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Mild and Practical Method for the α-Arylation of Nitriles with Heteroaryl Halides

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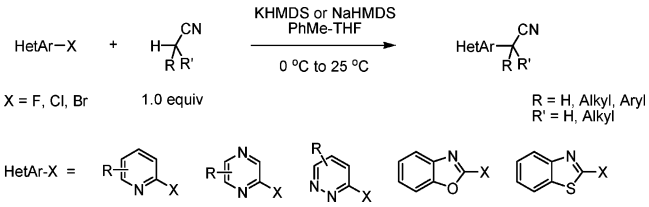
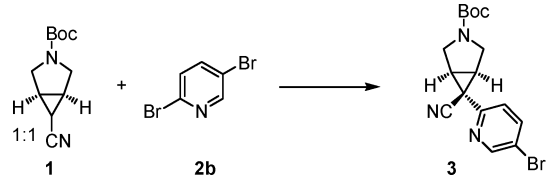


A mild and transition-metal-free method for the α-arylation of aliphatic nitriles with activated heteroaryl halides was developed using NaHMDS or KHMDS as base at ambient temperature. The key to the success of this method is generation of the nitrile anion in the presence of the heteroaryl halide. The method is applicable to both primary and secondary carbonitriles and a wide range of heteroaryl halides. Selective monoarylation was observed with primary carbonitriles. The operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative to the preparation of α-heteroaryl carbonitriles.

The α-arylation of aliphatic nitriles is a valuable synthetic transformation that has remained largely undeveloped. The Pd-catalyzed α-arylation of nitriles has recently emerged as a major advancement;[1] however, its utility is still limited by the relatively harsh coupling conditions (i.e., strong base, high reaction temperature) which may not be compatible with complex substrates containing base-sensitive groups. Direct nucleophilic aromatic substitution (S_NAr) provides an alternative approach but also suffers from the use of strong bases such as ^{n}BuLi[2] or $NaNH_2$[3] as well as high reaction temperatures and moderate yields.[4] An improved procedure for the S_NAr arylation of secondary nitriles with various aryl fluorides, even including electron-rich aryl fluorides, was recently disclosed by Caron.[5] However, only one example of a heteroaryl fluoride was included, and applicability of this method to heteroaryl halides other than fluorides was not addressed.

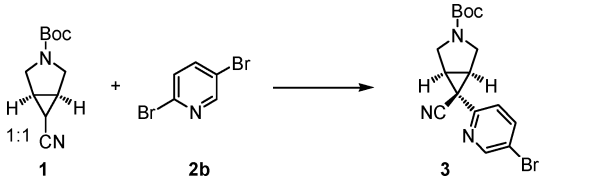
While developing a route to a drug candidate, we encountered a particularly challenging α-arylation reaction of a functionalized cyclopropanecarbonitrile **1** (available as a 1:1 mixture of diastereomers) with 2,5-dibromopyridine (**2b**) (eq 1). Several Pd-catalyzed coupling



(1)

conditions were applied to this transformation, yet only the procedure reported by Verkade[1a] provided any of the desired product in a modest 44% yield (Table 1, entry 1). A single diastereomer of **3** was obtained, which was presumably due to severe steric hindrance from the concave side of the metalated nitrile intermediate. Interestingly, the yield of the coupling reaction could be improved to 53% if the reaction was performed at room temperature instead of 60 °C (entry 2). This result was somewhat unexpected because the reported examples of Pd-catalyzed arylation of nitriles have typically required elevated temperatures. In our case, the heteroaryl halide **2b** was highly activated, and we suspected that the nitrile anion could undergo an uncatalyzed substitution at the pyridine ring.[6] Indeed, a comparable yield of 57% and >99% de was obtained if the Pd catalyst was omitted

TABLE 1. Arylation of Nitrile 1 with 2,5-Dibromopyridine 2b[a]



entry	catalyst	base, equiv	*T*, °C	conv of **1**, %	conv of **2b**, %	yield of **3**,[b] %
1	Verkade[c]	1.2	60	n.d.	n.d.	44
2	Verkade[c]	1.2	25	90	80	53
3	none	1.2	25	86	74	57
4	none	1.2 (sep)[d]	25	54	31	5
5	none	1.0	25	86	82	65
6	none	1.5	25	93	94	42
7	none	1.2	−40 to 25[e]	89	86	61

[a] General procedure: A 1.0 M solution of NaHMDS was added to a solution of **1** (1.0 equiv) and **2b** (1.0 equiv) in toluene at 25 °C, and the reaction was aged for 15−20 h. [b] HPLC assay yield. [c] 4 mol % of $Pd(OAc)_2$ and 8 mol % of 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane. [d] NaHMDS was added to a solution of nitrile **1** in toluene at 25 °C, and the mixture was aged at 25 °C for 1 h and then added to bromide **2b**. [e] NaHMDS was added to a solution of **1** and **2b** in toluene at −40 °C, and the reaction mixture was allowed to warm to 25 °C over 15 h.

(1) (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (d) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.

(2) Skerlj, R. T.; Bogucki, D.; Bridger, G. J. *Synlett* **2000**, 1488.

(3) (a) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M.; Fricano, R. *J. Am. Chem. Soc.* **1951**, *73*, 5752. (b) Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sadcheva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, *48*, 1180.

(4) (a) Loupy, A.; Philippon, N.; Pigeon, P.; Galons, H. *Heterocycles* **1991**, *32*, 1947. (b) Sleevi, M. C.; Cale, A. D. Jr.; Gero, T. W.; Jaques, L. W.; Welstead, W. J.; Johnson, A. F.; Kilpatrick, B. F.; Demian, I.; Nolan, J. C.; Jenkins, H. *J. Med. Chem.* **1991**, *34*, 1314.

(5) Caron, S.; Vazquez, E.; Wojcik, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 712.

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TABLE 2. Stability Tests in the Presence of NaHMDS at 25 °C[a]

entry	compd	time	assay,[b] %
1	**1**	15 h	40
2	**2b**	15 h	17
3	**3**	15 h	18
4	2-bromopyridine	15 h	96
5	3-bromopyridine	5 min	93
6	3-bromopyridine	1 h	45
7	3-bromopyridine	15 h	0.5

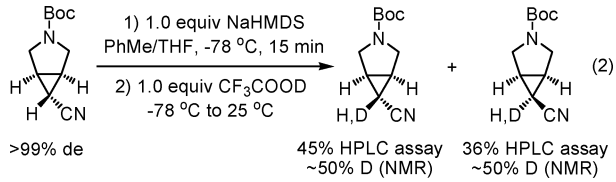
[a] General procedure: A 1.0 M solution of NaHMDS in THF was added to a solution of the compound in toluene at 25 °C and aged at 25 °C for the time indicated in the table. [b] HPLC assay of the compound remaining in the reaction mixture.

(entry 3). This promising lead invited further explorations of the uncatalyzed nucleophilic aromatic substitution reaction.

In the preceding examples (Table 1, entries 1−3), sodium hexamethyldisilazide base (NaHMDS) was added to a mixture of both starting materials. When the deprotonation of nitrile **1** was carried out separately and was then followed by addition of bromide **2b**, a dramatically reduced yield of product **3** was obtained (Table 1, entry 4). Even when the base was added to a mixture of both starting materials **1** and **2b**, only a partial conversion was observed using 1.2 and 1.0 equiv of base (Table 1, entries 3 and 5). When 1.5 equiv of the NaHMDS base was used in an effort to drive the reaction to completion, a significantly lowered yield of **3** was actually observed despite some of the starting material still remaining (Table 1, entry 6). These results strongly indicated that a base-promoted decomposition was competing with the desired α-arylation reaction.

The decomposition pathways were investigated in more detail. When starting materials **1**, **2b**, and product **3** were separately treated with 1.5 equiv of NaHMDS under the conditions mimicking the α-arylation reaction, a significant decomposition was observed in all three cases (Table 2, entries 1−3). The bromide ion was detected by HPLC as the only identifiable decomposition product of compounds **2b** and **3**. This observation was consistent with a decomposition mechanism involving an unstable pyridyne intermediate.[7] A brief exploration of two model systems, 2-bromopyridine and 3-bromopyridine, showed that 2-bromopyridine was perfectly stable in the presence of NaHMDS (Table 2, entry 4) while 3-bromopyridine decomposed rapidly (Table 2, entries 5−7). This allowed us to pinpoint the 3-bromo substituent as the most likely source of instability in the starting material **2b** and product **3**.

Decomposition of nitrile **1** was addressed next. Starting with a pure convex diastereomer of **1**, clean epimerization and the expected 50% deuterium incorporation[8] were observed when the deprotonation and deuterium quenching was carried out at −78 °C (eq 2). The deprotonated



nitrile was stable only at low temperatures because a significantly lower assay (35% total of both diastereomers) was obtained at 0 °C along with a complex mixture of unidentified decomposition products.[9] In an attempt to minimize the decomposition of the deprotonated nitrile, one α-arylation experiment was performed wherein the NaHMDS base was added to a solution of both starting materials **1** and **2b** at −40 °C, and the reaction mixture was allowed to slowly reach room temperature (Table 1, entry 7). However, very little improvement in the product yield was observed, which could be due to an insufficient rate of α-arylation at −40 °C.

It became clear that in order to overcome the base-promoted decomposition of the starting materials and the product, the relative rate of the α-arylation had to be increased. Several solvents[10] and bases[11] were screened with the bromide **2b** under the premise that an S_NAr reaction would exhibit a strong dependence on the solvent polarity and the counterion, yet no improvements over the original conditions (THF/toluene solvent, NaHMDS base) could be achieved. We then resorted to a different approach whereby the reactivity of the pyridine electrophile was tuned through the choice of the leaving group. Gratifyingly, replacing the 2-bromo substituent in **2b** with a 2-fluoro substituent (**2d**) resulted in a dramatic increase in the product yield (Table 3, entry 9).[12] Interestingly, the effects of the metal cation and the leaving group were interrelated because NaHMDS provided the best results with the bromide **2b** (Table 3, entry 3) while KHMDS gave the highest yield with fluoride **2d** (Table 3, entry 10). The latter example was demonstrated on a 2 g scale in a 96% assay yield, and the product was isolated in a 92% yield (99 wt % purity) after crystallization from 2:1 water−ethanol.

Although the optimized conditions for the α-arylation of the sensitive nitrile **1** with fluoropyridine **2d** resembled the procedure developed by Caron,[5] which mainly targeted the α-arylation of nitriles with unactivated aryl fluorides,[13] we found that in our case the reaction proceeded under significantly milder conditions. The reaction could be performed at room temperature instead of heating at 70 °C; furthermore, we were able to use 1.0 equiv of the nitrile and 1.0 equiv of base instead of 4.0 and 1.5 equiv, respectively, without compromising the

(6) Displacement of halo substituents at α- and γ-positions of pyridines via an addition−elimination mechanism is well precedented with other nucleophiles. See: Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*; Chapman and Hall: London, 1995; p 82.

(7) (a) Zoltewicz, J. A.; Smith, C. L. *Tetrahedron* **1969**, *25*, 4331. (b) Mallet, M.; Queguiner, G. *Tetrahedron* **1982**, *38*, 3035. (c) Connon, S. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245.

(8) We expect only 50% deuterium incorporation because hexamethyldisilazane, which was formed in the NaHMDS deprotonation step, contains an exchangeable proton.

(9) The concave diastereomer of **1** provided comparable results in the deprotonation−deuteration experiments.

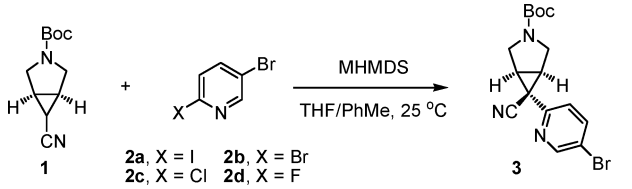
(10) The following solvents provided lowered yields of **3** compared to PhMe/THF: DMSO, DMA, PhCN, ^{t}BuCN, THF.

(11) A low yield of **3** was obtained with the following bases: DBU/PhMe at 80 °C, NaO^{t}Bu/^{t}BuOH at 50 °C, NaO^{t}Bu/PhMe at 80 °C, NaH/THF at 60 °C, KO^{t}Bu/PhMe at rt, ^{n}BuLi at −78 °C to rt, LiTMP at −78 °C to rt.

(12) The same product **3** was obtained from either **2b** and **2d**, which is consistent with the 2-halo and not the 5-bromo substituent being displaced on the pyridine ring.

(13) Only one example of a heteroaryl fluoride was reported by Caron.

TABLE 3. Effect of the Leaving Group and the Cation on the Arylation of Nitrile 1[a]



entry	X	M	conv of **1**, %	conv of **2**, %	yield of **3**,[b] %
1	I	Na	86	78	48
2	Br	Li	81	18	10
3	Br	Na	82	76	63
4	Br	K	71	75	35
5	Cl	Li	71	7	8
6	Cl	Na	73	75	62
7	Cl	K	58	65	40
8	F	Li	97	36	29
9	F	Na	96	92	83[c]
10	F	K	>99	96	96[d]

[a] General procedure: A solution of MHMDS was added to a solution of **1** (1.0 equiv) and **2b** (1.0 equiv) in toluene at 25 °C, and the reaction mixture was aged for 15−20 h. [b] HPLC assay yield. [c] Demonstrated on 1 g of **1** in 89% assay and 86% isolated yield (99 wt % purity, heptane as crystallization solvent). [d] Demonstrated on 2 g of **1** in 96% assay and 92% isolated yield (99 wt % purity, 2:1 water−ethanol as crystallization solvent).

product yield. Consequently, we became interested if these mild conditions were applicable to α-arylation of nitriles with other heteroaryl halides.

The α-arylation of cyclopropanecarbonitrile (**4**) with bromide **2b** turned out to be even more challenging than the arylation of **1** (Table 4, entry 2). Nevertheless, the use of the fluoride **2d** provided a 75% isolated yield (Table 4, entry 1). These results were in contrast to the arylation of isobutyronitrile, which proceeded in a high yield even with the base-sensitive bromide **2b** (Table 4, entry 3).[14] Exploring the substrate scope further, we observed that a 2-chloro group reacted exclusively in the presence of a 3-fluoro group on the pyridine ring (Table 4, entry 4). The reaction also tolerated relatively hindered secondary nitriles (Table 4, entries 5 and 6). We then turned our attention to primary nitriles, which according to Caron are unreactive toward unactivated aryl fluorides.[5] In our case, primary nitriles turned out to be excellent substrates for arylation with heteroaryl halides (entries 7−12). Moreover, only the monoarylation products were observed even if 2 equiv of the arylating agent was used (entry 8). This selectivity is interesting considering that the products of the monoarylation reactions are sterically similar to 2-phenylbutyronitrile in entry 6, which is a competent arylation substrate. Apparently, the electron-withdrawing pyridyl group is detrimental to the nucleophilicity of the nitrile anion. In fact, the reactions with primary nitriles proceeded best with 2 equiv of base (cf. entries 9 and 10), presumably because 1 equiv of the base was consumed to deprotonate the product. Acetonitrile suffered extensive dimerization when 2-chloropyridine was used as the arylating agent (entry 12). Fortunately, the dimerization was suppressed when the more reactive 2-fluoropyridine was used as the arylating agent (entry 11).

The reaction could be extended to other activated heteroaryl halides (Table 4, entries 13−18). Although 2-chloropyrimidine (entry 15) turned out to be a challenging substrate, the arylation was highly successful with other heterocycles including an isoquinoline, pyridazine, pyrazine, benzoxazole, and benzothiazole. These reactions could be readily carried out with heteroaryl chlorides, which are generally more available and less expensive than the corresponding heteroaryl fluorides.

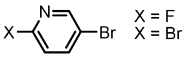
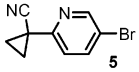
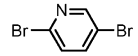
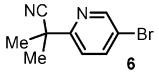
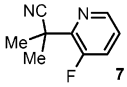
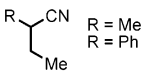
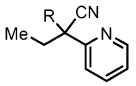
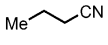
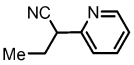
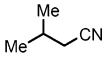
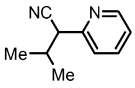
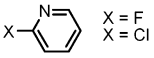
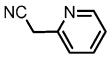
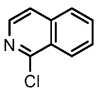
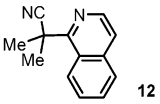
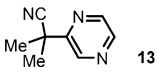
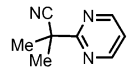
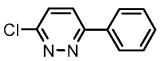
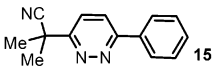
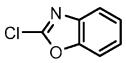
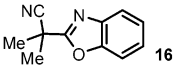
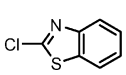
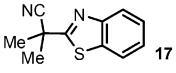
In summary, we have developed a mild, practical, and transition-metal-free method for the α-arylation of aliphatic nitriles with activated heteroaryl halides using NaHMDS or KHMDS as base at ambient temperature. The key to the success of this method is generation of the nitrile anion in the presence of a heteroaryl halide whereby any competing decomposition pathways are minimized. The method is applicable to both primary and secondary carbonitriles and a wide range of heteroaryl halides. Selective monoarylation is observed with primary carbonitriles. In most cases, either heteroaryl bromides, chlorides, or fluorides could be used as the arylating agents although the more reactive aryl fluorides provided better results with particularly sensitive substrates. We believe that the operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative to the preparation of α-heteroaryl carbonitriles.

Experimental Section

(1*R,5*S**,6*S**)-6-(5-Bromopyridin-2-yl)-6-cyano-3-azabicyclo[3.1.0]hexane-3-carboxylic Acid *tert*-Butyl Ester (3).** An oven dried 100 mL round-bottom flask with magnetic stirring and an internal temperature probe was evacuated and backfilled three times with nitrogen. The flask was charged with nitrile **1** (a 1:1 mixture of diastereomers, 2.00 g, 9.60 mmol, 1.0 equiv) and 10 mL of dry toluene and cooled to 0 °C. 2-Fluoro-5-bromopyridine (1.69 g, 9.60 mmol, 1.0 equiv) was added followed by KHMDS (20.4 mL of 0.47 M solution in toluene, 9.60 mmol, 1.0 equiv) over 20 min, maintaining the internal temperature below 3 °C. The reaction was stirred at 0 °C for 1 h, after which time the cold bath was removed and the viscous brown mixture was stirred at room temperature overnight. The solution darkened as it warmed to room temperature. The reaction was checked for completeness by TLC analysis, and the reaction mixture was diluted with 80 mL of MTBE and washed with water (3 × 40 mL). The organic layer was separated and concentrated to ~30 mL and the solvent switched to ethanol (3 × 30 mL). Water (40 mL) was added dropwise with stirring for 90 min at room temperature to precipitate the product. A single diastereomer of the product (3.24 g, 93%) was then isolated as a tan powder: 98.9 HPLC area %; 99.4 wt % by HPLC; mp 146.7−148.5 °C; IR (film) 1699.78, 1403.86, 1372.92, 1171.97, 1122.46 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 2.4 Hz, 1H, pyridine H-6), 7.82 (dd, J = 2.4, 8.4 Hz, 1H, pyridine H-4), 7.67 (d, J = 8.4 Hz, 1H, pyridine H-3), 3.96 (d, 1H, J = 12.2 Hz), 3.87 (d, 1H, J = 12.1 Hz), 3.73 (m, 2H), 2.66 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 152.4, 150.8, 139.5, 122.5, 119.3, 116.2, 80.4, 47.3, 47.0, 35.7, 35.1, 28.7, 26.5. Anal. Calcd for $C_{16}H_{18}O_2N_3Br$: C, 52.75; H, 4.98; N, 11.54. Found: C, 52.72; H, 4.94; N, 11.47.

(14) The lowered acidity of cyclopropanecarbonitrile, caused by the nonplanar nature of the carbanion, can be invoked to explain the reactivity difference between cyclopropanecarbonitrile and isobutyronitrile. See: (a) Peerboom, R. A. L.; de Koning, L. J.; Nibbering, N. M. M. *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 159. (b) Juchnovski, I. N.; Tsenov, J. A.; Binev, I. G. *Spectrochim. Acta A* **1996**, *52*, 1145. However, we were able to show that the anion of the functionalized cyclopropanecarbonitrile **1** could be generated even at −78 °C using NaHMDS. Interference from an unidentified decomposition pathway thus appears to be a more likely explanation for the poor reactivity of cyclopropanecarbonitriles in these α-arylation reactions.

TABLE 4. Coupling of Various Nitriles with Heteroaryl Halides

Entry	Nitrile	Electrophile	Base (equiv)	Product	Isolated Yield (%)
1 2	 **4**	 X = F X = Br	KHMDS (1.0) NaHMDS (1.0)	 **5**	75 decomp.
3			NaHMDS (1.0)	 **6**	92
4			NaHMDS (1.0)	 **7**	87
5 6	 R = Me R = Ph		KHMDS (1.0) KHMDS (1.0)	 **8**	56 (**8a**, R = Me) 91 (**8b**, R = Ph)
7 8		 X = F (1.0 equiv) X = Cl (2.0 equiv)	KHMDS (2.0) NaHMDS (2.0)	 **9**	88 61
9 10			NaHMDS (1.0) NaHMDS (2.0)	 **10**	31 71
11 12	MeCN	 X = F X = Cl	KHMDS (2.0) NaHMDS (2.0)	 **11**	83 15
13			NaHMDS (1.0)	 **12**	98
14			NaHMDS (1.0)	 **13**	65
15			NaHMDS (1.0)	 **14**	decomp.
16			NaHMDS (1.0)	 **15**	52
17			NaHMDS (1.0)	 **16**	89
18			NaHMDS (1.0)	 **17**	88

General Procedure for Coupling of Nitriles with Heteroaryl Halides (Table 4). An oven-dried Schlenk tube with magnetic stir bar was evacuated and backfilled with nitrogen three times and charged with nitrile (1.00 mmol), aryl halide (1.00 mmol), and dry toluene. The reaction mixture was cooled to 0 °C, and hexamethyldisilazide base (1.00 mmol for tertiary nitriles and 2.00 mmol for primary and secondary nitriles) was added dropwise over 5 min. For heteroaryl fluorides, a 0.47 M solution of KHMDS in toluene was used. For heteroaryl chlorides or bromides, a 1.0 M solution of NaHMDS in THF was used. The total reaction volume was 3 mL. The solution was then stirred at 0 °C for 1 h and then at rt overnight. Reaction completion was checked by TLC analysis, the reaction mixture was filtered through a syringe filter (0.45 μm), and the filtrate was purified by silica gel column chromatography to afford the coupled products.

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

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