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The synthesis of *N*-arylcyclopropylamines via palladium-catalyzed C–N bond formation

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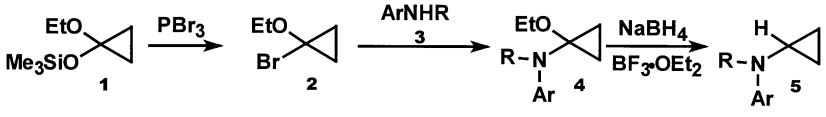
Abstract—A variety of *N*-arylcyclopropylamines has been prepared in one step, by the $Pd_2(dba)_3$/BINAP/NaO*t*Bu-catalyzed amination of an aryl bromide with cyclopropylamine. Compounds bearing the *N*-aryl substitutent (phenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 1-napthyl, 9-anthryl, 9-phenanthryl, and 3-pyridyl) were prepared in isolated yields ranging from 43 to 99%. Overall, this chemistry represents a vast improvement over the previous multi-step procedures for the synthesis of compounds of this type.

1. Introduction

Numerous *N*-substituted cyclopropylamines exhibit biological activity.[1–5] Many such compounds play a significant role in the pharmaceutical industry. However, their importance extends beyond this niche. They are not only valuable synthetic intermediates,[6] but they also serve as valuable probes in organo- and biochemical mechanistic studies.[1,4,5,7–9] Our attention was recently directed at the use of *N*-arylcyclopropylamines in this latter context as indicators of single electron transfer from nitrogen. When one electron is removed from the nitrogen atom of a cyclopropylamine, the cyclopropyl ring opens rapidly. This property provides a powerful tool for detecting the presence of nitrogen-centered radicals.[1,4,5,7–9]

While aliphatic cyclopropylamines can often be prepared by the direct displacement of a leaving group by the appropriate amino nitrogen, this route is rarely open to the synthesis of *N*-arylcyclopropylamines. The reverse process, amination of a cyclopropyl halide, for example is, of course, rendered unpractical by the poor reactivity of these halides toward nucleophiles.[10] In our initial work, the desired compounds were prepared by the set of three transformations shown in Scheme 1, which is the best available method for the synthesis of *N*-arylcyclopropylamines. This process begins with the conversion of ((1-ethoxycyclopropyl)oxy)trimethylsilane (**1**) to 1-bromo-1-ethoxycyclopropane (**2**) which is then reacted with an aromatic amine to generate the cyclopropylaminal (**4**) (Scheme 1).[11] Reduction of this compound then produces the desired amine. In a newly improved version of this method,[12] a one-step reductive amination with ((1-ethoxycyclopropyl) oxy)trimethylsilane (**1**) was shown to cyclopropylate the aromatic amines (Scheme 2), but the yields were low.

Because of the cumbersome nature of the chemistry shown in Scheme 1 and the relatively poor yield of its one pot derivative (Scheme 2), our attention was directed at the versatile palladium-catalyzed amination reactions of aryl halides with amines, recently developed by the Buchwald[13–15] and the Hartwig[16,17] groups, as a possible simple route to *N*-arylcyclopropylamines. Despite the attractiveness of this unique technique for aromatic C–N bond formation, however, we were concerned that the methodology may not work with cyclopropylamines because of possible opening reactions of the strained three membered ring. Such transformations are not only well known to emanate from electron transfer (see above), but cyclopropane ring opening is also well known to be catalyzed by palladium species, as well as by other metals and their complexes.[18–20] The possible application of the Buchwald



Scheme 1.

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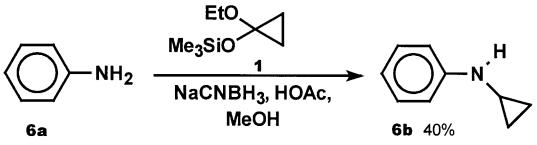


Scheme 2.

or Hartwig procedures to synthesis of *N*-arylcyclopropylamines might well rest on relative rates of catalytic substitution compared to catalyzed ring opening. Here we report the successful synthesis of *N*-arylcyclopropylamines in excellent to good yields through the application of a palladium-catalyzed transformation which does not open the cyclopropane ring. While none of the organometallic chemistry is new, the procedure gives good yields of the *N*-arylcyclopropylamines in a one-pot reaction. This represents a vastly improved method for the synthesis of these cyclopropylamines.

2. Results and discussion

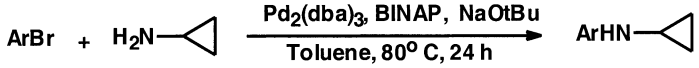
Many efforts have been made to increase the scope of the palladium-catalyzed aromatic C–N bond formation. It is well known that aromatic bromides can couple with primary and secondary amines, using Pd(0)/BINAP catalyst, in high yields.[13] Replacement of BINAP with other ligands can produce a more efficient transformation, occurring at room temperature, which can even be used to aminate aryl chlorides.[15,17] In the work described here, the catalytic system used consisted of $Pd_2(dba)_3$ (2% equiv.) and (±)-BINAP in the presence of NaO*t*Bu at 80°C. (±)-BINAP was chosen because it is easy to handle and commercially available among those ligands[13–17,21] developed recently for use in this chemistry. The general procedure is described in Section 3. Since the boiling point of cyclopropylamine is only 51°C, we employed a sealed pressure tube to prevent the loss of cyclopropylamine under our experimental conditions. With all nine substrates, the starting materials are not completely consumed after 6 h and we used a 24 h reaction time as optimal. The aromatic cyclopropylamines are light and oxygen sensitive, and require special care during preparation, isolation and storage.

In all cases, we used aryl bromides and coupled them to cyclopropyl amine according to Scheme 3. Product yields are reported in Table 1 and, with each of the nine substrates, the conversion of the starting material is good. The products are obtained in moderate to excellent yields (43–99%). In some cases, the relatively low yield is due to the decomposition of the products during the reaction course. In two cases, entries 3 and 6 of Table 1, respectively, the yields of *N*-cyclopropyl-1-napthylamine (**11b**) and *N*-cyclopropyl-2-methoxyaniline (**8b**) were excellent. The much slower oxidative addition reaction of aryl chlorides compared to aryl bromides toward the Pd catalyst[15] leaves the Cl unsubstituted in the benzene ring in of 4-chlorobromobenzene (entry 5). In one case, entry 7, using the unmodified workup procedure, the major product isolated in 47% yield from the reaction was 9-cyclopropylazaanthraquinone (**12c**) (Scheme 4) that decomposed to anthraquinone within a few hours. The formation of this oxidation product **12c** of the parent amine **12b** was avoided by conducting the workup procedure and the isolation in the absence of O_2. The product **12b** was isolated in 64% yield with special care. In all cases, none of the diarylated cyclopropyl amines were found in the products. Although the extent of our investigation is limited, the coupling of aryl bromides with electron deficient rings did not occur under the standard conditions. Neither 3-bromopyridine nor 4-nitrobromobenzene reacted, but with the former substrate the product (entry 9) could be obtained in 52% yield by increasing the Pd amount to 4%. This did not work for 4-nitrobromobenzene and starting material was obtained upon workup.

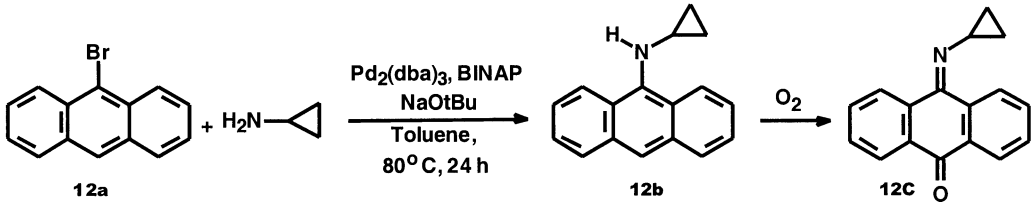
Table 1. Yields of *N*-arylcyclopropylamines synthesized according to Scheme 3

Entry	Compound	Ar	% Yield
1	**6**	Phenyl	53
2	**7**	4-Methylphenyl	43
3	**8**	2-Methoxyphenyl	98
4	**9**	3-Methoxyphenyl	76
5	**10**	4-Chlorophenyl	67
6	**11**	1-Naphthyl	99
7	**12**	9-Anthryl	64
8	**13**	9-Phenanthryl	69
9	**14**	3-Pyridyl	52

The simple method reported here for the synthesis of *N*-arylcyclopropylamines is far superior to and has many advantages over the previously reported procedures for the generation of *N*-arylcycloproylamines. The overall yields of previous methods are low. The starting material ((1-ethoxycyclopropyl)oxy)trimethylsilane **1** is relatively expensive. Also, the key intermediate, 1-bromo-1-ethoxycyclopropane



Scheme 3.



Scheme 4.

2, in the two-step reductive amination (Scheme 1) is not stable at room temperature and is relatively hard to prepare. Even though the yields of some *N*-cyclopropyl aromatic amines are not as high as would be desirable, the procedure is still a major advance over the previous methods for the synthesis of these amines. The results presented here indicate that cyclopropylamine and its derived *N*-cyclopropyl aromatic amines are able to survive in the synthetic procedure without opening of the cyclopropyl ring. Palladium-catalyzed C–N bond formation provides a simple method for the synthesis of *N*-cyclopropylaromatic amines.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere in an oven-dried pressure tube manufactured by ACE Glass. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Some of the compounds were too unstable toward oxidation and confirmation of their elemental composition was obtained by high resolution mass spectroscopy, which was done by the Center for Biomedical and Bioorganic Mass Spectrometry, Washington University, St. Louis, MO. Toluene was distilled from sodium/benzophenoneketyl under nitrogen. Aryl bromides were purchased from commercial sources and used without further purification. Cyclopropylamine was purchased from Acros Chemical. Sodium *t*-butoxide was purchased from Aldrich Chemical and stored in a vacuum desiccator. Tris(dibenzylideneacetone)dipalladium(0) and (±)-BINAP were purchased from Strem Chemical and used without further purification.

3.2. General method for synthesis of *N*-arylcyclopropylamines

An oven-dried 10 mL pressure tube was charged with 1 mmol of the aromatic bromide, 1.5 mmol of NaO*t*Bu, 0.03 mmol of BINAP, 0.01 mmol of $Pd_2(dba)_3$, 1.6 mmol of cyclopropylamine, 1–2 mL of toluene and a stir bar. After purging with argon for a few seconds, the tube was closed tightly with a Teflon screw cap and wrapped with aluminum foil. The mixture was stirred and heated at 80°C for 24 h. The resulting mixture was then cooled, diluted with ether, filtered through Celite and absorbed onto silica gel.[†] The silica gel containing reaction mixture was dried in vacuo and then applied to flash chromatography on silica gel (10% ethyl acetate in hexanes). The corresponding *N*-cyclopropylamine was obtained.

3.2.1. *N*-Cyclopropylaniline (6b). Starting with bromobenzene, the general procedure gave 0.072 g (53%) of *N*-cyclopropylaniline[11,12] (colorless oil).

3.2.2. 4-Methyl-*N*-cyclopropylaniline (7b). Starting with 4-bromotoluene, the general procedure gave 0.063 g (43%) of 4-methyl-*N*-cyclopropylaniline (colorless oil). ^{1}H NMR ($CDCl_3$, 250 MHz) (7.00 (d, 2H, *J*=8.4 Hz), 6.71 (d, 2H, *J*=8.4 Hz), 4.03 (s, br, 1H), 2.44–2.35 (m, apparent septet, 1H), 2.24 (s, 3H), 0.73–0.66 (m, 2H), 0.52–0.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (146.4, 129.6, 126.9, 113.2., 25.5, 20.4, 7.3; IR (neat, cm^{-1}) 3391, 3094, 3022, 2969, 2916, 2863, 1628, 1516, 1457, 1378, 823; HRMS (EI): *m/z*147.1043 (calcd for $C_{10}H_{13}N$ 147.1048).

3.2.3. 2-Methoxyl-*N*-cyclopropylaniline (8b). Starting with 2-bromoanisole, the general procedure gave 0.160 g (98%) of 2-methoxyl-*N*-cyclopropylaniline (colorless oil). ^{1}H NMR ($CDCl_3$, 250 MHz) (7.01 (dd, 1H, *J*=8, 1.5 Hz), 6.88 (ddd, 1H, *J*=8, 7.2, 1.8 Hz), 6.71 (m, 2H), 4.63 (s, br, 1H), 3.90 (s, 3H), 2.40–2.35 (m, apparent septet, 1H), 0.720–0.67 (m, 2H), 0.55–0.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (146.6, 138.6, 121.2, 116.9, 111.1, 109.3, 55.3, 24.9, 7.1; IR (neat, cm^{-1}) 3414, 3079, 3006, 2954, 2835, 1604, 1512 1453, 1368, 749; HRMS (EI): *m/z* 163.0999 (calcd for $C_{10}H_{13}NO$ 163.0997).

3.2.4. *N*-Cyclopropyl-3-methoxylaniline (9b). Starting with 3-bromoanisole, the general procedure gave 0.124 g (76%) of *N*-cyclopropyl-3-methoxylaniline (colorless oil). ^{1}H NMR ($CDCl_3$, 250 MHz) (7.07 (t, 1H, *J*=8.5 Hz), 6.37–6.27 (m, 3H), 4.16 (s, br, 1H), 3.76 (s, 3H), 2.42–2.37 (m, apparent septet, 1H), 0.73–0.66 (m, 2H), 0.51–0.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (160.7, 150.1, 129.8, 106.4, 102.7, 99.1, 55.0, 25.2, 7.1; IR (neat, cm^{-1}) 3401, 3092, 3006, 2954, 2835, 1618, 1506, 1460, 1374, 828, 775, 696; Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 7.97; N, 8.58; Found: C, 73.41; H, 8.09; N, 8.48.

3.2.5. 4-Chloro-*N*-cyclopropylaniline (10b). Starting with 4-chlorobromobenzene, the general procedure gave 0.112 g (67%) of 4-chloro-*N*-cyclopropylaniline (colorless oil).[9]

3.2.6. *N*-Cyclopropyl-1-napthylamine (11b). Starting with 1-bromonaphthalene, the general procedure gave 0.187 g (99%) of *N*-cyclopropyl-1-napthylamine (white solid), mp 36–37°C[11,12]. ^{1}H NMR ($CDCl_3$, 250 MHz) (7.74 (dd, 1H *J*=7.6, 1.6 Hz), 7.60 (dd, 1H, *J*=7.7, 0.9 Hz) 7.41–7.22 (m, 4H) 7.00 (dd, 1H, *J*=5.8, 1.1 Hz), 4.73 (s, br, 1H), 2.50–2.42 (m, apparent septet, 1H), 0.78–0.70 (m, 2H), 0.57–0.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (143.8, 134.1, 128.5, 126.5, 125.5, 124.5, 123.1, 119.7, 117.7, 105.7, 25.4, 7.5; IR (KBr, cm^{-1}) 3401, 3059, 3013, 1585, 1519, 1472, 1368, 760.

3.2.7. *N*-Cyclopropyl-9-anthracenamine (12b). Starting with 9-bromoanthracene, following the general reaction procedure, the resulting mixture was immediately absorbed onto silica gel. During separation by flash column chromatography, to avoid oxygen, argon was applied to generate pressure on the top of the column. *N*-Cyclopropyl-9-anthracenamine **12b** (0.150 g (64%)) was isolated as yellow oil. The product was stored under argon. ^{1}H NMR ($CDCl_3$, 250 MHz) (8.30–8.25 (m, 2H), 8.05 (s, 1H), 7.92–7.88 (m, 2H), 7.41–7.35 (m, 4H), 4.45 (s, br, 1H), 3.03–2.94 (m, apparent septet, 1H), 0.62–0.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz) (140.5, 132.3, 128.7, 125.1, 125.0, 124.3, 123.5, 120.9, 32.9, 8.6; IR (neat, cm^{-1}) 3414, 3072, 3012, 1600, 1420, 1360, 788, 736, 696; HRMS (EI): *m/z* 233.1205 (calcd for $C_{17}H_{15}N$ 233.1204).

[†] An alternative isolation procedure involved the direct absorption of the reaction mixture onto silica gel without the addition of ether and subsequent filtration. This alternative is better for oxygen labile products that can be destroyed by the trace amounts of peroxide in the ether.

3.2.8. *N*-Cyclopropyl-9-azaanthraquinone (12c). *N*-Cyclopropyl-9-azaanthraquinone, 0.110 g (47%), was obtained from the reaction of 9-bromoanthracene as described above when the workup was carried out in air. ^{1}H NMR ($CDCl_3$, 250 MHz) (8.35–8.12 (m, 4H), 7.70–7.48 (m, 4H), 3.75–3.67 (m, 1H), 1.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 63 MHz) (184.5, 154.7, 139.9, 133.5, 133.2, 131.9, 131.6, 131.2, 130.2, 129.4, 128.2, 127.8, 126.1, 125.2, 37.4, 12.2; IR (neat, cm^{-1}) 3072, 3006, 1670, 1597, 1466, 1302, 802, 742, 702; HRMS (EI): *m/z* 247.0991 (calcd. for $C_{17}H_{13}NO$ 247.0997).

3.2.9. *N*-cyclopropyl-9-phenanthrenamine (13b). The general procedure gave 0.160 g (69%) of *N*-cyclopropyl-9-phenanthreneamine (yellow oil). ^{1}H NMR ($CDCl_3$, 250 MHz) (8.66 (d 1H J=8.3 Hz), 8.58 (d 1H J=8.3 Hz), 7.74–7.28 (m, 6H) 7.19 (s, 1H), 4.74 (s, br, 1H), 2.63–2.55 (m, apparent septet, 1H), 0.875–0.79 (m, 2H), 0.65–0.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (141.5, 133.7, 130.9, 126.8, 126.7, 126.4, 126.1, 125.5, 125.2, 123.4, 122.9, 122.4, 120.0, 103.6, 25.5, 7.5.; IR (neat, cm^{-1}) 3408, 3072, 3013, 2967, 1611, 1519, 1435, 1368, 834, 742; HRMS (EI): *m/z* 233.1209 (calcd for $C_{17}H_{15}N$ 233.1204).

3.2.10. *N*-Cyclopropyl-3-pyridinamine (14b). The reaction was run under the same condition as the general procedure except 4 mol% Pd was employed and the flash column was eluted with 33% EtOAc in hexane. *N*-Cyclopropyl-3-pyridinamine (yellow oil) (0.07 g (52%)) was isolated. ^{1}H NMR ($CDCl_3$, 250 MHz) (8.1 (s, 1H), 7.94 (t, 1H, J=3.1 Hz), 7.04 (m, 2H), 4.29 (s, br, 1H), 2.42–2.35 (m, 1H), 0.76–0.69 (m, 2H), 0.51–0.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) (144.6, 139.1, 136.1, 123.5, 119.5, 24.7, 7.4; IR (neat, cm^{-1}) 3250, 3085, 3026, 1591, 1486, 1374, 802, 709; Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88; Found: C, 71.19; H, 7.47; N, 20.24.

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