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Palladium-Catalyzed Intramolecular N-Arylation of Heteroarenes: A Novel and Efficient Route to Benzimidazo[1,2-*a*]quinolines

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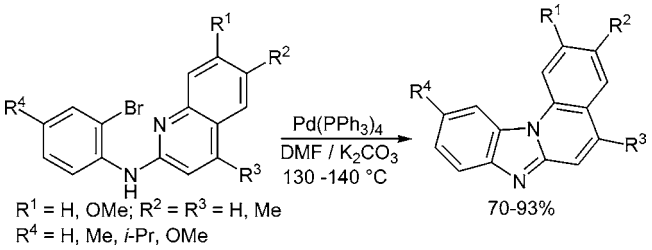
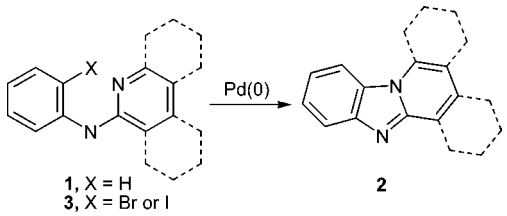


An efficient new route for the synthesis of benzimidazo-[1,2-*a*]quinolines has been developed via the palladium-catalyzed intramolecular Buchwald−Harwtig aryl amination of newly synthesized 2-(2′-bromoanilino)quinolines.

Substituted benzimidazoles and their azino fused variants such as pyrido[1,2-*a*]benzimidazoles have attracted considerable attention from medicinal and synthetic organic chemists because of the wide range of biological activities[1] (anxiolytic,[2] antifungal/antibacterial,[3] antineoplastic,[4] anticancer,[5] DNA intercalator[6]) displayed by this class of compounds. On the other hand, the corresponding benzoannulated analogues such as benzimidazo-[1,2-*a*]quinolines, benzimidazo[2,1-*a*]isoquinolines, and benzimidazo[1,2-*f*]phenanthridines have remained unexplored for their biological activity which may be because of the lack of general synthetic methods for these classes of heteroaromatics from easily accessible precursors. A few of the pyrido[1,2-*a*]- and pyridazino[1,6-*a*]benzoimidazolium salts with fused aromatic rings to the cationic heterocycles are reported to exhibit enhanced DNA intercalation properties.[6,7] Among the various routes[1,6−10] available for the synthesis of pyrido[1,2-*a*]benzimidazole and its condensed analogues, one of the approaches involves formation of a five-membered heterocyclic ring via intramolecular ring closure of an intermediate of the type **1** (usually a radical) containing an aryl group attached to a six-membered heteroaromatic ring via nitrogen (Scheme 1). This approach usually involves thermal or photochemical cyclization and often affords systems such as **2** in low yields.[11−13] Besides, the precursors for the intermediate **1** (often a benzotriazole derivative) are usually synthesized starting from *o*-chloronitrobenzenes[14] which further narrows the scope for diversification in these fused target systems. During the course of our continued interest in the development of new general synthetic routes for substituted and condensed heteroaromatics,[7,15−17] we became interested in examining the ring closure of the systems of the type **3** via palladium-catalyzed intramolecular N-arylation of heteroarenes, analogous to the Buchwald−Hartwig aryl

SCHEME 1



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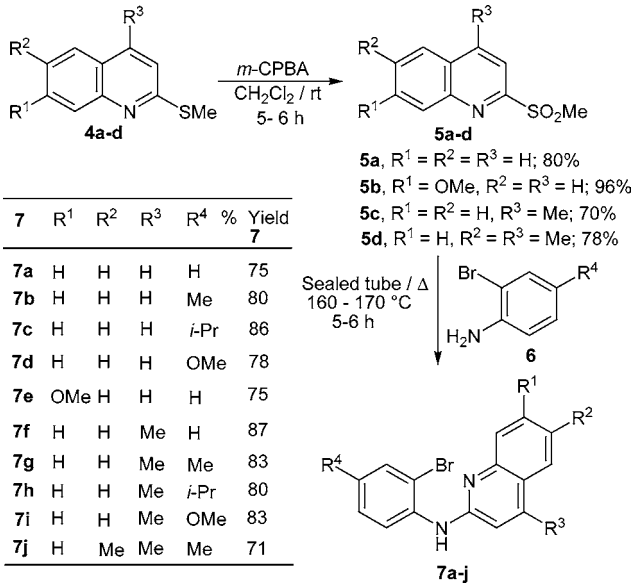
SCHEME 2



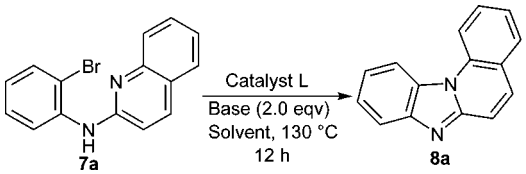
7	R^1	R^2	R^3	R^4	% Yield 7
7a	H	H	H	H	75
7b	H	H	H	Me	80
7c	H	H	H	*i*-Pr	86
7d	H	H	H	OMe	78
7e	OMe	H	H	H	75
7f	H	H	Me	H	87
7g	H	H	Me	Me	83
7h	H	H	Me	*i*-Pr	80
7i	H	H	Me	OMe	83
7j	H	Me	Me	Me	71

amination.[23] A recent report by Batey for the synthesis of 2-aminobenzimidazoles[18] via intramolecular C−N bond formation between an aryl halide and a guanidine moiety in the presence of a palladium (Buchwald−Hartwig coupling)[19,20] or copper catalyst further prompted us to attempt this type of cyclization on 2-(2-bromoanilino)quinolines **7** with a view to develop a novel approach for the synthesis of benzimidazo-[1,2-*a*]quinolines. We have successfully achieved this goal and report herein the results of our investigation.

The requisite cyclization precursors, i.e., 2-(2-bromoanilino)-quinolines **7a**−**j**, are readily synthesized by the methods developed in our laboratory (Scheme 2).[21] Thus, the substituted 2-(methylthio)quinolines **4a,b** were obtained by the reported procedure involving acid-induced cyclocondensation of anilines with bis(methylthio)acrolein,[21] whereas the 4-methyl-2-(methylthio)quinolines **4c,d** were prepared in high yields by a Combe's-type cyclization[22] of the respective α-acetyl-*N*,*S*-anilinoacetals in the presence of PPA. The oxidation of 2-(methylthio)quinolines **4a**−**d** with *m*-CPBA furnished the respective 2-(methylsulfonyl)quinolines **5a**−**d** (70−96%) which underwent facile displacement of the methylsulfonyl group with various 2-bromoanilines **6** under thermal conditions**,** affording the desired 2-(2-bromoanilino)quinolines **7a**−**j** in overall high yields (Scheme 2).

The 2-(2-bromoanilino)quinoline **7a** was chosen as a representative substrate for the synthesis of **8a**, and optimization studies with various palladium sources, ligands, solvents, temperatures, and bases were undertaken (Table 1). Intramolecular cyclization of **7a** using $Pd(OAc)_2$ (10 mol %) and PPh_3 (40 mol %) with base-like K_2CO_3 was first investigated with various solvents (DMF, DME, and CH_3CN) which gave only moderate yields of benzimidazo[1,2-*a*]quinoline **8a** (Table 1, entries 2−4). Use of the tris(*o*-tolyl)phosphine ligand also led to only a moderate conversion at 130 °C (Table 1, entries 5 and 6). Interestingly, the use of sodium bicarbonate as base in DMF gave **8a** (55%) along with the formation of indolo[2,3-*b*]quinoline[17b] **9a** (25%) via intramolecular Pd-catalyzed C-arylation on the 3-position of the quinoline ring of **7a** (Table 1, entry 7). Use of $PdCl_2$ or $Pd_2(dba)_3$ also resulted in only lower conversion to **8a** (Table 1, entries 8−10). On the other hand, use of $Pd(PPh_3)_4$ (10 mol %) in DMF with K_2CO_3 as base showed maximum conversion of **7a** to **8a** (75%) at 130 °C (Table 1, entry 11). Reaction at a lower temperature with a Pd-$(PPh_3)_4$ catalyst resulted in a decreased yield of **8a** (entry 12) or failure of the reaction (entry 13), as did lowering the amount of $Pd(PPh_3)_4$ catalyst (Table 1, entry 14).

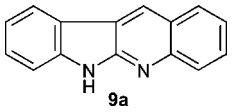
TABLE 1. Palladium-Catalyzed Intramolecular N-Arylation: Catalyst, Ligand, Temperature, and Solvent Effects on the Cyclization of 7a to 8a



(Eq. 1)

entry	catalyst	mol %	L	mol %	base	temp	solvent	% yield[a]
1					K_2CO_3	130 °C	DMF	0
2	$Pd(OAc)_2$	10	PPh_3	40	K_2CO_3	130 °C	DMF	57
3	$Pd(OAc)_2$	10	PPh_3	40	K_2CO_3	130 °C	DME	50
4	$Pd(OAc)_2$	10	PPh_3	40	K_2CO_3	130 °C	CH_3CN	45
5	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	12.5	K_2CO_3	130 °C	toluene	48
6	$Pd(OAc)_2$	10	P(*o*-tol)$_3$	12.5	K_2CO_3	130 °C	DMF	52
7	$Pd(OAc)_2$	10	PPh_3	40	$NaHCO_3$	130 °C	DMF[b]	55
8	$PdCl_2$	10	PPh_3	40	K_2CO_3	130 °C	CH_3CN	38
9	$PdCl_2$	10	dppp	12.5	Cs_2CO_3	130 °C	DMF	33
10	$Pd_2(dba)_3$	10	PPh_3	40	K_2CO_3	130 °C	DMF	51
11	$Pd(PPh_3)_4$	10			K_2CO_3	130 °C	DMF	75
12	$Pd(PPh_3)_4$	10			K_2CO_3	80 °C	DMF	43
13	$Pd(PPh_3)_4$	10			K_2CO_3	rt	DMF	0
14	$Pd(PPh_3)_4$	5			K_2CO_3	130 °C	DMF	40

[a] Isolated yields. [b] The indoloquinoline **9a** (25%) was formed along with **8a**.



9a

The intramolecular, heteroarene N-arylation was applied to various substituted 2-(2-bromoanilino)quinolines **7b**−**j** using optimized reaction conditions with the goal to examine the scope and generality of this novel cyclization reaction. In general, excellent yields (70−93%) of substituted benzimidazo[1,2-*a*]-quinolines **8b**−**j** are obtained from the substrates **7b**−**j** bearing various substitutents (methyl, isopropyl, or methoxy groups) in different positions of either the quinoline ring or the anilino moiety (Table 2).

The probable mechanism for the formation of benzimidazo-[1,2-*a*]quinolines **8a**−**j** from **7a**−**j** under palladium catalysis is shown in Scheme 3. The intermediate **10** formed by the oxidative addition of palladium(0) to **7** undergoes intramolecular nucleophilic attack by basic quinoline nitrogen with elimination

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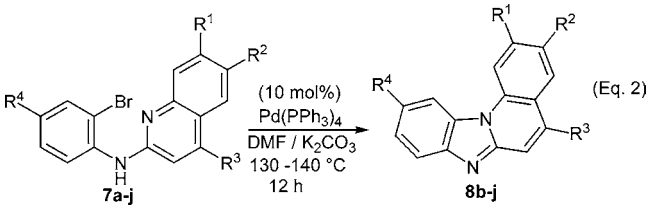
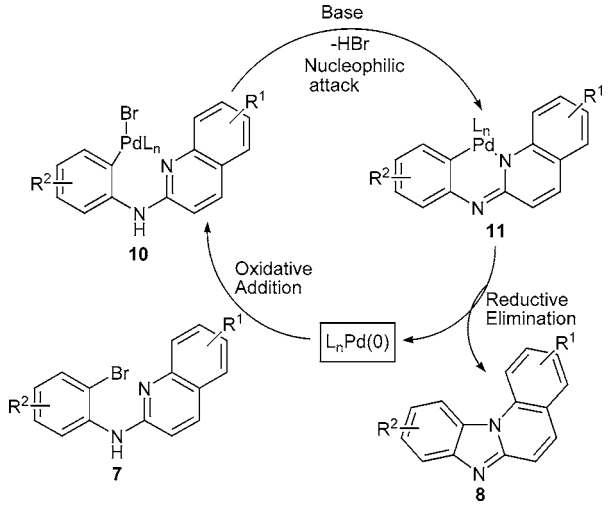
TABLE 2. Synthesis of Benzimidazo[1,2-*a*]quinolines 8



entry	8	R^1	R^2	R^3	R^4	% yield[a] 8
1	**8b**	H	H	H	Me	70
2	**8c**	H	H	H	*i*-Pr	82
3	**8d**	H	H	H	OMe	88
4	**8e**	OMe	H	H	H	91
5	**8f**	H	H	Me	H	93
6	**8g**	H	H	Me	Me	88
7	**8h**	H	H	Me	*i*-Pr	87
8	**8i**	H	H	Me	OMe	92
9	**8j**	H	Me	Me	Me	92

[a] Isolated yields.

SCHEME 3



of HBr to give six-membered palladacycle intermediate **11** which subsequently yields the benzimidazo[1,2-*a*]quinolines **8a**−**j** via reductive elimination accompanied by N−C bond formation.

In conclusion, we have developed a new high-yielding route for benzimidazo[1,2-*a*]quinolines via palladium-catalyzed intramolecular heterocyclization of readily accessible 2-(2-bromoanilino)quinolines. The overall process involves Buchwald−Hartwig intramolecular aryl amination in which a heteroarene ring nitrogen participates in N−C bond formation.[23,24] We are currently investigating the construction of other biologically important azino-fused heteroaromatics such as pyrido[1,2-*a*]-benzimidazoles, benzothiazoles, benzimidazo[2,1-*a*]isoquinolines, benzimidazo[1,2-*f*]phenanthridines, imidazo[1,2-*a*]pyridines, and other related ring systems[25] following this approach with a hope to expand the scope of this methodology.

Experimental Section

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$. TMS was used as an internal reference. Melting points are uncorrected. Chromatographic purification was conducted by column chromatography using 100−200 mesh silica gel obtained from a commercial supplier. DMF and CH_2Cl_2 were distilled over CaH_2 and stored over molecular sieves. THF and toluene were distilled over sodium/benzophenone prior to use. *n*-BuLi (1.6 M solution in hexane) and substituted 2-bromoanilines were purchased from standard firms and used directly. *m*-CPBA (50−55% suspension in water) was diluted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. $Pd(PPh_3)_4$ was freshly prepared according to the reported procedure.[26a] All the known[21] (**4a**−**c**) and unknown quinoline (**4d**) was prepared according to our previously reported method.

General Procedure for the Synthesis of 2-(2′-Bromoanilino)-quinolines 7a−j. A mixture of 2-(methylsulfonyl)quinolines **5a**−**d** (2.0 mmol) and the corresponding 2-bromoanilines (8.0 mmol) was heated at 160−170 °C in a sealed tube for 5−6 h (monitored by TLC) with constant stirring. It was then cooled, diluted with $CHCl_3$ (25 mL), and washed with water (2 × 25 mL) followed by brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the crude products **7a**−**j**, which were purified by column chromatography over silica gel using hexanes−EtOAc as eluent.

2-(2′-Bromoanilino)quinoline (7a): yield 75% (0.45 g); colorless crystals; mp 69−70 °C; R_f 0.82 (10:1 hexanes/EtOAc); IR (KBr) 3388, 1621, 1525, 1316, 1019, 808, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, J = 7.70, 1.72 Hz, 1H), 6.94 (d, J = 9.00 Hz, 1H), 7.12 (brs, 1H), 7.33 (dd, J = 8.04, 8.42 Hz, 2H), 7.57 (dd, J = 8.06, 1.48 Hz, 1H), 7.60 (dt, J = 7.82, 1.48 Hz, 1H), 7.65 (dd, J = 8.06, 1.24 Hz, 1H), 7.83 (d, J = 8.56 Hz, 1H), 7.94 (d, J = 9.04 Hz, 1H), 8.62 (dd, J = 8.18, 1.68 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 113.7, 120.4, 123.1, 123.6, 124.3, 127.0, 127.3, 128.1, 129.8, 132.5, 137.7, 138.0, 147.3, 153.2; MS (*m*/*z*, %) 299 (M + 1, 100), 301 (M + 1, 80). Anal. Calcd for $C_{15}H_{11}N_2Br$ (299.17): C, 60.22; H, 3.71; N, 9.36. Found: C, 60.11; H, 3.84; N, 9.48.

2-(2′-Bromoanilino)-7-methoxyquinoline (7e): yield 75% (0.49 g); colorless crystals; mp 108−109 °C; R_f 0.75 (10:1 hexanes−EtOAc); IR (KBr) 3402, 2363, 1625, 1593, 1526, 1451, 1413, 1370, 1312, 1215, 1022, 826, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.74 (d, J = 8.80 Hz, 1H), 6.85 (dt, J = 7.58, 1.48 Hz, 1H), 6.91 (dd, J = 8.76, 2.44 Hz, 1H), 7.12 (d, J = 2.44 Hz, 1H), 7.28 (dt, J = 8.54, 1.44 Hz, 1H), 7.47 (d, J = 8.80 Hz, 1H), 7.51 (dd, J = 7.92, 1.24 Hz, 1H), 7.81 (d, J = 8.80 Hz, 1H), 8.41 (dd, J = 7.68, 1.20 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 105.8, 109.9, 114.1, 116.0, 119.0, 120.8, 123.4, 128.1, 128.4, 132.6, 137.6, 137.9, 148.6, 153.7, 161.3; MS (*m*/*z*, %) 329 (M+, 75), 331 (M + 1, 73). Anal. Calcd for $C_{16}H_{13}N_2OBr$ (329.19): C, 58.38; H, 3.98; N, 8.51. Found: C, 58.14; H, 3.76; N, 8.69.

2-(2′-Bromo-4′-methylanilino)-4,6-dimethylquinoline (7j): yield 71% (0.48 g); colorless crystals; mp 105−106 °C; R_f 0.78 (10:1 hexanes−EtOAc); IR (CH_2Cl_2) 3408, 2923, 1604, 1523, 1264, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.48 (s, 3H), 2.55 (s, 3H), 6.73 (s, 1H), 7.13 (dd, J = 8.30, 1.68 Hz, 1H), 7.39 (d, J = 1.20 Hz, 1H), 7.41 (dd, J = 8.56, 1.96 Hz, 1H), 7.56 (s, 1H), 7.71 (d, J = 8.52 Hz, 1H), 8.28 (d, J = 8.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 20.4, 21.5, 112.5, 114.2, 121.0, 122.8, 124.3, 126.8, 128.7, 131.4, 132.7, 132.8, 133.2, 135.5, 145.1, 145.3, 152.8; MS (*m*/*z*, %) 341 (M + 1, 100), 343 (M + 1, 96).

(23) Only one report has recently appeared for this kind of cyclization involving Pd-catalyzed one-pot tandem inter- and intramolecular Buchwald−Hartwig amination of 2-chloro-3-iodopyridine with aminoazines and diazines to give dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues: Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemiere, G. L. F. *Chem. Commun.* **2004**, 2466.

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Anal. Calcd for $C_{18}H_{17}N_2Br$ (341.25): C, 63.35; H, 5.02; N, 8.21. Found: C, 63.14; H, 5.21; N, 8.43.

General Procedure for the Palladium-Catalyzed Intramolecular N−C Coupling: Synthesis of Benzimidazo[1,2-*a*]quinolines 8a−j. A mixture of 2-(2′-bromoanilino)quinolines **7a−j** (2.0 mmol), freshly prepared $Pd(PPh_3)_4$ (10 mol %), and anhydrous K_2CO_3 (4.4 mmol) in 5 mL of DMF was heated at 130−140 °C in a pressure tube for 10−12 h with constant stirring. The reaction mixture was cooled and filtered, and the filtrate was diluted with $CHCl_3$ (25 mL) and washed with water (2 × 25 mL) followed by brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in a vacuum to give crude benzimidazo[1,2-*a*]quinolines **8a−j** which were purified by silica gel column chromatography using hexanes−EtOAc (3:1) as eluent.

Benzo[4,5]imidazo[1,2-*a*]quinoline (8a):[9a] yield 75% (0.33 g); colorless crystals; mp 98−99 °C; R_f 0.30 (4:1 hexanes−EtOAc); IR (KBr) 2364, 1610, 1539, 1451, 1392, 1329, 1017, 813, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.47 (m, 2H), 7.51 (t, J = 7.60 Hz, 1H), 7.57 (d, J = 9.52 Hz, 1H), 7.63 (d, J = 9.28 Hz, 1H), 7.69 (t, J = 7.56 Hz, 1H), 7.77 (d, J = 7.32 Hz, 1H), 7.99 (d, J = 8.08 Hz, 1H), 8.33 (d, J = 8.08 Hz, 1H), 8.50 (d, J = 8.08 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.0, 115.2, 117.4, 120.2, 122.7, 123.3, 124.2, 124.5, 129.5, 129.7, 130.7, 131.4, 135.5, 144.1, 147.9; MS (*m*/*z*, %) 219 (M + 1, 100). Anal. Calcd for $C_{15}H_{10}N_2$ (218.25): C, 82.55; H, 4.62; N, 12.84. Found: C, 82.41; H, 4.80; N, 12.70.

2-Methoxybenzo[4,5]imidazo[1,2-*a*]quinoline (8e): yield 91% (0.45 g); colorless crystals; mp 142−143 °C; R_f 0.25 (3:1 hexanes−EtOAc); IR (KBr) 2838, 1623, 1543, 1486, 1452, 1387, 1328, 1277, 1257, 1236, 1169, 1143, 1024, 819, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.04 (dd, J = 8.68, 2.44 Hz, 1H), 7.44 (d, J = 7.08 Hz, 1H), 7.47 (t, J = 8.28 Hz, 1H), 7.52 (t, J = 7.32 Hz, 1H), 7.62 (d, J = 9.52 Hz, 1H), 7.71 (d, J = 8.56 Hz, 1H), 7.97 (d, J = 2.20 Hz, 1H), 7.99 (d, J = 9.28 Hz, 1H), 8.29 (d, J = 8.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 100.2, 111.6, 113.8, 114.3, 117.3, 120.0, 122.4, 124.6, 130.5, 130.7, 131.4, 136.7, 148.3, 161.0; MS (*m*/*z*, %) 249 (M + 1, 100). Anal. Calcd for $C_{16}H_{12}N_2O$ (248.28): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.27; H, 4.71; N, 11.12.

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Supporting Information Available: ^1H and ^{13}C NMR spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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