Experimental Section

The ligand (c-$C_6H_{11})_8Si_8O_{11}(OH)_2$ was prepared according to a procedure previously described by Feher et al.[3] A solution of (c-$C_6H_{11})_8Si_8O_{11}(OH)_2$ (2.52g, 2.3 mmol) in diethyl ether (60 cm^3) was added to $[Ce\{N(SiMe_3)_2\}_3]$[9] (0.713 g, 1.15 mmol) at ca. 20 °C. The mixture was stirred for 3 h. Pyridine (2.1 g, 23 mmol) was added, and the mixture was stirred for 24 h. The mixture was then filtered, and the filtrate was concentrated to ca. 20 cm^3 in vacuo. Pale yellow crystals of **1** were gradually deposited. Further concentration of the remaining mother liquor (ca. 10 cm^3) in vacuo and cooling to −22 °C afforded an additional crop of crystals of **1** (total yield: 1.97 g, 67%). Analysis calcd for $C_{114}H_{191}CeN_3O_{26}Si_{16}$: C 53.4, H 7.45, N 1.6; found: C 52.9, H 7.36, N 1.4; ^1H NMR (400 MHz, [D$_6$]benzene, 22 °C): δ = 8.86 (m, 6H; py), 7.0 (m, 3H; py), 6.8 (m, 6H; py), 2.12–1.27 (brm, 160H; CH_2 in c-C_6H_{11}), 1.04 (m, 16H; CH in c-C_6H_{11}); ^{13}C NMR (125 MHz, [D$_6$]benzene, 22 °C): δ = 150.45, 136.28, 123.76 (py), 28.77, 28.36, 28.12, 27.92, 27.62, 27.46 (CH_2), 25.96, 25.16, 24.04 (CH); ^{29}Si NMR (99 MHz, [D$_6$]benzene, 22 °C): δ = −60.68, −63.81, −69.59 (2:4:2); IR (KBr): $\tilde{\nu}$ = 2923, 2850, 1599, 1448, 1108, 1067, 949, 847, 823, 750, 700, 622, 518, 403 cm^{-1}. Alternatively, complex **1** was prepared by heating anhydrous $CeCl_3$ (0.152 g, 0.615 mmol) for 24 h in THF under reflux and subsequent treatment with (c-$C_6H_{11})_8Si_8O_{11}(OH)_2$ (1.35 g, 1.23 mmol) in THF/pyridine (75 cm^3, 4/1). Crystallization from a concentrated solution in pyridine gave crystals of **1** (yield: 0.87g, 55%).

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[4] Crystal data: for **1**: $C_{111}H_{195}CeN_3O_{28}Si_{16}$, M_r = 1304.63, monoclinic, space group $C2/c$, a = 20.474(5), b = 21.244(5), c = 32.843(10) Å, β = 102.95(3)°, V = 13922(6) Å^3, Z = 4, ρ_{calcd} = 1.245 g cm^{-3}, $F(000)$ = 5552, T = 153(2) K, $\mu(Mo_{K\alpha})$ = 0.529 mm^{-1}, 3.60 < θ < 22.54°; of 13986 reflections 9079 were independent (R_{int} = 0.0356); the final R indices were R_1 = 0.0511 and wR_2 = 0.1358 ($I > 2\sigma(I)$), and R_1 = 0.0596, wR_2 = 0.1471 (all data); GOF on F^2: 1.094; max./min. residual electron density +1.211/−0.447 e Å^{-3}. Data were collected on a Siemens-Stoe AED2 diffractometer. The structure was solved by direct methods (SHELXTS-90) and refined by full-matrix least-squares methods on F^2. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were included by using a riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150263. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Differential Cleavage of Arylmethyl Ethers: Reactivity of 2,6-Dimethoxybenzyl Ethers[**]

J. R. Falck,* D. K. Barma, Rachid Baati, and Charles Mioskowski

Protecting groups (PGs) serve a fundamental, albeit often under-appreciated, role in synthesis.[1] The interplay of their physico-chemical properties, availability, economics, and, most importantly, their selective manipulation significantly influences their ultimate utility. Consequently, milder or more selective methodology applicable to the existing repertoire of PGs and the development of new PGs with different reactivities have the potential to expedite progress along a broad front. Herein, we describe a convenient, high-yield protocol for the selective cleavage of arylmethyl ethers with stoichiometric chromium(II) chloride/lithium iodide in moisture-containing EtOAc [Eq. (1)].[2] We also highlight the 2,6-dimethoxybenzyl moiety[3] as a versatile and cost-effective[4] PG that extends the range of options for the selective removal of arylmethyl ethers.

$$ROCH_2Ar \xrightarrow[\text{EtOAc } (H_2O)]{CrCl_2/LiI} ROH + ICH_2Ar \qquad (1)$$

The scope of the de-*O*-benzylation by $CrCl_2/LiI$[5] was evaluated with a panel of representative arylmethyl ethers (Table 1). Unsubstituted benzyl ethers were smoothly cleaved at 75 °C in moisture-containing[6] EtOAc to give, after aqueous isolation, the corresponding alcohol and benzyl iodide (e.g., the conversion of **1** into **2** (Table 1, entry 1)) in good to excellent yields. There was little or no reaction when we used $CrCl_2$ or LiI alone,[7] $CrCl_2$/LiBr, or $CrCl_2$/n-Bu_4NI.[8] On the other hand, CrI_2 was just as effective as $CrCl_2$/LiI, but its expense precluded further exploration. Yields were much lower in N,N-dimethylformamide, 1,2-dimethoxyethane, and acetonitrile; the use of THF was limited by its reaction with the reagent.

p-Phenylbenzyl ether[9] **3** likewise gave rise to **2** (Table 1, entry 2) in excellent yield under similar conditions as **1**. Notably, glycerol derivative **4** furnished secondary alcohol **5** (Table 1, entry 3) as the sole product. Such regioselectivity is reminiscent[10] of other transition metal promoted de-*O*-

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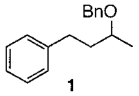
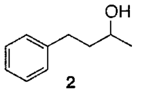
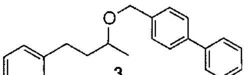
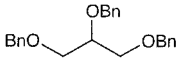
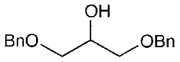
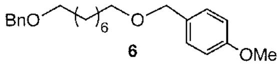
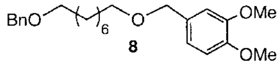
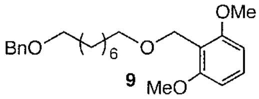
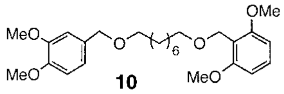
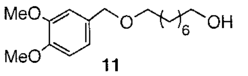
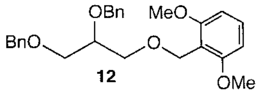
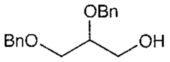
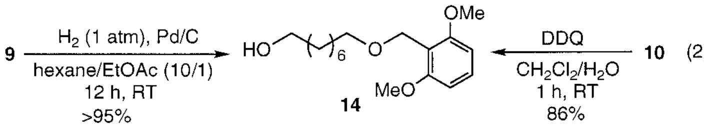
Table 1. Cleavage of benzylic ethers.[a]

Entry	Benzyl ether	Alcohol	Time [h]	Yield [%]
1	 **1**	 **2**	12	92
2	 **3**	**2**	14	92
3	 **4**	 **5**	8	95
4	 **6**	 **7**	10	85
5	 **8**	**7**	8	95
6	 **9**	**7**	3	98
7	 **10**	 **11**	2	85
8	 **12**	 **13**	3	95

[a] Reaction conditions: $CrCl_2$ (3 equiv), LiI (4 equiv), 75 °C, EtOAc:H_2O (1:0.005 v:v).



(2)

benzylations of **4** and suggests that a comparable cyclic chelation mechanism is operative, i.e., chromium coordinates to two or more oxygen atoms, thus rendering the benzylic carbon atom susceptible to nucleophilic attack by iodide (see below). The preferential cleavage of the electron-rich methoxy-substituted arylmethyl moieties of **6** (Table 1, entry 4) and **8** (Table 1, entry 5) in the presence of an unsubstituted benzyl ether is consistent with this hypothesis and prompted us to investigate the reactivity of 2,6-dimethoxybenzyl ethers whose stereoelectronic properties should enhance Cr coordination and accelerate displacement (Figure 1).

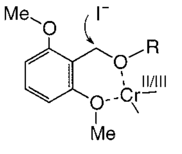
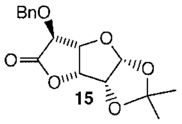
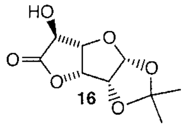
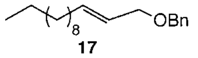
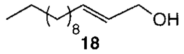
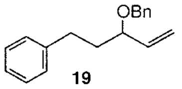
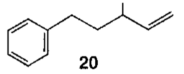
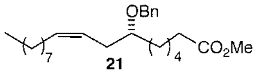
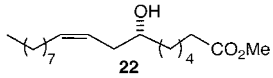
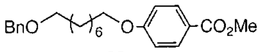
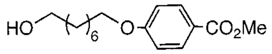
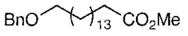
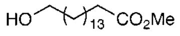
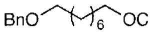
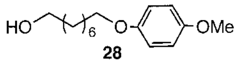
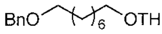
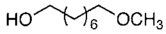
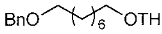
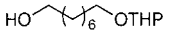
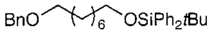
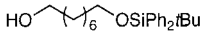
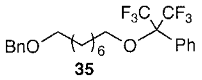
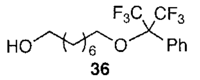
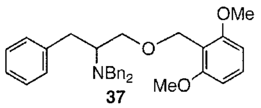
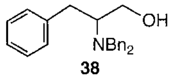


Figure 1. Coordinated intermediate.

The expectation of greater reactivity was validated by the facile liberation of **7** from **9** (Table 1, entry 6) in just 3 hours. Indeed, the 2,6-dimethoxybenzyl ether in **10** (Table 1, entry 7) was cleaved more readily with $CrCl_2$/LiI than was its 3,4-dimethoxybenzyl analogue and, as illustrated by the example of **12** (Table 1, entry 8), could even overcome the regiochemical bias displayed by glycerol **4** (Table 1, entry 3). Alternatively, the benzyl group in **9** or the 3,4-dimethoxybenzyl group in **10** could be selectively cleaved to **14** using conventional methodology (Eq. (2); DDQ = 2,3-dichloro-5,6,-dicyano-1,4-benzoquinone). In contrast with the simple benzyl ethers discussed above, the 2,6-dimethoxybenzyl iodide by-product was converted under the reaction conditions into the corresponding chromium(III) intermediate, which could be intercepted by electrophiles such as benzaldehyde, or gave 2,6-dimethoxytoluene upon quenching with water.[11]

Since the utility of a PG is ultimately linked to its ease of manipulation in the presence of other functional groups, a brief survey of the compatibility of the debenzylation conditions with some common functional groups was deemed important. Application of the standard deprotection conditions to D-glucuronolactone derivative **15** was instructive since alcohol **16** was obtained in good yield without compromising the anomeric center, acetonide, or lactone (Table 2, entry 1).[12] Primary (Table 2, entry 2) and secondary (Table 2, entry 3) allylic ethers **17** and **19**, respectively, showed no indications of isomerization or dehydration, nor did *cis* olefin **21** (Table 2, entry 4). In contrast, application of the popular[1] debenzylation reagents Me_3SiI, Na/NH_3, or H_2/Pd to **17** and **19** under typical conditions proved unsatisfactory and resulted

Table 2. Functional group specificity.[a]

Entry	Substrate	Alcohol	Time [h]	Yield [%]
1	 **15**	 **16**	16	82
2	 **17**	 **18**	12	89
3	 **19**	 **20**	11	89
4	 **21**	 **22**	12	89
5	 **23**	 **24**	16	87
6	 **25**	 **26**	14	92
7	 **29**	 **28**	12	88
8	 **31**	 **30**	16[b]	82
9	 **31**	 **32**	24[b]	80
10	 **33**	 **34**	18[b]	89
11	 **35**	 **36**	16	86
12	 **37**	 **38**	11[b,c]	89

[a] Reaction conditions: $CrCl_2$ (3 equiv), LiI (4 equiv), 75 °C, EtOAc/H_2O (1:0.005 v:v). [b] 65 °C. [c] $CrCl_2$ (6 equiv), LiI (10 equiv).

in iodine-containing by-products, hydrogenolysis of the allylic alcohol, and/or olefin saturation.

Methyl benzoate **23**, aliphatic ester **25**, and phenolic ether **27** readily afforded alcohols **24**–**28** (Table 2, entries 5–7), respectively. However, it was necessary to reduce the temperature and increase the reaction times for methyl ether **29**, tetrahydropyran (THP) **31**, and silyl ether **33** (Table 2, entries 8–10) to avoid any concomitant loss of these functional groups. 1,1,1,3,3,3-Hexafluoro-2-phenylisopropyl (HIP) ethers,[13] although classified as benzyl ethers, were stable to $CrCl_2$/LiI treatment, for example, **35** was converted into **36** (Table 2, entry 11). On the other hand, amines such as **37** tended to retard de-*O*-benzylation, but this could be surmounted with the use of excess reagent (Table 2, entry 12).

Experimental Section

De-*O*-benzylation procedure: An arylmethyl ether (1 equiv) was added to a purple suspension of $CrCl_2$ (3 equiv) and LiI (4 equiv; Aldrich Chem. Co, 99.99 %) in a solution of EtOAc/H_2O (1:0.005 v/v, 10 mL/100 mg arylmethyl ether). The reaction was heated at the indicated temperature (Tables 1 and 2) for 2–24 h, then cooled to room temperature, quenched with water, and extracted three times with Et_2O. The combined organic extracts were washed with saturated sodium sulfite solution and water, then dried and evaporated in vacuo. Chromatographic purification of the residue afforded the corresponding free alcohol.

Preparation of 2,6-dimethoxybenzyl bromide:[3] 2,6-Dimethoxytoluene (1 equiv) was heated at reflux with *N*-bromosuccinimide (NBS; 1.1 equiv) and benzoyl peroxide (2 mol %) in carbon tetrachloride (10 mL/1.5 g 2,6-dimethoxytoluene) for 30 min. After cooling the reaction mixture to room temperature, the precipitated succinimide was removed by filtration and the solvent was evaporated in vacuo to give crude 2,6-dimethoxybenzyl bromide (95 %), which was sufficiently pure to be used without further purification.

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[1] T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**.

[2] For the use of $CeCl_3$/NaI in the selective deprotection of allyl ethers, see R. M. Thomas, G. S. Reddy, D. S. Iyengar, *Tetrahedron Lett.* **1999**, *40*, 7293–7294; *p*-methoxybenzyl ethers: A. Cappa, E. Marcantoni, E. Torregiani, G. Bartoli, M. C. Belluci, M. Bosco, L. Sambri, *J. Org. Chem.* **1999**, *64*, 5696–5699.

[3] This group was previously studied as a PG that could be cleaved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ): N. Nakajima, R. Abe, O. Yonemitsu, *Chem. Pharm. Bull.* **1988**, *36*, 4244–4247.

[4] At less than $1.00/g from Aldrich Chem. Co., 2,6-dimethoxytoluene, from which 2,6-dimethoxybenzyl bromide is directly obtained by NBS bromination (see Experimental Section), is competitively priced with respect to the precursors of other methoxy-substituted benzylation reagents.

[5] Anhydrous LiI (99.99 %) from Aldrich gave a consistently good result, whereas samples purchased from Acros were inconsistent.

[6] 1:0.005 v:v EtOAc:H_2O. The reaction is impeded by ratios above 1:0.01.

[7] Inorganic iodides have been used for dealkylations and debenzylations of phosphate triesters: R. J. W. Cremlyn, G. W. Kenner, Sir A. Todd, *J. Chem. Soc.* **1958**, 528–530.

[8] $Cr^{III}Cl_3$ (6 equiv)/LiI (10 equiv) gave comparable or, in some cases, higher yields than $Cr^{II}Cl_2$ (3 equiv)/LiI (4 equiv). Evidently, Cr^{III} is reduced by LiI to Cr^{II} under the reaction conditions.

[9] *p*-Phenylbenzyl ethers are also cleaved by $FeCl_3$: M. H. Park, R. Takeda, K. Nakanishi, *Tetrahedron Lett.* **1987**, *28*, 3823–3824.

[10] H. Hori, Y. Nishida, H. Ohrui, H. Meguro, *J. Org. Chem.* **1989**, *54*, 1346–1353.

[11] Benzylic Cr^{III} species derived from the related benzyl halides are well known: F. A. L. Anet, E. Leblanc, *J. Am. Chem. Soc.* **1957**, *79*, 2649–2650.

[12] Results comparable to those in Table 2 were obtained when the benzyl ethers were replaced with more reactive methoxy-substituted arylmethyl ethers.

[13] H.-S. Cho, J. Yu, J. R. Falck, *J. Am. Chem. Soc.* **1994**, *116*, 8354–8355.

Indoloparacyclophanes: Synthesis and Dopamine Receptor Binding of a Novel Arylbioisostere**

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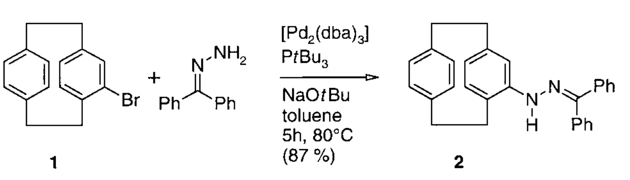
Dedicated to Professor Dieter Sellmann
on the occasion of his 60th birthday

Investigating the reaction of arylhydrazines with ketones in his laboratory in Erlangen, Emil Fischer discovered the formation of indoles.[1, 2] Very recent work published by Buchwald et al. and also by Hartwig further extended the scope of the Fischer indole synthesis.[3, 4] The major improvement of this variant is the Pd-catalyzed preparation of *N*-arylbenzophenone hydrazones used as key intermediates. As part of our exploration of novel types of pharmacophoric elements, we recently found that enyne moieties and aza-derivatives thereof can serve as nonaromatic arylbioisosteres.[5] Furthermore, the pyrazolo[1,5]pyridine nucleus turned out as an effective indole bioisostere.[6] As an extension of these studies, we were intrigued by the question whether a double-layered [2.2](4,7)indoloparacyclophane system with its close proximity of the face-to-face aromatic rings coupled to the rigid and highly strained skeleton could be exploited as a pharmacophoric element being able to coordinate to highly specific receptor binding sites.[7]

For the preparation of the hitherto unknown [2.2]indoloparacyclophane ring system,[8, 9] we planned to take advantage of Buchwald's variant of the Fischer indole synthesis.[3] Thus, we tried to prepare the *N*-([2.2]paracyclophanyl)benzophenone hydrazone **2** by Pd-catalyzed cross-coupling reaction of benzophenone hydrazone with 2-bromo[2.2]paracyclophane **1**, readily available by bromination of [2.2]paracyclophane [Eq. (1)].[10] Our initial attempts using 1.0 mol % $Pd(OAc)_2$



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