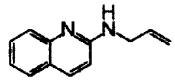
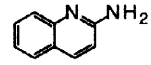
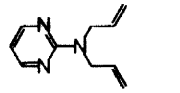
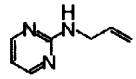
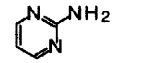
Table 1. Aminations and Dealkylations

Entry	Substrate	Product	Yield	Cleavage Product[d]	Yield[e]
1			100% (a)		100%
2			12% (b)	ND	ND
3			45% (c)		94%
4			37% (b)		84%
5			77% (c)		90%
6			28% (b)		65%
7			71% (c)		68%
8			76% (c)		63%
9			97% (c)		45%

(a) N,N-diallylamine, as a solvent, was refluxed with the substrate for 2 h. (b) 5.0 mol% Pd(P(*o*-tol)$_3$)$_2$Cl$_2$, 1.4 eq. NaO*t*Bu, 1.5 eq. N,N-diallylamine, toluene, 100 °C, 3 h. (c) 5.0 mol% (DPPF)PdCl$_2$, DPPF (3 eq./Pd), 1.5 eq. allylamine, 1.5 eq. NaO*t*Bu, dry THF, 80 °C, 3 h. (d) 1.0 eq. methanesulfonic acid, 10% Pd/C (w/w) in refluxing EtOH. (e) Yields are based on isolated, analytically pure compounds. ND = not determined. All new compounds were characterized using ^{1}H and ^{13}C NMR, mass spectroscopy and elemental analysis.

Table 2. Alpha Amination of N-Heterocycles

Entry	Substrate	Product	Yield	Cleavage Product[d]	Yield[e]
1			77% (b)	NR	
2			73% (c)		68%
3			79% (b)	NR	
4			76% (c)		71%
5			100% (a)	NR	
6			100% (a)		100%

(a) allyl- or N,N-diallylamine, as a solvent, was refluxed with the substrate for 2 h. (b) 5.0 mol% $Pd(P(o\text{-tol})_3)_2Cl_2$, 1.4 eq. NaO*t*Bu, 1.5 eq. N,N-diallylamine, toluene, 100 °C, 3 h. (c) 5.0 mol% (DPPF)$PdCl_2$, DPPF (3 eq./Pd), 1.5 eq. allylamine, 1.5 eq. NaO*t*Bu, dry THF, 80 °C, 3 h. (d) 1.0 eq. BF_3:Et_2O, 10% Pd/C (w/w) in refluxing EtOH. (e) Yields are based on isolated, analytically pure compounds. NR = no reaction, starting material recovered unchanged. All new compounds were characterized using ^1H and ^{13}C NMR, mass spectroscopy and elemental analysis.

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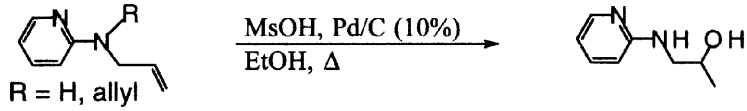
References and Notes:

1. Larock, R. C. in "Comprehensive Organic Transformations." VCH Publishers Inc., New York, **1989**, pp. 399-400.
2. Hoffmann, R. W. in "Dehydrobenzene and Cycloalkynes." Verlag Chemie, Weinheim, **1967**, pp. 115-122.
3. Reinecke, M. G.*Tetrahedron* **1982**, *38*, 427.
4. a) Giam, C. S. in "Pyridine and its Derivatives." Ed. by Abramovitch, R. A. Part 3. John Wiley and Sons, New York, **1974**, pp. 47-48. b) Smally, R. K. in "Quinolines." Part 1. Ed. by Jones, G. John Wiley and Sons, New York, **1977**, pp. 543-547. c) Mathison, I. W., Solomons, W. E. in "Isoquinolines." Part 2. Ed. by Kathawala, F. G.; Coppola, G. M.; Schuster, H. F. John Wiley and Sons, New York, **1990**, pp. 368-378.
5. a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348. b) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. d) Wagaw, S.; Buchwald, S. L. *J. Org. Chem* **1996**, *61*, 7240. e) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568. f) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**,*38*, 6359.
6. a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.***1994**, *116*, 5969. b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708. d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. e) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1264.

7. a) Davydov, I. P.; Beletskaya *Russ. Chem. Bull.* **1995**, *44*, 1141. b) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181. c) Ward, Y. D.; Farina, V. *Tetrahedron Lett.*, **1996**, *37*, 6993. c) Kang, S.-K.; Lee, H.-W.; Choi, W.-K.; Hong, R.-K.; Kim, J.-S. *Synth. Commun.* **1996**, *26*, 4219. d) Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**, 1135. e) Zhao, S.-H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463. f) Barta, N. S.; Pearson, W. H. *Chemtracts: Org. Chem.* **1996**, *9*, 88. g) Beller, M.; Matthias, B.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073. h) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. i) Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393. j) Beletskaya, I.P.; Bessermertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 2287.
8. We thank Professor L. E. Overman, U. C. Irvine for suggesting this point.
9. Neither allyl- nor diallylamine have been previously reported to take part in palladium catalyzed amination of aryl halides.
10. a) Laguzza, B. C.; Ganem, B.; *Tetrahedron Lett.* **1981**, *22*, 1483. b) Picq, D.; Cottin, M.; Anker, D.; Pacheco, H. *Tetrahedron Lett.* **1983**, *24*, 1399. c) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109. d) Lemaire-Adoire, S.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **1995**, *36*, 1267.
11. Mono- and diallylamino products illustrated in Table 2 gave β-hydroxyaminopropyl derivatives when treated with 1 eq. of methanesulfonic acid, 10% Pd/C (w/w) in refluxing EtOH, e.g.



No reaction occurs in the absence of palladium. As yet, we do not fully understand this interesting transformation.
12. In most cases catalytic amination was superior to thermal amination, eg. 2-chloropyridine in refluxing N, N-diallylamine required 2 weeks for 5% conversion, while the catalytic amination using the Buchwald protocol (5.0 mol% $Pd(P(o\text{-tol})_3)_2Cl_2$, 1.4 eq. NaO*t*Bu, 1.5 eq. N,N-diallylamine) was complete in 3 hours (77% yield). This result was surprising given that Buchwald reports 2-bromopyridine failed to give amination products using this catalyst (Ref. 5e).
13. A representative experimental procedure is as follows: synthesis of 3-aminoquinoline (Table 1, entry 9). A mixture of 3-bromoquinoline (2.08 g, 1.35 mL, 10 mmol), allylamine (1.12 mL, 15 mmol, 1.5 eq.), sodium tert-butoxide (1.44 g, 15 mmol, 1.5 eq.), $Pd(DPPF)_2Cl_2$ (400 mg, 0.5 mmol, 0.05 eq.) and DPPF (831 mg, 1.5 mmol, 0.15 eq.) in 10 mL anhydrous THF was heated to 80 °C for 2 h. TLC indicated the complete disappearance of the starting 3-bromoquinoline. The dark red reaction mixture was filtered through Celite and concentrated in vacuo leaving a dark colored oil. The oil was chromatographed on silica gel using hexanes/EtOAc (70:30) to give 1.79 g of an oily product (3-allylaminoquinoline, 97% yield). ^{1}H NMR ($CDCL_3$, 300 Mhz) δ (ppm) 8.46 (d, J = 2.9 Hz, 1H), 7.94 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.03 (d, J = 2.9 Hz, 1H), 6.00 (ddt, J = 17.1, 10.2, 5.3 Hz, 1H), 5.35 (ddt, J = 17.1, 1.6, 1.6, 1H), 5.24 (ddt, J = 10.2, 1.5, 1.6, 1H), 4.17 (br s, 1H), 3.90 (m, 2H). ^{13}C NMR ($CDCL_3$, 75 Mhz) δ (ppm) 142.65 (CH), 141.48 (C), 140.72 (C), 133.57 (CH), 128.85 (C), 128.35 (CH), 126.37 (CH), 125.40 (CH), 116. 38 (CH_2), 110.08 (CH), 45.55 (CH_2). A mixture of 3-allylaminoquinoline (184 mg, 1 mmol), 10% Pd/C (184 mg) and methanesulfonic acid (64 μL, 1 mmol, 1 eq.) in 10 mL of absolute ethanol was heated for 2 h. TLC indicated the disappearance of starting 3-allylaminoquinoline. The reaction mixture was filtered through a Celite pad and concentrated in vacuo to give a solid residue. The residue was chromatographed on silica gel using hexanes/EtOAc (70: 30) to give 64 mg of a solid (45%). The product was spectroscopically identical to an authentic sample obtained from Aldrich Chem. Co.
14. Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.