Palladium-catalyzed cyanation of bromocalix[4]arenes at the upper rim †

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Palladium-catalyzed cyanation of bromocalix[4]arenes possessing various kinds of functional groups at the lower rim is investigated. The yields varied depending on the functional groups. Most of the substrates are cyanated in excellent yield by treatment with $Pd_2(dba)_3$ or DPPF as the catalyst and $Zn(CN)_2$ as the cyanide source.

Introduction

Calixarenes are useful building blocks in host–guest chemistry.[1] To synthesize host molecules for selective binding to a substrate, a number of methods for the functionalization of calixarenes have been reported.[1] Cyanocalixarenes are useful intermediates for the construction of many calixarene-based host molecules because they can easily access compounds possessing various types of functional groups (*e.g.*, aldehyde, carboxylic acid, amide, amine, and aminomethyl) in short steps. Although CuCN-mediated cyanation of bromocalix[4]arenes has been reported, the yield was not high in some cases because a substantial amount of reduced compound was formed.[2] Recently, some groups succeeded in palladium-catalyzed cyanation of electron-rich aryl triflates[3a,3b] or halides,[3c,3d] which are resistant to undergoing a palladium-catalyzed reaction, such as *o*-bromoanisole.[3c] These reports prompted us to apply palladium-catalyzed cyanation to calixarenes. We report the conversion of bromocalix[4]arenes to corresponding cyanides using a palladium catalyst.

Results and discussion

Tetramethoxydibromocalix[4]arene **1a** was selected as a model substrate for cyanation of calix[4]arenes. The results are summarized in Table 1. Dinitrile **2a** was obtained in quantitative yield following Maligres' conditions[3c] although the reaction period was a rather lengthy 3 days (entry 1). $Pd(OAc)_2$ was also effective as the palladium catalyst (entry 2). When using KCN instead of $Zn(CN)_2$, the yield of the product drastically decreased (entry 3). DPEPhos[4] {bis[2-(diphenylphosphino)-phenyl] ether} can be used instead of DPPF [1,1′ bis(diphenylphosphino)ferrocene], but not Ph_3P (entries 4 and 5).

Next, we investigated the cyanation of **1b**, which has ethoxyethyl and benzyl groups at the lower rim, shown in Table 2. Remarkably, the expected reaction did not occur under $Pd(OAc)_2$–DPPF or DPEPhos conditions, under which cyanation of **1a** proceeded smoothly. Only the $Pd_2(dba)_3$–DPPF system successfully underwent the reaction. The cone conformation[5] of **1b** possessing bulky groups at the lower rim might reflect the difference in reactivity between **1a** and **1b**.

We investigated the scope and limitation of this reaction for various functional groups at the lower rim under optimal conditions [$Zn(CN)_2$–$Pd_2(dba)_3$–DPPF system] shown in Table 3. The substrates were prepared in good yield by the standard method in the literature.[1b,6] Although cyanation of tetrakisethoxyethyl derivative **1c** efficiently proceeded in 96% yield, the benzyl groups in **1d** were completely eliminated to afford **2e** in 74% yield. The non-alkylated dibromocalix[4]arene **1e** also reacted in 74% yield but required 7 days to complete the cyanation. In the case of the tetrakisMOM (methoxymethyl) derivative **1f**, **2f** was obtained in 47% yield along with 35% of **2e**, which did not have any MOM groups. Mono-, bis-, or tris-MOM derivatives were not detected under these conditions. Phenolic hydroxy groups might assist in the elimination of the groups at the lower rim.[7] Two methyl groups in **1g** were also eliminated, but MOM protection of the hydroxy group in **1g** (to give **1h**) suppressed the elimination (entry 8). Ethoxyethyl groups in **1i** were not removed under these conditions even in the presence of phenolic hydroxy groups. Compounds **1j** and **1k**, which are known to be effective metal-cation receptors,[1a] were not suitable substrates for the palladium-catalyzed cyanation. Because the reaction proceeded in good yield when R^1 was changed to a benzyl group (entry 12), chelation of the palladium ion to **1j** and **1k** might prevent the cyanation.

Finally, we examined cyanation of tetrabromocalix[4]arene **3** (Scheme 1). Although the reaction required 5 days, tetracyano derivative **4** was obtained in good yield.

In summary we investigated the scope and limitation of palladium-catalyzed cyanation of bromocalix[4]arenes. Although some functional groups at the lower rim were eliminated, various kinds of bromocalix[4]arenes, except tetraester and tetraamide derivatives, were cyanated in excellent yield. Cyanocalix[4]arene derivatives would be good intermediates for the synthesis of calixarene-based supramolecules.

Experimental

Melting points were taken on a hot-plate microscope apparatus and are uncorrected. NMR spectra were recorded at 200 MHz (^{1}H) and at 50 MHz (^{13}C). The synthesis and full characterization of bromocalixarenes employed in this study are described in the Electronic Supplementary Information.

General procedure for cyanation of bromocalix[4]arenes

A suspension of bromocalixarene (0.25 mmol) and $Pd_2(dba)_3$ [tris(dibenzylideneacetone)dipalladium(0), 0.025 mmol], DPPF (0.05 mmol) and $Zn(CN)_2$ (1.00 mmol) in DMF (2.5 mL) was warmed to 140 °C under an argon atmosphere. After stirring for 72 h, the reaction mixture was cooled to room temperature, and passed through silica gel to remove excess of $Zn(CN)_2$. The

† Electronic supplementary information (ESI) available: experimental details for compound **1**. See http://www.rsc.org/suppdata/p1/b1/b109083f/

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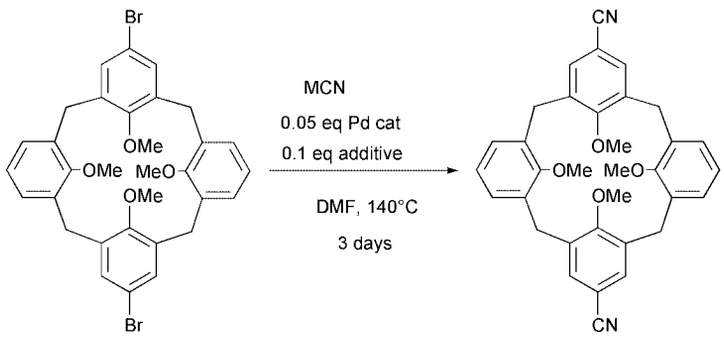
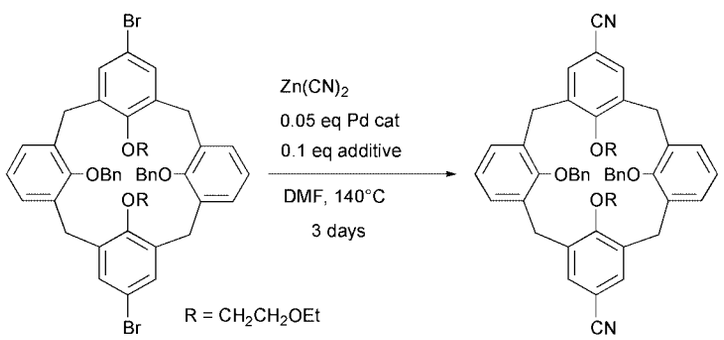
Table 1 Palladium-catalyzed cyanation of tetramethoxycalix[4]arene **1a** under various conditions



1a **2a**

Entry	MCN	Pd cat.	Additive	Yield (%)
1	$Zn(CN)_2$	$Pd_2(dba)_3$	DPPF	100
2	$Zn(CN)_2$	$Pd(OAc)_2$	DPPF	99
3	KCN	$Pd(OAc)_2$	DPPF	9
4	$Zn(CN)_2$	$Pd(OAc)_2$	DPEPhos	100
5	$Zn(CN)_2$	$Pd(OAc)_2$	Ph_3P	no reaction

Table 2 Palladium-catalyzed cyanation of calix[4]arene **1b**



1b **2b**

Entry	Pd cat.	Additive	Yield (%)
1	$Pd(OAc)_2$	DPPF	0
2	$Pd(OAc)_2$	DPEPhos	no reaction
3	$Pd_2(dba)_3$	DPPF	85

silica gel was washed successively with $CHCl_3$ and AcOEt. The solvent was evaporated off *in vacuo*. The residue was purified by silica gel chromatography ($CHCl_3$–AcOEt) to yield the cyanocalixarene as a colorless solid.

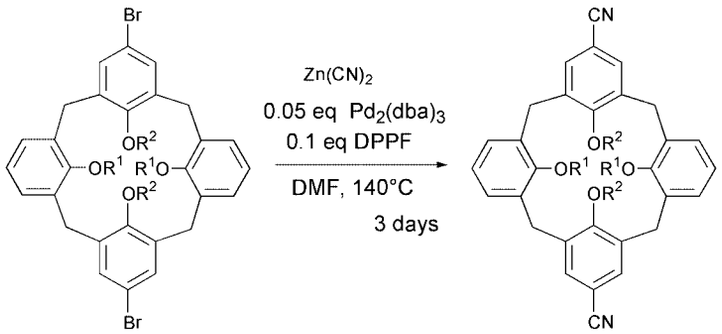
5,17-Cyano-25,26,27,28-tetramethoxycalix[4]arene 2a. Mp 289–290 °C; IR (KBr) ν 2224, 1470, 1007 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.90–4.20 (20 H, m), 6.30–7.60 (10 H, m); MS (FAB) *m*/*z* 531 (base, $M^+ + H$), 569 ($M^+ + K$); HRMS (FAB) *m*/*z* Calc. for $C_{34}H_{31}N_2O_4$: $(M + H)^+$, 531.2284. Found: *m*/*z*, 531.2293.

5,17-Cyano-25,27-dibenzyloxy-26,28-bis(2-ethoxyethoxy)-calix[4]arene 2b. Mp 185–186 °C; IR (KBr) ν 2224, 1456, 1122 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 1.09 (6 H, t, J = 7.0 Hz), 3.06 (4 H, d, J = 13.9 Hz), 3.31 (4 H, q, J = 7.0 Hz), 3.61 (4 H, t, J = 5.5 Hz), 4.07 (4 H, t, J = 5.5 Hz), 4.34 (4 H, d, J = 13.9 Hz), 4.96 (4 H, s), 6.49 (2 H, d, J = 5.9 Hz), 6.49 (2 H, d, J = 8.8 Hz), 6.60 (2 H, dd, J = 5.9, 8.8 Hz), 7.03 (4 H, s), 7.31–7.43 (10 H, m); ^{13}C NMR (50 MHz; $CDCl_3$) δ 15.1 (q), 30.7 (t), 66.2 (t), 69.5 (t), 73.5 (t), 77.0 (t), 105.7 (s), 119.2 (s), 123.2 (d), 128.5 (d), 129.7 (d), 132.3 (d), 133.9 (s), 137.0 (s), 137.1 (s), 154.8 (s), 160.8 (s); MS (EI) *m*/*z* 618, 707, 798 (base, M^+) (Calc. for $C_{52}H_{50}N_2O_6$: C, 78.17; H, 6.31; N, 3.51. Found: C, 77.97; H, 6.39; N, 3.51%).

5,17-Dicyano-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]-arene 2c. Mp 163–165 °C; IR (KBr) ν 2226, 1450, 1123 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 1.17 (6 H, t, J = 7.0 Hz), 1.19 (6 H, t, J = 7.0 Hz), 3.17 (4 H, d, J = 13.8 Hz), 3.50 (4 H, q, J = 7.0 Hz), 3.51 (4 H, q, J = 7.0 Hz), 3.79 (4 H, t, J = 5.2 Hz), 3.81 (4 H, t, J = 5.2 Hz), 4.10 (4 H, t, J = 5.2 Hz), 4.53 (4 H, t, J = 5.2 Hz), 4.53 (4 H, d, J = 13.8 Hz), 6.62 (6 H, m), 6.99 (4 H, s); ^{13}C NMR (50 MHz; $CDCl_3$) δ 15.1 (q), 30.5 (t), 66.2 (t), 69.4 (t), 69.6 (t), 73.2 (t), 73.7 (t), 105.7 (s), 119.0 (s), 123.0 (d), 128.5 (d), 132.0 (d), 133.9 (s), 136.7 (s), 156.0 (s), 160.3 (s); MS (EI) *m*/*z* 73 (base), 500, 572, 618, 690, 762 (base, M^+) (Calc. for $C_{46}H_{54}N_2O_8$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.48; H, 7.12; N, 3.68%).

5,17-Dicyano-25,26,27,28-tetrahydroxycalix[4]arene 2e. Mp >300 °C; IR (KBr) ν 3441, 2218, 1473 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 3.63 (4 H, br s), 4.33 (4 H, br s), 6.85 (2 H, t, J = 7.7 Hz), 7.11 (4 H, d, J = 7.7 Hz), 7.38 (4 H, s), 10.09 (4 H, br s); ^{13}C NMR (50 MHz; $CDCl_3$) δ 31.2 (t), 105.8 (s), 118.8 (s), 123.1 (d), 127.0 (s), 129.4 (s), 129.6 (d), 133.1 (d), 148.3 (s),

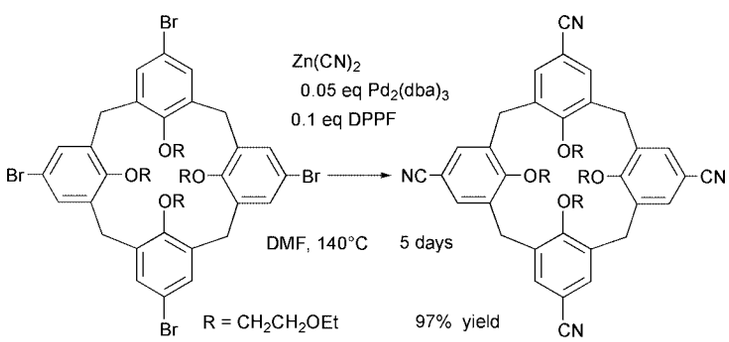
Table 3 Palladium-catalyzed cyanation of calix[4]arenes possessing various groups at the lower rim



1 **2**

Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**1a**	Me	Me	**2a**	100
2	**1b**	Bn	CH_2CH_2OEt	**2b**	85
3	**1c**	CH_2CH_2OEt	CH_2CH_2OEt	**2c**	96
4	**1d**	Bn	Bn	**2e**: $R^1 = R^2 = H$	74
5[a]	**1e**	H	H	**2e**	74
6	**1f**	MOM	MOM	**2f**	47
				2e	35
7	**1g**	Me	H	**2e**	50
8	**1h**	Me	MOM	**2h**	85
9	**1i**	CH_2CH_2OEt	H	**2i**	98
10	**1j**	$CH_2CO_2Bu^t$	$CH_2CO_2Bu^t$	**2j**	0
11	**1k**	CH_2CONEt_2	CH_2CONEt_2	**2k**	0
12	**1l**	Bn	CH_2CONEt_2	**2l**	85

[a] Reaction period was 7 days.



3 **4**

Scheme 1 Palladium-catalyzed cyanation of tetrabromocalix[4]arene **3**.

153.1 (s); MS (FAB) *m*/*z* 475 (M^+ + H), 497 (M^+ + Na); HRMS (FAB) *m*/*z* Calc. for $C_{30}H_{22}N_2O_4$: *M*, 475.1658. Found: M^+, 475.1682.

5,17-Dicyano-25,26,27,28-tetrakis(methoxymethoxy)calix[4]-arene 2f. Mp 217–218 °C; IR (KBr) *ν* 2224, 1464, 1161, 970 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) *δ* 3.26 (4 H, d, *J* = 14.0 Hz), 3.53 (6 H, s), 3.60 (6 H, s), 4.49 (4 H, d, *J* = 14.0 Hz), 5.08 (4 H, s), 5.11 (4 H, s), 6.85 (4 H, s), 6.86 (6 H, s); ^{13}C NMR (50 MHz; $CDCl_3$) *δ* 31.2 (t), 58.0 (q), 58.1 (q), 100.4 (t), 100.6 (t), 106.7 (s), 118.6 (s), 124.0 (d), 129.1 (d), 132.1 (d), 134.6 (s), 136.0 (s), 154.7 (s), 157.9 (s); MS (EI) *m*/*z* 45 (base), 498 (Calc. for $C_{38}H_{38}N_2O_8$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.41; H, 5.99; N, 4.26%).

5,17-Cyano-25,27-dimethoxy-26,28-bis(methoxymethoxy)-calix[4]arene 2h. Mp 246–247.5 °C; IR (KBr) *ν* 2220, 1470, 1155, 1067, 982 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) *δ* conformational isomers mixture 3.00–5.03 (28 H, m), 6.62–7.40 (10 H, m); MS (EI) *m*/*z* 45, 451, 483, 514 (base), 590 (base, M^+); HRMS (EI) *m*/*z* Calc. for $C_{36}H_{34}N_2O_6$: *M*, 590.2417. Found: M^+, 590.2408.

5,17-Cyano-25,27-bis(2-ethoxyethoxy)-26,28-dihydroxycalix-[4]arene 2i. Mp 279–280 °C; IR (KBr) *ν* 3260, 2214, 1480, 1453, 1125, 1050 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) *δ* 1.27 (6 H, t, *J* = 7.0 Hz), 3.38 (4 H, d, *J* = 13.6 Hz), 3.70 (4 H, q, *J* = 7.0 Hz), 3.92 (4 H, m), 4.17 (4 H, m), 4.42 (4 H, d, *J* = 13.6 Hz), 6.84 (2 H, dd, *J* = 5.9, 8.4 Hz), 6.92 (2 H, d, *J* = 5.9 Hz), 6.92 (6 H, 2 H, d, *J* = 8.4 Hz), 8.79 (2 H, s); ^{13}C NMR (50 MHz; $CDCl_3$) *δ* 15.1 (q), 30.7 (t), 66.9 (t), 68.9 (t), 75.6 (t), 101.7 (s), 119.8 (s), 125.7 (d), 129.0 (s), 129.4 (d), 132.2 (d), 132.5 (s), 151.7 (s), 157.6 (s); MS (EI) *m*/*z* 91 (base), 546, 618 (M^+) (Calc. for $C_{38}H_{38}N_2O_6$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.60; H, 6.06; N, 4.65%).

5,17-Dicyano-25,27-dibenzyloxy-26,28-bis(diethylcarbamoyl-methoxy)calix[4]arene 2l. Mp 281.5–282 °C; IR (KBr) *ν* 2218, 1672, 1456, 754 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) *δ* 0.92 (6 H, t, *J* = 7.0 Hz), 1.11 (6 H, t, *J* = 7.0 Hz), 2.88 (4 H, q, *J* = 7.0 Hz), 3.14 (4 H, d, *J* = 13.7 Hz), 3.37 (4 H, q, *J* = 7.0 Hz), 4.49 (4 H, s), 4.56 (4 H, d, *J* = 13.7 Hz), 5.10 (4 H, s), 6.68 (4 H, d, *J* = 7.2 Hz), 6.69 (2 H, t, *J* = 7.2 Hz), 6.92 (4 H, s), 7.24–7.30 (6 H, m), 7.42–7.48 (4 H, m); ^{13}C NMR (50 MHz; $CDCl_3$) *δ* 13.1 (q), 14.1 (q), 31.3 (t), 40.0 (t), 40.5 (t), 70.9 (t), 77.1 (t), 105.9 (s), 118.9

(s), 123.4 (d), 128.0 (d), 128.6 (d), 130.1 (d), 132.3 (d), 134.5 (s), 136.3 (s), 137.4 (s), 155.0 (s), 159.8 (s), 166.8 (s); MS (FAB) *m*/*z* 721, 812, 903 (M^+ + Na, base) (Calc. for $C_{56}H_{56}N_4O_6$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.40; H, 6.49; N, 6.31%).

5,11,17,23-Tetracyano-25,26,27,28-tetrakis(2-ethoxyethoxy)-calix[4]arene 4. Mp 225–227 °C; IR (KBr) *ν* 2226, 1471, 1454, 1118 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) *δ* 1.16 (12 H, t, *J* = 7.0 Hz), 3.22 (4 H, d, *J* = 13.8 Hz), 3.48 (8 H, q, *J* = 6.8 Hz), 3.76 (8 H, t, *J* = 4.8 Hz), 4.19 (8 H, t, *J* = 4.8 Hz), 4.59 (4 H, d, *J* = 13.8 Hz), 7.00 (8 H, s); ^{13}C NMR (50 MHz; $CDCl_3$) *δ* 15.0 (q), 30.3 (t), 66.2 (t), 69.4 (t), 74.0 (t), 106.7 (s), 118.2 (s), 132.3 (d), 135.8 (s), 160.0 (s); MS (EI) *m*/*z* 812 (M^+) (Calc. for $C_{48}H_{52}N_4O_8$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.76; H, 6.49; N, 7.07%).

Acknowledgements

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6 The substrates and products except for **1a**, **2a**, **1e**, **2e**, and **1g** had a cone conformation at room temperature, which was determined by NMR analyses.
7 Another possibility (suggested by the references) is that the high Lewis acidity of the resulting $ZnBr_2$ released in the reaction caused the elimination of the acid-labile protecting groups.