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N-Arylation of Aziridines

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Abstract: A range of *N*-arylaziridines were prepared by the palladium or copper catalyzed amination reaction between N−H aziridines and aryl bromides or arylboronic acids. These results showcase the synthetic utility of metal-bound aziridine species in nitrogen transfer processes.

Palladium-catalyzed carbon−nitrogen bond-forming reactions have received considerable attention in recent years.[1,2] A wide range of amines, amides, indoles, and imines participate in this useful process. Our interest in the synthetic applications of functionalized aziridines,[3,4] and more recently in metal-bound aziridine species (Figure 1), led us to investigate the possibility of reductive elimination of the arylated aziridines from a variety of transition metal complexes. An intriguing question is whether the alkylated aziridine ring can tolerate the Lewis acidic character of some of the late transition metal-based catalysts and resist concomitant ring-opening.

Traditional routes to *N*-arylated aziridines are based on (a) ring closure of *N*-aryl-*β*-amino alcohols,[5−8] (b) addition of carbenoid species to imines,[9−12] and (c) nucleophilic aromatic substitution reactions between aziridine nucleophiles and activated aryl halides.[13] Transition metal-catalyzed amination of aryl halides is well-known but, to the best of our knowledge, has not been applied in the amination with aziridines. This is partly due to the difficulties associated with the preparation of N−H aziridines. Hartwig reported an example of the reaction between Ar−Pd−Br complexes and parent ethyleneimine lithium amide to produce *N*-arylated aziridine but, to the best of our knowledge, no investigation into the scope and potential applications of this process has been documented.[14]

FIGURE 1. Metal-bound aziridine species.

We prepared the aziridine starting materials using one of the following two methods: (a) ring closure of 1-azido-2-hydroxycyclohexane with triphenylphosphine,[15] and (b) 1,4-addition of methoxylamine to α,*β*-unsaturated ketone followed by ring closure.[16] It was subsequently found that $Pd_2(dba)_3$/BINAP served as an effective catalyst for amination of N−H aziridines. Using this methodology, several types of *N*-arylated products have been synthesized. BINAP and 1,3-bis(diphenylphosphino)propane (DPPP) were tried as ligands for the reaction between *o*-bromopyridine (**2a**) and cyclohexeneimine (**1a**), which revealed that BINAP was an effective ligand in this process, whereas DPPP did not give the desired product. This contrasts with the success of DPPP in the amination of **2a** with various arylamines or cyclic amines.[17]

In the case of pyridine substrates, direct nucleophilic displacement of halide has been ruled out: heating the mixture of **1a** and **2a** did not give the desired product. Uncatalyzed processes in the case of the nitro- and cyano-substituted substrates have also been ruled out: without $Pd_2(dba)_3$ and BINAP, 1-bromo-4-nitrobenzene (**2h**) and 1-bromo-4-cyanobenzene (**2i**) did not react with **1a** in the presence of sodium *tert*-butoxide at 70 °C. To our delight, the insertion of palladium into the nitrogen−carbon bond was not observed in any of these cases, although oxidative addition of Ni to *N*-tosylaziridines has been reported[18] and oxidative addition of transition metals to aziridines has been invoked in catalytic carbonylation of aziridines to give *β*-lactams.[19,20]

The scope of *N*-arylation of **1a** with Pd/BINAP was investigated (Scheme 1). The results are shown in Table 1. Both electron-withdrawing and electron-donating groups on the aryl halide moiety can be tolerated. Electron-withdrawing groups tend to increase reactivity (Table 1, entry 8), while electron-rich substrates, such as 2-bromoanisole (**2f**), needed more forceful conditions to complete the reaction (Table 1, entry 6). In the case of 4-bromoanisole (**2g**), the reaction was sluggish and did not reach completion after 12 h at 80 °C (Table 1, entry 7). For such substrates, the copper-catalyzed amination described below was found to be the method of choice. Aryl chlorides did not react under the reaction conditions (Table 1, entry 10). Thus, *o*-bromochlorobenzene (**2d**) led to *N*-(2-chlorophenyl)aziridine (**3d**) with high chemo-

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SCHEME 1. *N*-arylation of Cyclohexeneimine

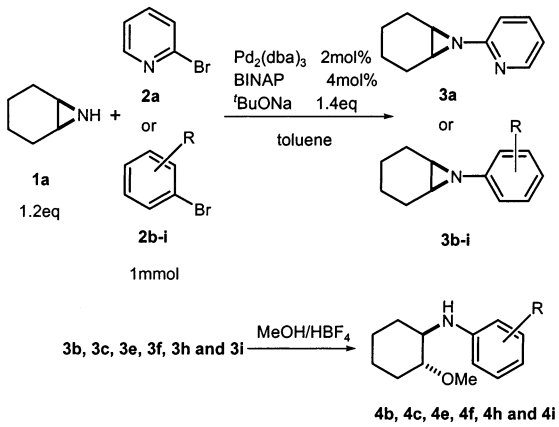
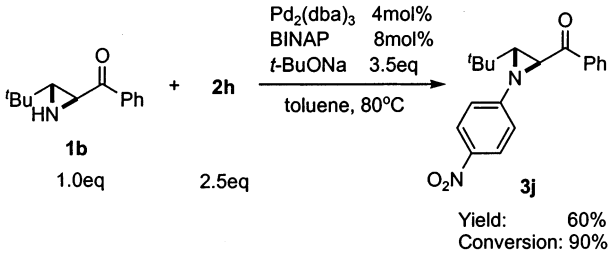


TABLE 1. The Scope of *N*-Arylation of Aziridine 1a

entry	substrate	product	reaction temp (°C)	reaction time (h)	yield (%)
1	**2a**	**3a**	50	12	70[b]
2	R = H (**2b**)	**3b**	70	14	53[a]
3	R = *o*-F (**2c**)	**3c**	80	7	58[a]
4	R = *o*-Cl (**2d**)	**3d**	80	19	95[b]
5	R = *o*-Me (**2e**)	**3e**	70	24	64[a]
6	R = *o*-OMe (**2f**)	**3f**	80	22	78[a]
7	R = *p*-OMe (**2g**)	**3g**	80	12	35[c]
8	R = *p*-NO_2 (**2h**)	**3h**	70	3	96[a]
9	R = *p*-CN (**2i**)	**3i**	50 → 60	15 → 2	79[a]
10	*p*-cyanochlorobenzene	**3i**	80	24	trace

[a] Yield was determined after ring opening reaction with MeOH/HBF_4 (i.e. as **4b**, **4c**, **4e**, **4f**, **4h**, and **4i**). [b] Yield was determined after purification on alumina (for **3a**) or silica (for **3d** and **3g**) column. [c] Conversion was determined by ^{1}H NMR.

SCHEME 2. *N*-Arylation of 2-Benzoyl-3-*tert*-butylaziridine



selectivity (Table 1, entry 4). Benzoyl-N-H aziridines also gave *N*-aryl aziridines under these conditions with moderate selectivity. The reaction between 2-benzoyl-3-*tert*-butylaziridine (**1b**) and **2h** gave 1-(4-nitrophenyl)-2-benzoyl-3-*tert*-butylaziridine (**3j**) in moderate yield (Scheme 2).

The copper-catalyzed amination system developed by Buchwald for the arylation of anilines, acyclic amines, and piperidines[21] was also effective for the synthesis of *N*-arylated aziridines. Coupling between **1a** or **1b** and arylboronic acids (**5a**−**f**) catalyzed by copper acetate/myristic acid gave *N*-arylated aziridines (**3b**, **3e**, **3g**, and **3k**−**m**) in good to moderate yields (Table 2, Scheme 3 and Scheme 4).

These results showcase the utility of aziridinyl N−metal complexes in amination reactions.[22] Further studies

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SCHEME 3. *N*-Arylation of Cyclohexeneimine with Use of Arylboronic Acids

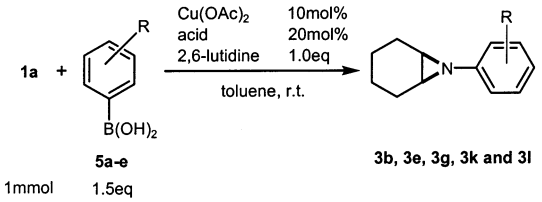
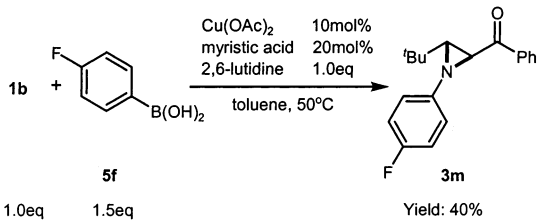


TABLE 2. The Scope of *N*-Arylation of Aziridine 1a with Use of Arylboronic Acids

entry	substrate	product	acid	yield (%)
1	R = H (**5a**)	**3b**	myristic acid	87
2	**5a**	**3b**	camphanic acid	40
3	**5a**	**3b**	2-phenylbutyric acid	no reaction
4	R = *o*-Me (**5b**)	**3e**	myristic acid	78
5	R = *m*-Br (**5c**)	**3k**	myristic acid	68
6	R = *m*-NO_2 (**5d**)	**3l**	myristic acid	60
7	R = *p*-OMe (**5e**)	**3g**	myristic acid	65

SCHEME 4. *N*-Arylation of 2-Benzoyl-3-*tert*-butylaziridine with Use of 4-Fluorophenylboronic Acid



aimed at understanding the reactivity of aziridine−Pd(II) complexes, as well as other aziridine−metal species, are in progress and will be reported in due course.

Experimental Section

Procedure for the palladium-catalyzed arylation reaction (Table 1, entry 1): To $Pd_2(dba)_3$ (73 mg, 2 mol %) in 30 mL of toluene was added *rac*-BINAP (100 mg, 4 mol %), 2-bromopyridine (**2a**, 640 mg, 4 mmol), NaO^tBu (540 mg, 5.6 mmol), and 7-azabicyclo[4.1.0]heptane (**1a**, 470 mg, 4.8 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 12 h. After the reaction was complete, the mixture was washed with water (3 × 30 mL) and dried over sodium sulfate. The solvent was subsequently removed under reduced pressure. Hexane was added to the crude product, the precipitated solid was removed by filtration, and the filtrate was evaporated. Pentane and neutral alumina were added to the residue with stirring for a few minutes at room temperature and then filtered. The filtrate was concentrated under reduced pressure, to give 490 mg of 7-(2-pyridinyl)-7-azabicyclo[4.1.0]heptane (**3a**, yield: 70%).

7-(2-Pyridinyl)-7-azabicyclo[4.1.0]heptane (3a): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (dd, J = 5.2 Hz, 2.0 Hz, 1H), 7.54 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.88 (dd, J = 7.6 Hz, 5.2 Hz), 2.61−2.65 (m, 2H), 2.08−2.15 (m, 2H), 1.92−1.99 (m, 2H), 1.51−1.60 (m, 2H), 1.30−1.39 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 148.3, 137.5, 117.8, 115.8, 38.9, 25.0, 20.8 ppm; HR-MS (EI) m/z calcd for $C_{11}H_{14}N_2$ 174.1157, found 174.1157.

Procedure for the palladium-catalyzed arylation reaction (Table 1, entry 8): To $Pd_2(dba)_3$ (18 mg, 2 mol %) in 10 mL of toluene was added *rac*-BINAP (25 mg, 4 mol %), *p*-nitro-

(22) For other known metal-aziridine species, see: Yamamoto, Y.; Asao, N.; Meguro, M.; Tsukada, N.; Nemoto, H.; Sadayori, N.; Wilson, J. G.; Nakamura, H. *J. Chem. Soc. Chem. Commun.* **1993**, 1201.

bromobenzene (**2h**, 202 mg, 1 mmol), NaO^{t}Bu (135 mg, 1.4 mmol), and **1a** (110 mg, 1.2 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 3 h and then at 50 °C overnight. After the reaction was complete, the mixture was washed with water (3 × 10 mL) followed by drying over sodium sulfate. The solvent was subsequently removed under reduced pressure, and 20 mL of methanol together with 48% aqueous tetrafluoroboric acid (200 mg) were added to the crude product. After the mixture was stirred at room temperature, the solvent was removed under reduced pressure. To the residue were added dichloromethane (10 mL) and dilute aqueous potassium carbonate (10 mL). The layers were separated, washed with water, and dried over sodium sulfate, and the solvent was evaporated. The residue was purified on a silica gel column (hexane/ethyl acetate 6/4) to give 239 mg of *trans*-1-methoxy-2-*p*-nitrophenylaminocyclohexane (**4h**, yield: 96%).

***trans*-1-Methoxy-2-*p*-nitrophenylaminocyclohexane (4h):** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 9.3 Hz, 2H), 6.57 (d, J = 9.0 Hz, 2H), 4.54 (br, 1H), 3.29−3.39 (m, 4H), 3.08 (dt, J = 9.0 Hz, 4.2 Hz, 1H), 2.11−2.20 (m, 2H), 1.68−1.85 (m, 2H), 1.17−1.46 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 137.7, 126.3, 111.7, 82.8, 56.5, 56.4, 31.4, 29.5, 24.1, 23.7 ppm; HR-MS (EI) *m*/*z* calcd for $C_{13}H_{18}N_2O_3$ 250.1317, found 250.1318.

General procedure for the copper-catalyzed arylation reaction (Table 2, entry 1): To the mixture of phenylboronic acid (**5a**, 183 mg, 1.5 mmol), $Cu(OAc)_2$ (18 mg, 0.1 mmol), and myristic acid (46 mg, 0.2 mmol) were successively added toluene (2 mL), 2,6-lutidine (107 mg, 1 mmol), and **1a** (97 mg, 1 mmol). The reaction mixture was stirred in air atmosphere at room temperature for 24 h, diluted with ethyl acetate (10 mL), filtered through a plug of silica gel, and then purified on a silica gel column (hexanes/ethyl acetate 9/1) to give 150 mg of 7-phenyl-7-azabicyclo[4.1.0]heptane (**3b**, yield: 87%).

7-Phenyl-7-azabicyclo[4.1.0]heptane (3b): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (t, J = 8 Hz, 1H), 6.89 (d, J = 8 Hz, 2H), 6.83 (t, J = 7.4 Hz, 2H), 2.23 (d, J = 4 Hz, 2H), 1.98−1.93 (m, 2H), 1.85−1.80 (m, 2H), 1.43−1.39 (m, 2H), 1.24−1.18 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 129.0, 122.0, 120.6, 38.9, 24.9, 20.6 ppm.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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