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COMMUNICATION

Selective functionalization of calix[4]arenes via tricarbonylchromium complexes

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Tricarbonylchromium complexes of 25,26,27,28-tetrapropoxycalix[4]arene conformers (1_4Pr) were synthesized. Since the benzene ring is activated through complexation with $Cr(CO)_3$, the functional groups (e.g. —D, —CH_3, and —CHO) could be selectively introduced into the $Cr(CO)_3$-complexed benzene ring. The substitution reaction occurred mainly at the *p*-position. The para selectivity was attributed to the steric crowding being relatively lower than that around the meta and benzyl position. This view was supported by the X-ray crystallographic study of 1,3-alternate-1_4Pr·$(CO)_3$. This is a novel and general methodology for selective introduction of functional groups into calix[*n*]arenes.

Calix[*n*]arenes are cyclic oligomers which belong to the class of [1_n]-metacyclophanes. As calix[*n*]arenes have a cavity-shaped architecture, they are useful as building blocks for designing host–guest-type catalysts through appropriate modification of the edges.[1–4] To design such functionalized calix[*n*]arenes, it is necessary to develop new methods for the selective introduction of desired functional groups into the benzene nuclei. In fact, a few groups have so far attempted to develop such synthetic methods,[5–11] but there exists no versatile methodology for the selective introduction of functional groups. When taking into account that calix[*n*]arenes belong to the class of [1_n]metacyclophanes, we noticed that the formation of arene–tricarbonylchromium complexes may be useful as a potential methodology for this purpose. It is known that tricarbonylchromium ($Cr(CO)_3$) forms stable η^6-arene complexes and the complexed benzene ring becomes extraordinarily 'reactive'.[12–16] We thus expected that the functional group would be selectively introduced into the benzene unit which was activated through complexation with $Cr(CO)_3$ (as shown in scheme 1).

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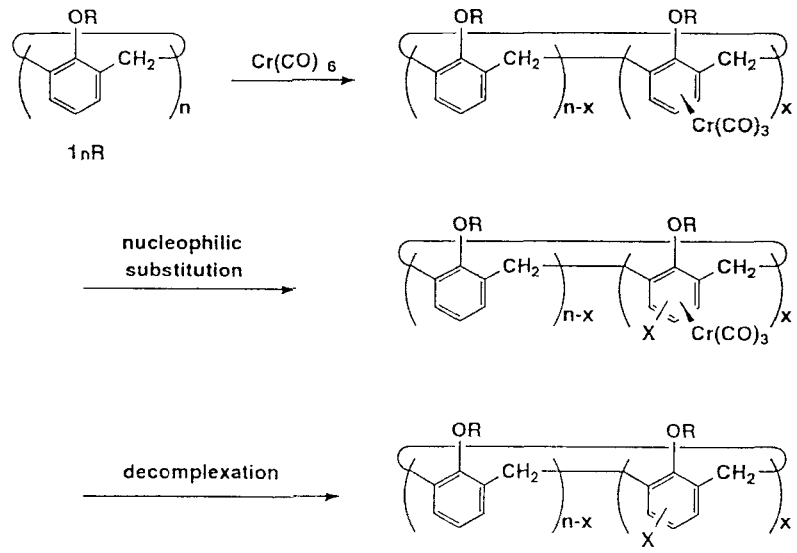
For ease of ^{1}H-NMR assignment we used conformationally immobile calix[4]arenes. As described previously,[17,18] the oxygen-through-the-annulus rotation, which causes the conformational isomerism, can be inhibited by using *O*-substituents bulkier than the ethyl group. We thus chose 25,26,27,28-tetrapropoxycalix[4]arene ($\mathbf{1}_4$Pr). The syntheses of conformational isomers of $\mathbf{1}_4$Pr and their $Cr(CO)_3$ complexes were reported previously.[19] When 2,6-dimethylpropoxybenzene·$Cr(CO)_3$ ($\mathbf{2}$·$Cr(CO)_3$ was used as a reference compound: 0.17 mmol) was lithiated with BuLi (0.19 mmol) at −78 °C in THF (5.0 ml) and then treated with methyl iodide (1.70 mmol), the methyl group was introduced into the *m*-, *p*-, and benzyl-positions in the ratio 21:50:29 (run 1 in Table 1).* A similar result was obtained from deuteration with D_2O (run 2).*

When $\mathbf{1}_4$Pr·$Cr(CO)_3$ with a cone conformation (cone-$\mathbf{1}_4$Pr·$Cr(CO)_3$) was treated in a similar manner, neither methylation nor deuteration took place (runs 3 and 6). We thus increased the concentration of BuLi to 2.5 mol equiv. and raised the reaction temperature to −30 to −40 °C. As shown in runs 7 and 8, deuteration proceeded smoothly and the substitution occurred at the *m*- and *p*-positions (but not at the benzyl position) in the $Cr(CO)_3$-complexed benzene nucleus. Methylation also proceeded smoothly but the substitution occurred only at the *p*-position (run 4). When DMF was used as a reagent at −30 °C, the *p*-formyl derivative was produced in 92% yield (run 9). On the other hand, when iso-propyl iodide, a bulky

* The isomer distribution in Table 1 was determined by the ^{1}H-NMR measurement of the product mixture after demetalation with I_2. The methyl derivatives of **2** and cone-$\mathbf{1}_4$Pr were identified spectrophotometrically after separation by column chromatography.



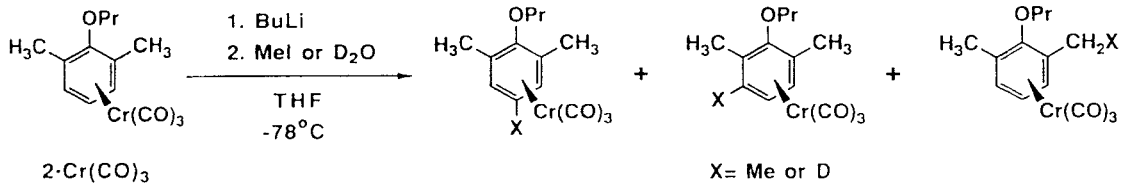
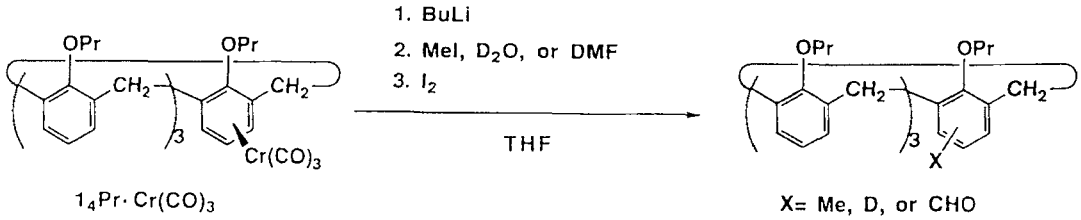


Table 1 Methylation, deuteration and formylation of tricarbonylchromium complexes of $\mathbf{1}_4$Pr and **2***

Run	Arene	Reagent	Lithation: Mol Equiv. of BuLi	Lithation: Temp. (°C)	Lithation: Time (h)	Substituted Position (%): m	Substituted Position (%): p	Substituted Position (%): benzyl	Unreacted arene (%)
1	**2**	MeI	1.1	−78	1.0	21	50	29	0
2	**2**	D_2O	1.1	−78	1.0	28	45	27	0
3	cone-$\mathbf{1}_4$Pr	MeI	1.1	−78	1.0	0	0	0	100
4	cone-$\mathbf{1}_4$Pr	MeI	2.5	−30	1.5	trace	87	0	9
5	cone-$\mathbf{1}_4$Pr	iso-PrI	2.5	−30	1.5	0	0	0	100
6	cone-$\mathbf{1}_4$Pr	D_2O	1.1	−78	1.0	0	0	0	100
7	cone-$\mathbf{1}_4$Pr	D_2O	2.5	−40	1.5	15	40	0	45
8	cone-$\mathbf{1}_4$Pr	D_2O	2.5	−30	1.5	15	75	0	10
9	cone-$\mathbf{1}_4$Pr	DMF	2.5	−30	1.5	4	92	0	4
10	1,3-alternate-$\mathbf{1}_4$Pr	MeI	1.1	−78	1.0	0	0	0	100
11	1,3-alternate-$\mathbf{1}_4$Pr	MeI	2.5	−30	1.5	1	40	0	59

* In 5.0 ml of THF, $\mathbf{1}_4$Pr·$Cr(CO)_3$ 0.069 mmol, or **2**·$Cr(CO)_3$ 0.17 mmol, BuLi 1.1 or 2.5 equiv. of the $Cr(CO)_3$ complex, and reagent 1.70 mmol.

alkylation reagent was used instead of methyl iodide, the alkylation reaction did not take place even at −30 °C (run 5). In the reaction with methyl iodide, 1,3-alternate-$\mathbf{1}_4$Pr·$Cr(CO)_3$ was also unreactive at −78 °C (run 10) but yielded the *p*-methyl derivative in 40% yield at −30 °C (run 11). In case the yield was low (e.g. in runs 5 and 11), we raised the reaction temperature up to −10 to 0 °C. We found, however, that the reaction mixture gradually turned brown and a number of the unknown byproducts resulted. The foregoing results support the idea that various functional groups can be introduced selectively into



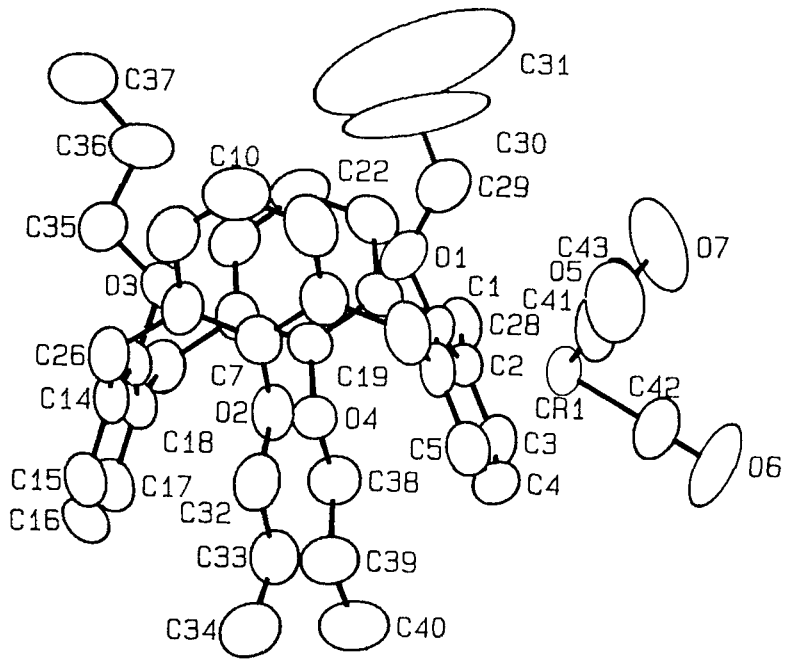


Figure 1 X-ray structure of 1,3-alternate-$1_4Pr \cdot Cr(CO)_3$. Hydrogen atoms are not shown for clarity.

the $Cr(CO)_3$-complexed benzene nucleus (particularly into the *p*-position).

Then why is $1_4Pr \cdot Cr(CO)_3$ less reactive than $2 \cdot Cr(CO)_3$, and what is the origin of the high *p*-selectivity in $1_4Pr \cdot Cr(CO)_3$? We and others have already found that conformationally immobile calix[4]arenes are considerably crowded and the benzene rings are sterically covered by the substituents.[7,20-23] This view is also supported by X-ray crystallographic studies.[23-26] Examination of Table 1 reveals that both the *m*- and *p*-positions can accept D^+ but only the *p*-position can accept Me^+, whereas neither D^+ nor Me^+ is accepted by the benzyl position. The results indicate that the steric crowding in $1_4Pr \cdot Cr(CO)_3$ increases in the order of para < meta < benzyl. This situation can be seen from the CPK molecular models. In the calix[4]arene ring the *m*- and benzyl-positions are more crowded than those in **2** because of the neighbouring benzene rings. In contrast, the *p*-position is scarcely influenced by such a ring effect. In the $Cr(CO)_3$ complexes not only the *m*- and benzyl-positions but also the *p*-position is crowded because of the 'umbrella effect' of the $Cr(CO)_3$ group. This is why $1_4Pr \cdot Cr(CO)_3$ is much less reactive than $2 \cdot Cr(CO)_3$. The *m*- and benzyl-positions are particularly deactivated because of both the ring effect and the 'umbrella effect'. In 1,3-alternate-1_4Pr, the *p*-position is sandwiched by two inversed phenyl rings and is therefore more crowded than that in cone-1_4Pr.[25] This is why the *p*-position in 1,3-alternate-$1_4Pr \cdot Cr(CO)_3$ is less reactive than that in cone-$1_4Pr \cdot Cr(CO)_3$.

To obtain further insights into the steric crowding we tried to isolate single crystals of the $1_4Pr \cdot Cr(CO)_3$ complexes. We succeeded in the X-ray crystallographic analysis of 1,3-alternate-$1_4Pr \cdot Cr(CO)_3$ (Fig 1). It is known that the benzene $\cdot Cr(CO)_3$ complex has neat

* Recrystallized from acetonitrile. Crystal data: chemical formula $C_{43}H_{48}O_7Cr$; Fw 728.85; crystal system monoclinic; space group $P2_{1/a}$; Z = 4; Dc = 1.243 g cm^{-3}; cell dimensions a = 19.496(3) Å, b = 11.118(2) Å, c = 19.121(2) Å; β = 109.95(1) deg; R = 0.055; Rw = 0.068.

C_3 symmetry and the distance between Cr and the six carbons is 2.23 Å.[27] On the other hand, the structure of 1,3-alternate-$\mathbf{1}_4$Pr · $Cr(CO)_3$ is considerably deformed to reduce the steric crowding. The $Cr(CO)_3$ moiety is largely inclined to the *p*-position side. The distances from Cr to each benzene carbon are 2.26 Å for C-1, 2.28 Å for C-2, 2.20 Å for C-3, 2.18 Å for C-4, 2.21 Å for C-5, and 2.26 Å for C-6. Also, it is worthwhile mentioning that the O—CH_2—CH_2—CH_3 group in the $Cr(CO)_3$-complexed phenol unit adopts a gauce conformation whereas those in the residual three phenol units adopt an anti conformation. It is clear that the gauche conformation is adopted here to reduce the steric crowding. It is seen from Figure 1 that the *m*- and benzyl-positions are covered by $Cr(CO)_3$ and the neighbouring benzene rings, whereas the *p*-position has the open space for the approach of reagents.

In conclusion, the present study demonstrates that various functional groups can be selectively introduced into calix[*n*]arenes via the formation of their $Cr(CO)_3$ complexes. We believe that this would serve as the first general methodology for the selective functionalization of calix[*n*]arenes.

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