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Organocatalytic Methods for Chemoselective *O-tert*-Butoxycarbonylation of Phenols and Their Regeneration from the *O-t*-Boc Derivatives

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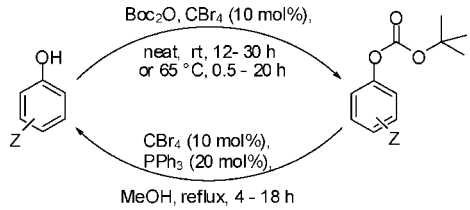
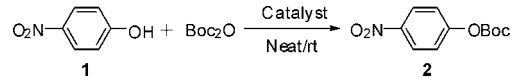
Received June 26, 2008



Carbon tetrabromide (CBr_4) catalyzes *O-tert*-butoxycarbonylation of functionalized phenols without any side reactions (bromination, addition of CBr_3 to a double bond, and formation of symmetrical diaryl carbonates, cyclic carbonates, or carbonic-carbonic anhydrides). The parent phenols are regenerated from the *O-t*-Boc derivatives by the catalyst system CBr_4-PPh_3 without affecting other protecting groups (aryl alkyl ether, alkyl ester, and thioacetal) or competitive side reaction such as bromination, nitrene (from NO_2) and α,α-dibromoolefine (with CHO/COMe) formation, and transesterification (with CO_2Me/Et) taking place.

The protection and deprotection of hydroxyl group are encountered with 30% and 14% frequency, respectively, in the preparation of drug candidates.[1] Acylation[2,3] is a common approach to protect hydroxyl groups, but the regeneration of the parent compounds requires hydrolysis under strong alkaline conditions[2] incompatible with other functional groups. Although chemoselective deacylation is achievable by "demand-based thiolate anion generation"[4] under neutral or virtually neutral and nonaqueous conditions, *O-tert*-butoxycarbonylation is a suitable alternative[2] as the *O-t*-Boc moiety is compatible with reaction conditions routinely adopted in organic synthesis. The limited methodologies[5] available for the preparation of *O-t*-Boc phenols have several drawbacks: the requirement of long reaction times,[5d,e] low/high temperatures,[5d,e] special efforts to prepare the *tert*-butoxycarbonylation reagents,[5d,e] and auxiliary substances (e.g., solvents, bases, etc.).[5] In analogy with the recent trend of Lewis acid catalyzed *N-tert*-butoxycarbonylation,[6] *O-t*-Boc formation does not become feasible as phenols form the *tert*-butyl ethers with Boc_2O in the presence of a strong Lewis acid[7] and a mild Lewis acid requires heating under reflux in DCM for 5−19 h.[5f] Therefore, the need to use/develop organocatalytic procedures was realized.

TABLE 1. Evaluation of Various Organocatalysts for *O-t*-Boc Formation of 1[a]



1 2

entry	catalyst	time (h)	yield (%)[b]
1	none	2 d	0[c]
2	CBr_4	11	93[d]
3	NBS	24	0[c]
4	NCS	24	0[c]
5	I_2	24	30[e,f]
6	$CHBr_3$	24	15
7	CH_2Br_2	24	15
8	$CHCl_3$	24	0[c]
9	CH_2Cl_2	24	0[c]
10	CCl_4	24	0[c]
11	HBr[g]	24	0[c]

[a] **1** (2.5 mmol) was treated with Boc_2O (2.5 mmol, 1 equiv) under neat conditions at room temperature (∼35−40 °C) in the presence of the organocatalyst (10 mol %). [b] Isolated yield of **2**. [c] Unreacted **1** was recovered. [d] **2** was obtained in 96% yield at 65 °C for 0.75 h. [e] **3** was the only product formed. [f] **2** was formed in 10% yield as the only product at 65 °C after 12 h. [g] 48% aqueous solution of HBr was used.

Only a few reports are available for *O-t*-Boc formation using nucleophilic organocatalyst.[5b−e,8] Some of these give side products such as symmetrical carbonates, cyclic carbonate, and carbonic-carbonic anhydrides.[5c]

In our search for an effective organocatalyst, we choose 4-nitrophenol **1** as a model substrate and treated it with Boc_2O in the presence of CBr_4, NBS, NCS, and I_2 (Table 1). The best results

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(4) (a) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 2541. (b) Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem.* **1999**, *64*, 8027.
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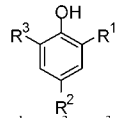
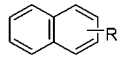
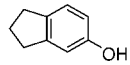
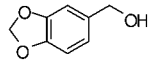
(7) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *J. Org. Chem.* **2006**, *71*, 9580.
(8) Chebolu, R.; Chankeshwara, S. V.; Chakraborti, A. K. *Synthesis* **2008**, 1448.

10.1021/jo8013325 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/10/2008

TABLE 2. CBr_4-Catalyzed *O-t*-Boc Formation of Phenols[a]

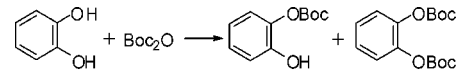
entry	substrate	method A t (h)/yield[b]	method B t (h)/yield[b]
			
1	$R^1 = R^2 = R^3 = H$	18/83	0.75/92
2	$R^1 = R^3 = H$; $R^2 = OMe$	6/94	1.5/92
3	$R^1 = R^3 = H$; $R^2 = Me$	12/83	2/88
4	$R^1 = R^3 = H$; $R^2 = {}^iPr$	22/85	1.5/90
5	$R^1 = R^3 = H$; $R^2 = OCH_2Ph$	---	1.5/92
6	$R^1 = R^3 = H$; $R^2 = Cl$	5/83	1/90
7	$R^1 = Cl$; $R^2 = R^3 = H$	nil/24	1.25/86
8	$R^1 = R^2 = R^3 = Cl$	20/77	4/80
9	$R^1 = R^3 = H$; $R^2 = Br$	13/88	1/89
10	$R^1 = OMe$; $R^2 = Br$; $R^3 = H$	9/94	1.5/90
11	$R^1 = R^3 = H$; $R^2 = NO_2$	11/93	0.5/96
12	$R^1 = NO_2$; $R^2 = R^3 = H$	nil/24	1/88
13	$R^1 = R^2 = R^3 = Me$	nil/36	12/80
			
14	R = 1-OH	12/83	2/90
15	R = 2-OH	9/89	1.5/91
16		---	2/95
17		nil/24	18/90

[a] The phenol (2.5 mmol) was treated with $(Boc)_2O$ (2.5 mmol, 1 equiv) under neat condition at room temperature (~35−40 °C; Method A) and at 65 °C (Method B) in the presence of CBr_4 (10 mol%). [b] Yield of the purified *O-t*-Boc derivative.

were obtained with CBr_4, affording the 4-(*tert*-butoxycarbonyloxy)nitrobenzene **2** in 93% yield at room temperature (35−40 °C) after 11 h and in 96% yield at 65 °C after 0.75 h (entry 2, Table 1). No significant amount of **2** was formed either in the absence of any catalyst (footnote, entry 1, Table 1) or in the presence of NBS, NCS, I_2 (entries 3−5, Table 1). Surprisingly, the use of I_2 resulted in the formation of 4-*tert*-butoxynitrobenzene **3**[9] as the only isolable product in 30% yield (entry 5, Table 1). Other bromocarbons such as $CHBr_3$ and CH_2Br_2 were less effective, affording **2** in 15% yield (entries 6 and 7, Table 1) but chlorocarbons such as CCl_4, $CHCl_3$, and CH_2Cl_2 were ineffective (entries 8−10, Table 1). To find the effect of solvent, the reaction of **1** with Boc_2O (1 equiv) was carried out in DCM, THF, MeCN, $MeNO_2$, and MeOH in the presence of CBr_4 (10 mol%), and **2** was formed in 50%, 0, 10%, 0, and 5% yields, respectively.

The use of CBr_4 circumvented the notable drawbacks of the reported procedures such as the use of THF,[5a] MeCN,[5c] PhH,[5e] and DCM[5f] as solvents that are not preferred by the recent solvent selection guide of the pharmaceutical industry from an environmental perspective[10] and the requirement of stoichiometric quantities or more of additional reagents, e.g., isoquinoline[5e] or K_2CO_3[5a] that add environmental burden. The generality was demonstrated with various phenols that afforded the desired *O-t*-Boc derivatives in excellent yields on treatment with Boc_2O at room temperature (Method A) and at 65 °C (Method B) (Table 2). No side reactions

TABLE 3. Reaction of 4 with Boc_2O under Various Conditions[a]



4 **5** **6**

entry	Boc_2O (equiv)	catalyst	solvent	temp (°C)	time (h)	yield (%)[b] **5**	yield (%)[b] **6**
1	1	$Zn(OAc)_2$[c]	DCM	reflux	12	50	20
2	2	$Zn(OAc)_2$[c]	DCM	reflux	12	30	60
3	1	$Zn(OAc)_2$[c]	neat	65	1	40	20
4	2	$Zn(OAc)_2$[c]	neat	65	1		70
5	1	K_2CO_3[d]	THF	rt	12	10	40
6	2	K_2CO_3[d]	THF	rt	12		90
7	1	K_2CO_3[d]	neat	65	1	5	40
8	2	K_2CO_3[d]	neat	65	1		95
9	1	DMAP[e]	MeCN	rt	0.5		40
10	2	DMAP[e]	MeCN	rt	0.5		95
11	1	DMAP[e]	neat	rt	0.5		45
12	2	DMAP[e]	neat	rt	0.5		95
13	1	CBr_4[c]	neat	rt	18	78	
14	2	CBr_4[c]	neat	65	1	83	
15	1	CBr_4[c]	neat	65	1	85	
16	2	CBr_4[c]	neat	65	5		90

[a] **4** (2.5 mmol) was treated with Boc_2O under various conditions. [b] Isolated yield. [c] 10 mol% of the catalyst was used. [d] Used in 1.5 equiv of **4**. [e] Used in 0.5 equiv of **4**.

such as bromination[11] and carbonic-carbonic anhydride formation[5c] were observed.

The reported procedure forms cyclic carbonate[5c] by the reaction of Boc_2O with 1,2-diols. Therefore, to demonstrate the advantage of this newly developed methodology over the reported procedures for selective *O-t*-Boc formation, the reaction of 1,2-dihydroxybenzene **4** with Boc_2O was carried in the presence of some of the reported catalysts/reagent and CBr_4 (Table 3).

The CBr_4-catalyzed reactions were found to be highly selective. The mono-*O-t*-Boc was the only product in using 1 equiv of Boc_2O at room temperature after 18 h and at 65 °C after 1 h. The use of 2 equiv of Boc_2O afforded the mono-*O-t*-Boc after 1 h at 65 °C and the di-*O-t*-Boc product as the only product at 65 °C after 5 h. The reactions performed with the reported catalysts (following reported experimental conditions or the conditions operative for the CBr_4-catalyzed reactions) were either nonselective (affording a mixture of the mono- and di-Boc compounds) or produced the di-Boc compound (entries 4, 6, and 8; Table 3). In case of DMAP, no significant amount of the mono-Boc compound was formed (entries 9−12, Table 3). None of the reported catalysts was effective for selective mono-Boc formation.

As the ultimate utility of a protecting group is judged by its ease of manipulation in the presence of other functional groups, we planned to test the compatibility of the reaction conditions with various functional/protecting groups such as nitrile, formyl, acetyl, silyl, carboalkoxy, dithiolane, acetoxy, α,β-unsaturated carbonyl, *N-t*-Boc, acetamido and benzamido (Table 4). The desired *O-t*-Boc compounds were formed in high yields with excellent chemoselectivity. No competitive side reactions such as bromination,[11] *N-t*-Boc formation at the NHCOR moiety (entries 11−13, Table 4),[12] addition of the CBr_3 radical to the α,β-unsaturated carbonyl moiety,[13] and desilylation[14] were

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(10) (a) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jenings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31. (b) Capello, C.; Fischer, U.; Hungerbühler, K. *Green Chem.* **2007**, *9*, 927.
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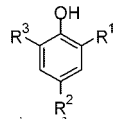
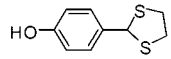
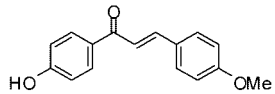
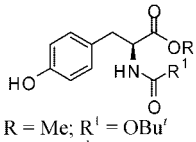
(14) (a) Lee, A. S.-Y.; Yeh, H.-C.; Shie, J.-J. *Tetrahedron Lett.* **1998**, *39*, 5249. (b) Chen, M.-Y.; Lee, A. S.-Y. *J. Org. Chem.* **2002**, *67*, 1384.

TABLE 4. CBr_4-Catalyzed *O-t*-Boc Formation of Phenols Containing Other Functional Groups[a]

entry	substrate	method A t (h)/yield[b]	method B t (h)/yield[b]
1	 $R^1 = R^3 = H$; $R^2 = CN$	11/94	1/93
2	$R^1 = R^3 = H$; $R^2 = CHO$	12/60	1/65
3	$R^1 = CHO$; $R^2 = R^3 = H$	18/74	2/95
4	$R^1 = R^3 = H$; $R^2 = COMe$	7/92	1/87
5	$R^1 = COMe$; $R^2 = R^3 = H$	nil/24	9/90
6	$R^1 = R^3 = H$; $R^2 = CO_2Me$	11/95	1/93
7	$R^1 = R^3 = H$; $R^2 = OCOMe$	10/92	1.5/90
8	$R^1 = R^3 = H$; $R^2 = OTBDMS$	---	1/99
9		---	1.5/92
10		---	6/65[c,d]
11	 R = Me; $R^1 = OBu^t$	---	1.5/92[c]
12	R = Et; $R^1 = Me$	---	1.5/90[c]
13	R = Et; $R^1 = Ph$	---	8/83[c]

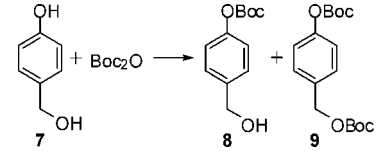
[a] The phenol (2.5 mmol) was treated with $(Boc)_2O$ (2.5 mmol, 1 equiv) under neat condition at room temperature (~35−40 °C; Method A) and at 65 °C (Method B) in the presence of CBr_4 (10 mol %). [b] Yield of the purified *O-t*-Boc derivative. [c] 2 equiv of $(Boc)_2O$ was used. [d] Unreacted starting material was recovered.

observed. The chiral substrates (entries 11−13, Table 4) afforded optically pure products. The difference of rate of reaction for 4- and 2-hydroxyacetophenones (entries 4 and 5, Table 4) were in consonance with those observed for 4- and 2-chlorophenols (entries 7 and 8, Table 2) and for 4- and 2-nitrophenols (entries 11 and 12, Table 2).

As in the case of alcoholic hydroxyl group, no *O-t*-Boc formation took place at room temperature (Method A) and the reaction took longer time following Method B (entry 17, Table 2) we thought that the difference in the rate of reactions with phenolic and alcoholic hydroxyl groups may form the rationale for chemoselective *O-t*-Boc formation of the phenolic OH group in the presence of the alcoholic OH group. Further, the intramolecular competition between a phenolic OH and alcoholic OH group may serve to measure the advantage of this new methodology over the reported procedures.

The reaction of 3-hydroxybenzyl alcohol with Boc_2O has been reported[5a] to be nonselective giving a mixture of the mono- and di-Boc derivatives. The $Zn(OAc)_2$ catalyzed reaction[5f] of 3-(4-hydroxyphenyl)-1-propanol afforded a mixture of primary mono-protected and diprotected diol. We chose 4-hydroxybenzyl alcohol **7** as the model substrate for adjudging the selectivity of Boc formation under various methodologies (Table 5). The use of DMAP has been reported to be nonselective and resulted in the formation of the di-Boc derivative.[8] The other reported catalyst/reagent such as $Zn(OAc)_2$ and K_2CO_3 were also nonselective forming 60:20 to 30:70 mixtures of the mono- and di-Boc derivatives. Compared to these observations, the present method

TABLE 5. Reaction of 7 with Boc_2O under Various Conditions[a]

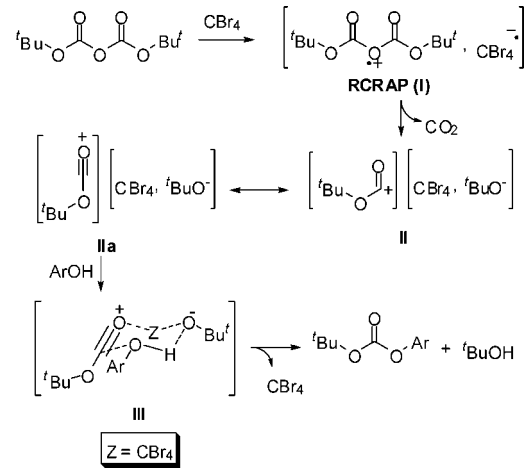


7 **8** **9**

entry	Boc_2O (equiv)	catalyst	solvent	temp (°C)	time (h)	yield (%)[b] **8**	yield (%)[b] **9**
1	1	$Zn(OAc)_2$[c]	DCM	reflux	12	60	20
2	2	$Zn(OAc)_2$[c]	DCM	reflux	12	60	40
3	1	$Zn(OAc)_2$[c]	neat	65	1	60	20
4	2	$Zn(OAc)_2$[c]	neat	65	1	50	50
5	1	K_2CO_3[d]	THF	rt	12	60	20
6	2	K_2CO_3[d]	THF	rt	12	40	60
7	1	K_2CO_3[d]	neat	65	1	40	50
8	2	K_2CO_3[d]	neat	65	1	30	70
9	1	CBr_4[c]	neat	rt	10	83	
10	2	CBr_4[c]	neat	65	0.75	96	
11	1	CBr_4[c]	neat	65	0.75	98	

[a] **7** (2.5 mmol) was treated with Boc_2O under various conditions. [b] Isolated yield. [c] 10 mol % of the catalyst was used. [d] 1.5 equiv with respect to **7** was used.

SCHEME 1. Role of CBr_4 in *O-t*-Boc Formation of Phenols



showed selective formation of the Boc derivative of the phenolic OH group and clearly demonstrated its advantage.

The lack of *O-t*-Boc formation of **1** in the presence of I_2, an organocatalyst with Lewis acidic character, and generation of the undesired product **3** (entry 5, Table 1) tempted us to speculate the plausible role of CBr_4 (Scheme 1).[15] The lack of formation of any significant amount of **2** by the reaction of **1** with Boc_2O in the presence of HBr (entry 11, Table 1) ruled out the possibility of any in situ formed HBr (by the reaction of **1** with CBr_4) as the actual catalytic agent. We invoke a radical-cation-radical-anion pair (RCRAP) **I**, through n−σ^* transition[16] by interaction of the C−Br bond dipole and the dipole of $(Boc)_2O$, and a cation-neutral-anion pair (CNAP) **II** that is involved in complex formation with the phenol in the six-membered cyclic transition state **III**. The charge transfer complex formation between CBr_4 and electron-rich substrates (e.g., aromatic hydrocarbon)[17] and halide anion[18] is known and forms the basis of the proposition/involvement of the charge

(15) CBr_4 has been used as organocatalyst, but its role has not been defined except for the proposition of its mild Lewis acid property. Zhang, L.; Luo, Y.; Fan, R.; Wu, J. *Green Chem.* **2007**, *9*, 1022, and references therein.
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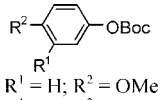
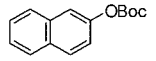
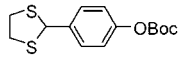
TABLE 6. Regeneration of Phenols from *O-t*-Boc Phenols Catalyzed by CBr_4-PPh_3[a]

entry	substrate	time (h)	yield (%)[b]
			
1	R^1 = H; R^2 = OMe	4	92
2	R^1 = H; R^2 = OCH_2Ph	4	95
3	R^1 = H; R^2 = Cl	6	88
4	R^1 = H; R^2 = CN	6 (1)[c]	90 (95)[c]
5	R^1 = H; R^2 = NO_2	12	92
6	R^1 = H; R^2 = CHO	18	83
7	R^1 = H; R^2 = COMe	12	80
8	R^1 = H; R^2 = CO_2Me	18	93
9	R^1 = CF_3; R^2 = H	9	90
10		12 (2)[c]	80 (92)[c]
11		18	90

[a] The *O-t*-Boc phenol (2.5 mmol) in MeOH (5 mL) was treated with CBr_4 (10 mol %) and Ph_3P (20 mol %) under reflux (bath temp ~80 °C). [b] Yield of the purified phenol. [c] Figures in parentheses are the corresponding values when the reaction was carried out in the presence of CBr_4 (2.5 mmol, 1 equiv) and Ph_3P (5 mmol, 2 equiv).

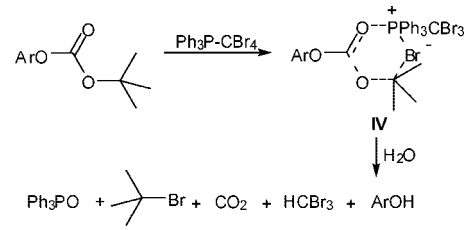
transfer complexes **I** and **II**. The more polar O−H bond in phenol compared to that of alcohol forms the hydrogen-bonded structure corresponding to **III** with the phenolic OH moiety of **7** and provides rationale for selective *O-t*-Boc formation with the phenolic OH group (entries 9−11, Table 5).

The lack of formation of **2** during the CBr_4-catalyzed reaction of **1** with Boc_2O in the presence of solvents may be rationalized due to inhibition of formation of the hydrogen-bonded structure **III**.

We next focused our attention to *O-t*-Boc deprotection. The regeneration of phenols from the corresponding *O-t*-Boc derivatives is carried out with TFA[5b] that is often associated with side reaction and excess of base.[20] We observed that a combination of CBr_4 (10 mol %)−Ph_3P (20 mol %) constitutes an excellent catalyst system[21] to regenerate the parent phenols from the corresponding *O-t*-Boc derivatives in MeOH under reflux (Table 6). The use of CBr_4 or PPh_3 alone was ineffective. The deprotection is achievable in shorter times (1−2 h) with higher amounts of the catalyst system (footnote, entries 4 and 10, Table 6). The reaction conditions were compatible with other groups such as OMe/OBn, CO_2Me, and thioactal (entries 1, 2, 8, and 11, Table 6). No side reactions such as bromination,[11] α,α-dibromoolefine formation[22] with the CHO/COMe groups (entries 6 and 7, Table 6), nitrene formation of the NO_2 group,[23] and transesterification[24] for substrate bearing CO_2Me group (entry 8, Table 6) took place.

The deprotection may be rationalized by the proposed mechanism (Scheme 2) involving coordination of the electrophilic phosphonium adduct of CBr_4 and PPh_3 with the carbonyl

SCHEME 2. Role of CBr_4-PPh_3 in *O-t*-Boc Deprotection



oxygen atom of the Boc[25] followed by the formation of a six-membered intermediate **IV**.

In summary, organocatalytic procedures have been developed for chemo- and regioselective *O-tert*-butoxycarbonylation of phenols and their regeneration from the *O-t*-Boc derivatives. No side reactions such as symmetrical diaryl carbonate, cyclic carbonate, carbonic-carbonic anhydride, or α,α-dibromoolefin formation, bromination, nitrene formation, or transesterification were observed. A mechanistic rationale for the catalytic action of CBr_4 in *O-t*-Boc formation has been formulated by invoking radical-cation-radical-anion pair (RCRAP) and cation-neutral-anion pair (CNAP) intermediates.

Experimental Section

Typical Experimental Procedures. Protection. To a mixture of 4-nitrophenol (**1**) (0.35 g, 2.5 mmol) and CBr_4 (0.083 g, 10 mol %) was added Boc_2O (0.54 g, 2.5 mmol, 1 equiv), and the reaction mixture was stirred magnetically at room temperature (~40 °C, Method A). After complete consumption of **1** (TLC, 12 h), the reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined EtOAc extracts were concentrated under vacuum rotary evaporation. The residue was passed through a bed of silica gel (10 g; no. 60−120) and eluted with 5% EtOAc in hexane (100 mL) to afford the 4-(*tert*-butoxycarbonyloxy)nitrobenzene (entry 11, Table 2) as a pale yellow solid (0.57 g, 93%). Mp: 73−74 °C. IR (KBr) *ν*: 3119, 2985, 1757, 1616, 1594, 1525, 1491, 1369, 1347, 1274, 1220, 1143, 850 cm^{-1}. ^1H ($CDCl_3$, 300 MHz, TMS) *δ*: 8.25 (d, *J* = 8.9 Hz, 2 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 1.57 (s, 9 H). ^{13}C ($CDCl_3$, 75 MHz, TMS) *δ*: 156.2, 151.0, 145.6, 125.7, 122.4, 85.3, 28.1. MS (EI) *m/z*: 239 [M^+]; identical with an authentic compound.[5e]

Deprotection. To the mixture of 4-(*tert*-butoxycarbonyloxy)-benzonitrile (0.57 g, 2.5 mmol) were added CBr_4 (0.083 g, 10 mol %) and PPh_3 (0.12 g, 20 mol %), and the reaction mixture was stirred magnetically under reflux (bath temp ~80 °C). After complete consumption of the starting material (TLC, 6 h), the reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined EtOAc extracts were concentrated under vacuum rotary evaporation. The residue was passed through a bed of silica gel (10 g; no. 60−120) and eluted with 5% EtOAc in hexane (100 mL) to afford the 4-hydroxybenzonitrile as an off-white solid (0.27 g, 90%) (entry 4, Table 6). Mp: 111−112 °C. IR (KBr) *ν*: 3180, 2925, 2850, 2223, 1590, 1505 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz, TMS) *δ*: 7.56 (d, *J* = 8.6 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 6.79 (bs, 1 H). MS (EI) *m/z*: 119 [M^{+1}].

Acknowledgment. R.C. thanks UGC, New Delhi for the award of JRF. The authors also thank OPCW, Hague, The Netherlands for financial support.

Supporting Information Available: Spectral data of all compounds and scanned spectra of a few representative known and all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8013325

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