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The Suzuki Coupling of Aryl Chlorides in Aqueous Media Catalyzed by in situ Generated Calix[4]arene-Based N-Heterocyclic Carbene Ligands

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We report on the use of an in situ system for the catalytic Suzuki cross-coupling reaction of chlorobenzenes and benzeneboronic acid to yield biphenyls. Calix[4]arene-based imidazolium salts were used as precursors of N-heterocyclic carbene ligands and $Pd(OAc)_2$ as the palladium source. In dioxane as the organic medium, the steric demands of the substituents on the calixarene skeleton and on the imidazolium moiety parallel the catalytic activity; the best catalytic results were obtained by using dimesityl- or 2,6-diisopropylphenyl-substituted calixarene-imidazolium salts. Among the bases tested Cs_2CO_3 and CsF were the most effective. The catalytic protocol established for organic solvents could also be used for the Suzuki cross-coupling reaction in aqueous solution. In dioxane/water (50:50) the activity is nearly the same as in pure dioxane and in pure water, an environmentally friendly and cheap solvent, a 60 % level of reactivity was maintained; here the calixarene ligand precursor **3a** showed the highest activity. Nonmacrocyclic compounds used for comparison showed considerably lower catalytic ability proving that calix[4]arene-based imidazolium salts are attractive supramolecular skeletons for the N-heterocyclic carbene ligands used in selective Suzuki cross-coupling reactions of aryl chlorides in aqueous solution.

Introduction

The formation of C–C bonds is an important task for the synthetic organic chemist. In particular, the palladium-catalyzed Suzuki–Miyaura reaction[1,2] has attracted much attention because the synthetic protocol tolerates many functional groups and also because the coupling reaction occurs under mild conditions. In recent years the Suzuki reaction of aryl chlorides has been extensively investigated.[3–5] N-Heterocyclic carbenes (NHCs)[6–10] have emerged as an effective class of ligands for palladium-catalyzed cross-coupling reactions of aryl chlorides.[11,12] This important finding has led to the vigorous development of the Suzuki coupling of aryl chlorides. Besides the application of well-defined Pd–NHC metal complexes,[13,14] a simple in situ system[15–18] in which the catalytically active species was formed prior to cross-coupling by the reaction of an imidazolium salt, a source of palladium and a base could be used to avoid preparative problems such as the instability[19,20] of the catalyst.

In addition to the search for new starting materials and catalytic systems, there is considerable interest in transition-metal-catalyzed reactions in aqueous media.[21] Water is not only an environmentally friendly and cheap reaction medium,[22,23] but also interesting from a mechanistic point of view.[24] For example, efficient Suzuki coupling of aryl halides in aqueous solution using surfactants,[25] tetrabutylammonium bromide (TBAB),[26] Pd/C,[27] tetradentate NHCs[28] as ligands, or the use of microwaves[29,30] has been reported.

Owing to our ongoing interest in organic transformations in aqueous solution and our observations that water-soluble calixarenes can act as inverse phase-transfer catalysts[31,32] in Suzuki reactions we decided to develop catalytic systems based on calixarenes for Suzuki cross-coupling reactions in aqueous media. For this purpose, the macrocyclic backbone should provide a hydrophobic cavity or niche as well as a molecular platform to attach catalytic groups covalently to the wide rim of the macrocycle. Because calixarenes bearing imidazolium groups are water soluble, for example, calixarene **2c** has a solubility of 2.9 g L^{-1} in pure water, such heterocycles seem to be ideal candidates to render the supramolecular catalysts water-soluble and can act furthermore as a precursor for the formation of NHCs used in the catalytic process.

Results and Discussion

Following the general reaction procedure, the calix[4]-arene-imidazolium salts **2**–**4** (Scheme 1) were prepared by simple alkylation of the appropriate *N*-substituted imidazoles with chloromethylated calix[4]arene building blocks.[33] The noncyclic analogs **1** were chosen as reference compounds to check the possible electronic and steric effects of the substituents on the imidazolium moiety.

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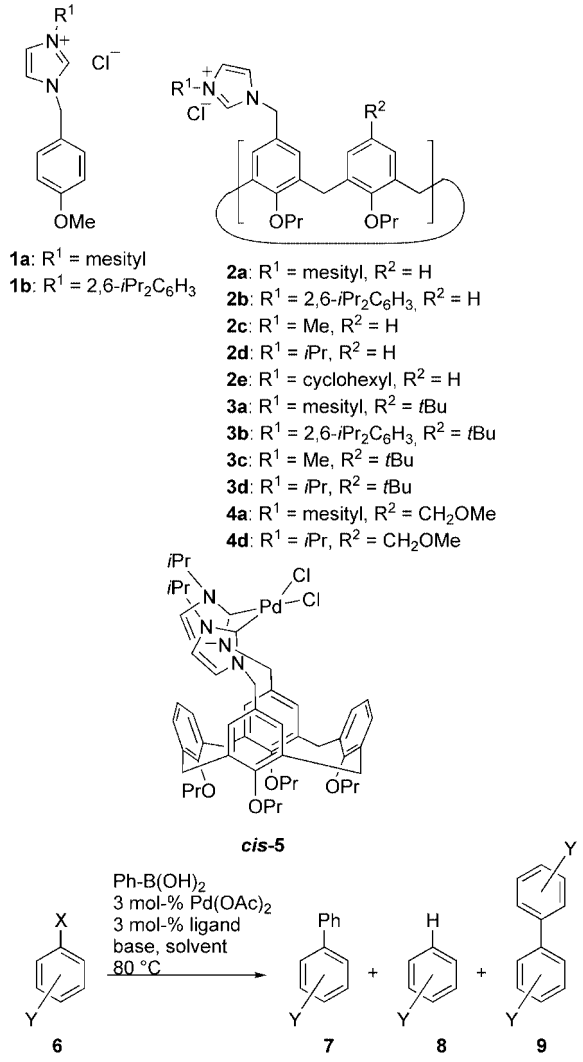
Furthermore, by comparing the calixarene derivatives **2**–**4** (**2**: the substituent on the calixarene backbone R^2 = H; **3**: R^2 = *t*Bu; **4**: R^2 = CH_2OMe) with the open-chain derivatives **1** possible participation of the macrocyclic cavity in the reaction can be detected.



Scheme 1.

To test the catalytic ability of he calixarene derivatives a standardized and parallel test reaction was used to avoid any source of error stemming from reactions carried out individually under slightly varying conditions. The results obtained by this approach are compiled in Table 1, Table 2 and Table 3.

Because of the possibility of ligand- or "metal-free" Suzuki coupling reactions[34] such a reaction pathway had to be ruled out first for the test reaction under investigation (Table 1, entry 1).

In pure dioxane as the reaction medium the catalyst derived from calixarene **2a** exhibited basically the same activity as the open-chain analog **1a** (cf. entries 2 and 4, Table 1). By using the macrocyclic imidazolium salts as ligand precursors (Table 1, entries 4–13) the yield of biphenyl increased with increasing steric bulk of the substituents on the imidazolium moiety. The best results were obtained by using ligands bearing mesityl substituents on the imidazolium salt (**1a**, **2a**, **3a**).

Table 1. Suzuki cross-coupling reaction of 4-chlorotoluene (**6a**) with benzeneboronic acid in dioxane to yield 4-methylbiphenyl (**7a**): Ligand screening and variation of base.[a]

Entry	Ligand	*t* [h]	Base	R^1	R^2	Yield [%]
1	–	2	Cs_2CO_3	–	–	0
2	**1a**	2	Cs_2CO_3	mesityl	–	51[b]
3	**1b**	2	Cs_2CO_3	2,6-di-*i*PrPh	–	38[b]
4	**2a**	2	Cs_2CO_3	mesityl	H	50
5	**2b**	2	Cs_2CO_3	2,6-di-*i*PrPh	H	40
6	**2c**	2	Cs_2CO_3	CH_3	H	1
7	**2d**	2	Cs_2CO_3	*i*Pr	H	16
8	**3a**	2	Cs_2CO_3	mesityl	*t*Bu	60
9	**3b**	2	Cs_2CO_3	2,6-di-*i*PrPh	*t*Bu	38
10	**3c**	2	Cs_2CO_3	CH_3	*t*Bu	19
11	**3d**	*2*	Cs_2CO_3	*i*Pr	*t*Bu	24
12	**4a**	2	Cs_2CO_3	mesityl	CH_2OCH_3	2
13	**4d**	2	Cs_2CO_3	*i*Pr	CH_2OCH_3	24
14	**3a**	24	Cs_2CO_3	mesityl	*t*Bu	95
15	**3a**	24	NaOAc	mesityl	*t*Bu	3
16	**3a**	24	K_3PO_4	mesityl	*t*Bu	12
17	**3a**	24	KO*t*Bu	mesityl	*t*Bu	10
18	**3a**	24	KF	mesityl	*t*Bu	13
19	**3a**	24	CsF	mesityl	*t*Bu	80
20	**3a**	24	K_2CO_3	mesityl	*t*Bu	27

[a] Reagents and conditions: 1.5 mmol **6a**, 1.0 mmol benzeneboronic acid, 2 mmol base, 3 mol-% $Pd(OAc)_2$, 3 mol-% **1**–**3**, dioxane, 80 °C. [b] 6 mol-% ligand were used; entries 4–10, see ref.[32].

Table 2. Suzuki cross-coupling reaction of 4-aryl halides **6a**–**g** with benzeneboronic acid in dioxane: Variation of starting material.[a]

Entry		X	Y	Yield of **7** [%]
1	**6a**	Cl	4-CH_3	60
2	**6b**	Br	4-CH_3	91
3	**6c**	I	4-CH_3	99
4	**6d**	Cl	3-OCH_3	64
5	**6e**	Cl	4-CF_3	69
6	**6f**	Cl	3-CH_3	6
7	**6g**	Cl	2-CH_3	8

[a] Reagents and conditions: 1.5 mmol **6a**–**g**, 1.0 mmol benzeneboronic acid, 2 mmol Cs_2CO_3, 3 mol-% $Pd(OAc)_2$, 3 mol-% **2a**, dioxane, 80 °C, reaction time 48 h.

Assuming[14] that the precursor of the catalytic species formed by the in situ system is similar to the *cis*-Pd(L–L)Cl_2 complex **5** characterized by single-crystal structure analysis[33] it is likely that the steric bulk induced additional strain into the palladium chelate. This favors the dissociation of one NHC ligand to form a catalytically active complex.[15,35] This would explain the higher activity of the ligands **2a**,**b** and **3a**,**b** and why the activity of calixarene **3a** exceeds its nonmacrocyclic analog **1a**. In the case of 2,6-diisopropylphenyl-substituted ligand precursors (Table 1, entries 3, 5, and 9) identical efficiencies were revealed. Here, the steric stress induced by the 2,6-diisopropylphenyl groups seems to prevail.

Calixarenes **4** were included in the study to test the effect of possible dangling donor ligands in the proximity of the catalytic center. However, the introduction of a CH_2OMe

Table 3. Suzuki cross-coupling reaction of 4-chlorotoluene (**6a**) and benzeneboronic acid in mixtures of dioxane/water.[a]

Entry	Ligand	Dioxane/water	Yield of **7a** [%]	Yield of **8a** [%]	Yield of **9a** [%]
1	**1a**	100:0	56	7	0
2		50:50	54	3	1
3		0:100	3	1	0
4	**2a**	100:0	60	8	0
5		50:50	55	0	1
6		0:100	37	1	12
7	**2b**	100:0	64	10	0
8		50:50	32	2	4
9		0:100	2	0	0
10	**2d**	100:0	31	12	1
11		50:50	11	6	9
12		0:100	2	3	3
13	**2e**	100:0	46	15	0
14		50:50	5	6	5
15		0:100	8	2	5
16	**3c**	100:0	34	16	0
17		50:50	8	0	6
18		0:100	6	0	8
19	None	100:0	0	0	0
20		50:50	3	3	2
21		0:100	1	0	3

[a] Reagents and conditions: 1.5 mmol **6a**, 1.0 mmol benzeneboronic acid, 2 mmol Cs_2CO_3, 3 mol-% $Pd(OAc)_2$, 3 mol-% **1**–**3**, 80 °C, reaction time 48 h.

group did not improve the catalytic ability; the yields of biphenyl dropped from 60 and 50% for **3a** and **2a**, respectively, to 2% for **4a** in the case of R^1 = mesityl (Table 1, entries 8, 4, and 12). Surprisingly, this is not the case for R^1 = isopropyl. Here, yields remained around 20% in all three ligand systems (Table 1, entries 11, 7, and 13).

As expected[15] from all the bases tested (Table 1, entries 14–20) Cs_2CO_3 was the base of choice. By using ligand **3a** and Cs_2CO_3 and by extending the reaction time to 24 h, quantitative conversion to 4-methylbiphenyl is possible.

By using calixarene **2a** as the ligand precursor, the effect of different substrates was tested (Table 2). As expected, aryl iodides and bromides gave better yields of biaryls (Table 2, entries 1–3). Trifluoromethyl- or methoxy-substituted chlorobenzenes gave similar yields to 4-chlorotoluene. However, there was a striking difference between the activities of 2-, 3-, and 4-chlorotoluene (Table 2, entries 1, 6, and 7). Whereas, the *para* isomer gave the corresponding biaryl in 60% yield, the *ortho* and *meta* isomers gave less than 10% of the coupled product. With other catalysts, these three substrates usually give similar yields.[36,37] This striking difference can be rationalized in terms of the reaction taking place near a cavity/cleft formed by the calixarene backbone and the NHC center. Because organic substrates such as chlorotoluene are usually bound inside the cavity of cationic calixarenes [$K_{ass} \approx 200\ L\,mol^{-1}$($\Delta G \approx 3\ kcal\,mol^{-1}$) as determined by NMR titration experiments] with the methyl group of the substrate pointing inside the aromatic cavity,[31] it is likely that the geometry of the niche could not accommodate the *ortho* and *meta* isomers in a productive way.

To test the effect of different reaction media the solvent was changed systematically from pure dioxane to pure water (Table 3). Here, reactions performed in 80:20 and 60:40 dioxane/water were inhomogeneous and therefore are not included in further discussions. All other solvent mixtures led to homogeneous reaction mixtures.

The best results were obtained in the pure organic phase. In a 1:1 mixture of dioxane/water nearly similar yields as in pure dioxane were obtained for **1a** and **2a**. Beyond the 1:1 solvent mixture the efficiency of the Suzuki coupling dropped again despite the observed homogeneous reaction conditions. However, the calixarene-based ligand **2a** showed somewhat exceptional behavior. Here, 37% of the coupling product was observed (Table 3, entry 6); all the other ligands tested gave yields well below the 10% level although the macrocyclic ligands were usually still superior to the nonmacrocyclic precursor **1a**. Increasing the amount of added calixarene-based ligand precursor did not improve the yields in pure water.

Besides the desired 4-methylbiphenyl, homocoupling to give 4,4′-dimethylbiphenyl and dehalogenation to yield toluene were also observed. In dioxane, the calixarene ligands **2a**,**b**, **2d**,**e** and **3c** gave 8–16% toluene, but no homocoupling product was detected. In pure water virtually no toluene (<3%) was detected for any of the calixarene-based ligand precursors. In contrast, the amount of homocoupling product, 4,4′-dimethylbiphenyl, increased with increasing water content. In pure dioxane the yields of the homocoupling product were <1% in all cases, but increased significantly (**2a**: 12%; **2d**: 3%; **2e**: 5%; **3c**: 8%) in water. Here, the imidazolium salt **2a** exhibited the highest activity in both the desired cross-coupling and the homocoupling reactions.

It is somewhat difficult to compare the results obtained with ligand precursor **2a** directly with similar coupling reactions in aqueous solution because in the cases reported in the literature solvent mixtures were usually used.[25,27,38–40] However, yields of <35% of aryl–aryl coupling products

seem to be quite typical. For example, the use of Pd/C in DMA/H_2O (20:1) in the coupling of 4-chlorotoluene and $PhB(OH)_2$ (K_2CO_3, 80 °C, 48 h) gave 36% of the coupling product.[38] The use of a 1,1′-*N*-substituted ferrocenediyl-Pd^{II} complex did not catalyze the coupling of 4-CNC_6H_4Cl although this ligand was active in the coupling of aryl bromides.[39] In comparison, good results (62% yield) were obtained in the reaction of 4-chlorotoluene and benzeneboronic acid in pure water by using microwaves instead of conventional heating.[40]

It is known that polar calixarenes form host–guest complexes with aromatic compounds[31] and imidazolium groups can act as recognition elements for anions.[41] From this we could hypothesize that some kind of supramolecular effect is playing a crucial role in this Suzuki coupling reaction in pure water. Microsolubilization of hydrophobic starting material by a host–guest complex formed in an inverse phase-transfer catalysis is conceivable[31] as well as activation of the base[42] by complexation of the counteranion.[43]

Conclusion

In summary, catalytic species derived from calixarene-based imidazolium salts as ligand precursors show high activity in the Suzuki cross-coupling of aryl chlorides. Bulky substituents on both the heterocyclic and macrocyclic skeleton enhanced the catalytic efficiency. This is probably due to the strain induced into the catalytically active metal–organic species. The catalytic protocol tested in dioxane as the organic solvent could be used without further adaptation for the coupling of aryl chlorides in aqueous solution. Although the catalytic activity decreased it was still possible to form biaryls even in pure water indicating that calixarene-based imidazolium salts are promising as ligand precursors for selective organometallic catalysis in aqueous solution, an environmentally benign reaction media.

Experimental Section

General Remarks: Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Bruker Vector 22 instrument using KBr pellets unless otherwise stated. Absorptions ($\tilde{\nu}$) are given in wavenumbers (cm^{-1}). NMR spectra were recorded with a Bruker DRX 400 instrument (400.13 MHz for ^1H and 100.62 MHz for ^{13}C). Tetramethylsilane was used as the internal standard (δ = 0.00 ppm) for ^1H NMR spectroscopy and the solvent signals for ^{13}C NMR spectroscopy [δ ($CDCl_3$) = 77.0, δ ([D_6]DMSO) = 39.5, δ ([D_4]methanol) = 49.3 ppm]. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Assignments of ^{13}C chemical shifts are based on proton-coupled ^{13}C, (C,H) correlation, and DEPT-135 spectra. Mass spectra were obtained with a Finnigan MAT TSQ7000 (FAB) or Bruker Daltonics Reflex III (MALDI-TOF) spectrometer. All reaction mixtures were stirred magnetically. The synthesis of calixarenes **2** and **3** has been reported previously.[32]

General Procedure for the Synthesis of 1-Aryl-3-(4-methoxybenzyl)-imidazolium Chlorides (1):: A solution of *p*-methoxybenzyl chloride and the corresponding 1-arylimidazole in dichloromethane was refluxed for 1 d. After removal of the solvent the remaining residue was digerated for 3 h with hot Et_2O. The product was isolated by filtration and dried in vacuo.

1-Mesityl-3-(4-methoxybenzyl)imidazolium Chloride (1a): The product was obtained from the reaction of: 4-methoxybenzyl chloride (0.87 g, 5.60 mmol), 1-mesitylimidazole (1.09 g, 5.85 mmol), $CHCl_3$ (30 mL), and Et_2O (70 mL). Yield: 0.85 g (2.48 mmol, 42%). M.p. >205 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3109 (m), 3072 (m) (Ar-H), 2956 (s) (C–H), 1612 (m), 1586 (w), 1544 (m), 1514 (s) (C=C and C=N), 1487 (w), 1459 (m), 1379 (w), 1305 (w) (C–H), 1250 (s), 1212 (m), 1196 (w), 1177 (m), 1159 (w), 1030 (m) (Ar-O–C), 850 (w), 818 (w), 754 (w) (Ar-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 2.02 and 2.31 (2s, 6 H and 3 H, $ArCH_3$), 3.78 (s, 3 H, $ArOCH_3$), 5.85 (s, 2 H, $ArCH_2Im$), 6.86–6.89 (m, 2 H, Ar-H), 6.95 (s, 2 H, Ar-H), 7.15 (t, J = 1.8 Hz, 1 H, Im), 7.60–7.63 (m, 2 H, Ar-H), 7.87 (t, J = 1.4 Hz, 1 H, Im), 10.75 (s, 1 H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ_C = 17.5 and 20.9 ($ArCH_3$), 52.8 ($ArCH_2Im$), 55.2 (OCH_3), 114.6, 122.6, 123.1, 125.8, 129.7, 129.8, 130.7, 134.0, 138.0, 141.0, 160.1 (Ar-C and Im-C) ppm. MS:(CI): calcd. for $C_{20}H_{23}N_2O$: 307.2; found m/z = 307.0 [M – Cl]$^+$. $C_{20}H_{23}N_2OCl{\cdot}0.4H_2O$ (350.07): calcd. C 68.62, H 6.85, N 8.00; found C 68.55, H 6.85, N 8.57.

1-(2,6-Diisopropylphenyl)-3-(4-methoxybenzyl)imidazolium Chloride (1b): The product was obtained from the reaction of: 4-methoxybenzyl chloride (3.00 g, 19.2 mmol), 1-(2,6-diisopropylphenyl) imidazole (4.57 g, 20.0 mmol), $CHCl_3$ (30 mL), and Et_2O (70 mL). Yield: 7.00 g (18.2 mmol, 95%). M.p. 173–175 °C. IR (KBr): $\tilde{\nu}$ = 3153 (w), 3124 (m), 3073 (m) (Ar-H), 2964 (s), 2931 (s), 2870 (m), 2837 (m) (C–H), 1611 (m), 1585 (w), 1561 (m), 1537 (m), 1514 (s) (C=C and C=N), 1459 (s) (C–H), 1382 (m), [$C(CH_3)_2$], 1305 (m), (C–H), 1253 (s), 1176 (s), 1118 (m), 1032 (m) (Ar-O–C), 890 (w), 850 (w), 817 (m), 760 (m) (Ar-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 1.10 and 1.17 [d, 2× J = 6.8 Hz, 2×6 H, $CH(CH_3)_2$], 2.22 [sept, J = 6.8 Hz, 2 H, $CH(CH_3)_2$], 3.78 (s, 3 H, $ArOCH_3$), 5.91 (s, 2 H, $ArCH_2Im$), 6.84–6.88 (m, 2 H, Ar-H), 7.15 (t, J = 1.8 Hz, 1 H, Im), 7.26 (d, J = 7.8 Hz, 2 H, Ar-H), 7.50 (t, J = 7.8 Hz, 1 H, Ar-H), 7.65–7.69 (m, 2 H, Ar-H), 8.16 (t, J = 1.7 Hz, 1 H, Im), 10.81 (s, 1 H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ_C = 23.8 and 24.2 [$CH(CH_3)_2$], 28.5 [$CH(CH_3)_2$], 52.7 ($ArCH_2Im$), 55.1 (OCH_3), 114.4, 123.0, 123.9, 124.4, 126.1, 130.3, 130.6, 131.5, 138.3, 145.2, 160.1 (Ar-C and Im-C) ppm. MS (CI): calcd. for $C_{23}H_{29}N_2O$: 349.2; found m/z = 349 [M – Cl]$^+$. $C_{23}H_{29}N_2OCl$ (384.95): calcd. C 71.76, H 7.59, N 7.27; found C 71.35, H 7.61, N 7.41.

5,17-Bis[(3-mesitylimidazolium-1-yl)methyl]-11,23-bis(methoxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene Dichloride (4a): The product was obtained by refluxing 5,17-bis(chloromethyl)-11,23-bis(methoxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene (800 mg, 1.03 mmol), 1mesitylimidazole (402 mg, 2.16 mmol), $CHCl_{3(abs.)}$ (10.0 mL), and Et_2O (70 mL) for 2 d. Yield: 490 mg (0.48 mmol, 47%). M.p. >200 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 2962 (s), 2926 (s), 2874 (s) (C–H), 1607 (w), 1546 (m) (C=C and C=N), 1465 (s), 1379 (m), 1292 (w) (C–H), 1216 (m), 1145 (m), 1092 (m), 1067 (m), 1039 (m), (Ar-O–C and C–O), 861 (w), 751 (w) (Ar-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 0.88 and 1.10 (t, J = 7.5, 7.3 Hz, 2×6 H, CH_2CH_3), 1.85–1.96 (m, 8 H, CH_2CH_3), 2.04 and 2.31 (s, 12 H and 6 H, $ArCH_3$), 3.16 (d, J = 13.1 Hz, 4 H, $ArCH_2Ar$), 3.45 (s, 6 H, OCH_3), 3.70 and 4.01 (t, J = 6.8, 8.2 Hz, 2×4 H, $ArOCH_2$), 4.46 (d, J = 13.4 Hz, 4 H, $ArCH_2Ar$), 4.49 (s, 4 H, $ArCH_2O$), 5.25 (s, 4 H, $ArCH_2Im$), 6.33 (s, 4 H, Ar-H), 6.95 (s, 4 H, Ar-H), 7.12 (s, 4 H, Ar-H), 7.28 (s, 2 H, Im), 7.35 (s, 4 H, Im), 10.09 (s, 2 H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ_C = 9.7 and 10.6 (CH_2CH_3), 17.5 and 20.9 ($Ar\text{-}CH_3$), 22.8 and 23.4 (CH_2CH_3), 30.9 ($ArCH_2Ar$),

53.1 ($ArCH_2Im$), 58.3 (OCH_3), 74.8 ($ArCH_2O$), 76.4 and 77.1 ($ArOCH_2$), 122.2 and 123.3 (Im-C), 125.9, 128.6, 128.9, 129.6, 130.8, 132.0, 134.2, 134.8, 136.1 (Ar-C), 137.2 (Im-C), 140.8, 156.5, 157.1 (Ar-C) ppm. MS (MALDI-TOF): calcd. for $C_{60}H_{71}N_4O_5$: 927.5; found m/z = 927.0 $[M - 2HCl - OCH_3]^+$. $C_{60}H_{76}N_4O_6Cl_2$ (1020.18): calcd. C 70.64, H 7.51, N 5.49; found C 71.17, H 7.69, N 4.79.

5,17-Bis[(3-isopropylimidazolium-1-yl)methyl]-11,23-bis(methoxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene Dichloride (4d): The product was obtained by refluxing: 5,17-bis(chloromethyl)-11,23-bis(methoxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene (1.00 g, 1.29 mmol), 1isopropylimidazole (299 mg, 2.71 mmol), $CHCl_{3(abs.)}$ (10.0 mL), and Et_2O (70 mL) for 2 d. Yield: 0.81 g (0.81 mmol, 63%). M.p. 133–135 °C. IR (KBr): $\tilde{\nu}$ = 2966 (s), 2933 (s), 2875 (s) (C–H), 1606 (w), 1554 (m) (C=C and C=N), 1464 (s), 1379 (m), 1309 (m) (C–H), 1274 (m), 1222 (m), 1179 (m), 1147 (s), 1087 (m), 1040 (w) (Ar–O–C and C–O), 888 (w), 865 (w), 753 (w) (Ar-H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 0.88 and 1.10 (t, J = 7.6, 7.5 Hz, 2×6 H, CH_2CH_3), 1.59 [d, J = 6.8 Hz, 12 H, $CH(CH_3)_2$] 1.84–1.98 (m, 8 H, CH_2CH_3), 3.16 (d, J = 13.4 Hz, 4 H, $ArCH_2Ar$), 3.47 (s, 6 H, OCH_3), 3.68 and 4.01 (t, J = 6.8, 8.2 Hz, 2×4 H, $ArOCH_2$), 4.44 (d, J = 13.4 Hz, 4 H, $ArCH_2Ar$), 4.47 (s, 4 H, $ArCH_2O$), 4.74 [sept, J = 6.7 Hz, 2 H, $NCH(CH_3)_2$], 4.93 (s, 4 H, $ArCH_2Im$), 6.26 (s, 4 H, Ar-H), 6.80 (t, J = 1.6 Hz, 2 H, Im), 7.12 (s, 4 H, Ar-H), 7.65 (t, J = 1.6 Hz, 2 H, Im), 10.24 (s, 2 H, NCHN) ppm. ^{13}C NMR ($CDCl_3$): δ_C = 9.6 and 10.6 (CH_2CH_3), 22.7 (CH_2CH_3), 22.9 [$CH(CH_3)_2$], 23.3 (CH_2CH_3), 30.8 ($ArCH_2Ar$), 52.7 ($ArCH_2Im$), 53.0 [$NCH(CH_3)_2$], 58.3 (OCH_3), 74.7 ($ArCH_2O$), 76.4 and 77.1 ($ArOCH_2$), 120.1 and 121.0 (Im-C), 125.5, 128.7, 128.9, 131.8, 134.6 (Ar-C), 135.2 (Im-C), 136.1, 156.4, 157.0 (Ar-C) ppm. MS (MALDI-TOF): calcd. for $C_{58}H_{78}N_4O_6Cl$: 961.6; found m/z = 961.4 $[M - Cl]^+$. $C_{58}H_{78}N_4O_6Cl_2 \cdot 2H_2O$ (1034.21): calcd. C 67.36, H 7.99, N 5.42; found C 67.21, H 8.16, N 5.57.

Suzuki Cross-Coupling Reactions: The necessary ligand **1**–**4** (3 mol-%) was added to degassed solvent in vials that could be sealed with a screw-cap. After adding base (2 mmol) and $Pd(OAc)_2$ (3 mol-%) as the source of palladium the reaction mixture was heated to 80 °C for 30 min. During this period of time the solutions turned deep-red; the aryl halide (1.0 mmol) and benzeneboronic acid (1.5 mmol) were then added under an inert atmosphere and the sealed reaction vessels were heated to 80 °C in a heating block that held up to 24 test tubes. After the desired time of heating (Table 1) the reaction was stopped and the product ratio determined. For this purpose, an aliquot was withdrawn from the reaction mixture and analyzed by NMR spectroscopy. No volatiles were removed because such a procedure changed the product ratio as proven by blank experiments.

For the cross-coupling reaction in aqueous media the reaction mixture was extracted with $CHCl_3$. The combined organic extracts were filtered through a short pad of Celite, an aliquot (0.2 mL) was withdrawn, $CDCl_3$ (0.4 mL) was added, and the product ratio was determined by NMR spectroscopy as before. The product ratio over the whole concentration range was not affected by the extraction process as indicated by blank extraction experiments performed on all solvent mixtures. The yields quoted are the average yields obtained from two to five independent runs.

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