Nucleophilic Additions of Arylzinc Compounds to Aldehydes Mediated by $CrCl_3$: Efficient and Facile Synthesis of Functionalized Benzhydrols, 1(3*H*)-Isobenzofuranones, Benzyl Alcohols, or Diaryl Ketones

Yoshihiro Ogawa, Akihiro Saiga, Mitsuo Mori, Takanori Shibata, and Kentaro Takagi*

Department of Chemistry, Faculty of Science, Okayama University, Okayama 700-8530 Japan

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In the presence of a stoichiometric amount of $CrCl_3$ and trimethylchlorosilane (TMSCl), nucleophilic addition of arylzinc compounds **1c**−**h** to arylaldehydes **2a**,**b**,**g** smoothly proceeded at room temperature to yield corresponding benzhydrols **4a**−**f** in good yields. From arylzinc compounds **1a**,**b**, 3-aryl-1(3*H*)-isobenzofuranones **3a**−**f** were given by the $CrCl_3$-mediated reaction with arylaldehydes **2a**−**f**. Diaryl ketones **5a**−**e** were obtained in good yields by the addition of excess amount of benzaldehyde as an oxidant to the resulting solution after the $CrCl_3$-mediated reaction between arylzinc compounds **1c**−**g** and arylaldehydes **2b**,**g** was completed. In the nucleophilic additions of arylzinc compounds **1a**,**d**,**f** to alkyladehydes **6b**−**f**, the treatment of arylzinc compounds with $CrCl_3$ was required prior to the addition of the aldehydes in order to prevent the fast protodezincation of arylzinc compounds by the enolizable aldehydes. In these $CrCl_3$-mediated nucleophilic additions of arylzinc compounds to aldehydes, arylchromium(III) species are probably reactive intermediates.

Introduction

The utility of organozinc compounds in organic synthesis has been recognized to a great extent. The relatively weak ionic character of the C−Zn bond allows a high degree of chemoselectivity in reactions using organozinc compounds as carbon nucleophiles.[1] Thus, for example, nucleophilic additions of alkylzinc compounds (RZnX) containing electron-withdrawing groups such as ester, ketone, or nitrile at alkyl chains to aldehydes, with or without catalysts, provide a unique and efficient synthesis of functionalized secondary alcohols, which are not easily accessible by the conventional procedures using organolithium or Grignard reagents.[2] On the other hand, corresponding reactions of arylzinc compounds (ArZnX: Ar = aryl groups containing electron-withdrawing groups) with aldehydes have been scarcely reported. It is probably because arylzinc compounds are intrinsically less reactive than the alkyl derivatives,[3] and, moreover, arylzinc compounds containing such functional groups had been more difficult to obtain than other organozinc compounds.[4] Indeed, the nucleophilic additions to aldehydes or to α,β-unsaturated ketones have been attained only with arylzinc compounds, of strongly nucleophilic behavior, like $ArZnR_2^-$ (R = Me or *t*-Bu), $ArZnCH_2SiMe_3$, or Ar_2Zn with electron-donating additives.[3] Recently, we and Knochel et al. independently developed the facile preparation of arylzinc compounds of the ArZnX type by the direct reaction of aryl iodides with zinc powder.[4] Thus, a new methodology achieving their addition to aldehydes is much needed. Hereupon, we were interested in the transmetalation reactions by which arylzinc compounds are transformed into more reactive species: it is well-known that aryl groups are easily transferable from Zn^{2+} to other metals such as Pd^{2+}, Cu^+, Ni^{2+}, or Co^{2+}, and the resulting arylmetallic species often shows different reactivities from those of starting arylzinc compounds (Scheme 1).[5] In this paper, we report the novel Cr^{3+}-mediated procedures, whereby the otherwise impossible additions of arylzinc compounds to aldehydes are accomplished.[6]

Results and Discussion

The effect of transition metal complexes was examined for the nucleophilic addition to aldehyde **2a** using arylzinc compound **1a**, which was prepared from the corresponding aryl iodide and zinc powder in 1,1,3,3-tetramethylurea (TMU) and was used as such solution.[4d] Among

(1) For example, see: (a) Carruthers, W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 7, p 662. (b) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 211. (c) Knochel, P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: Oxford, 1995; Vol. 11, p 159.

(2) For example, see: (a) Ochiai, H.; Nishihara, T.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 1343. (b) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 3887. (c) Gosmini, C.; Rollin, Y.; Gebehenne, C.; Lojou, E.; Ratovelomanana, V.; Perichon, J. *Tetrahedron Lett.* **1994**, *35*, 5637.

(3) (a) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717. (b) Kondo, Y.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 799. (c) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496. (d) Soai, K.; Kawase, Y.; Oshiro, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613. (e) Dosa, P.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (f) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222.

(4) (a) Takagi, K.; Hayama, N.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3691. (b) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413. (c) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (d) Takagi, K. *Chem. Lett.* **1993**, 469. (e) Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, 39, 3001.

(5) (a) Negishi, E.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 1998; p 1. (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577. (c) Knochel, P.; Singer, D. R. *Chem. Rev.* **1993**, *93*, 2117. (d) Knochel, P.; Almena, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

(6) Preliminary communication: Ogawa, Y.; Mori, M.; Saiga, A.; Takagi, K. *Chem. Lett.* **1996**, 1069.

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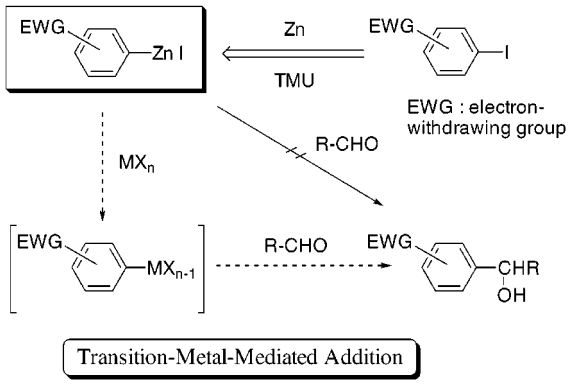
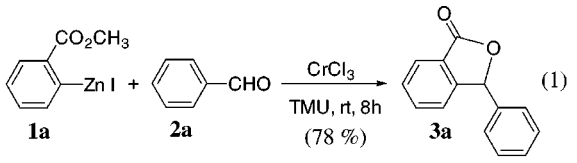
Scheme 1

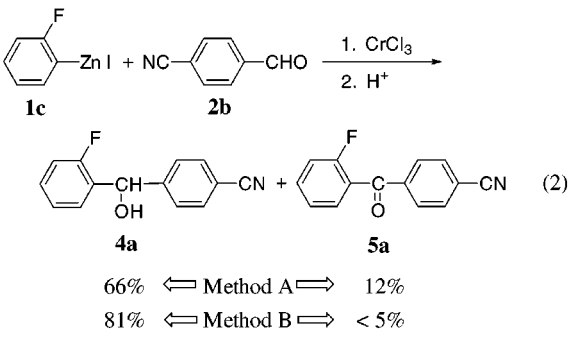


various transition metal complexes, $CrCl_3$ most efficiently promoted the reaction and 3-phenyl-1(3*H*)-isobenzofuranone (**3a**), the product of nucleophilic addition along with the subsequent lactonization, was obtained in 78% yield after stirring for 8 h as shown in eq 1. The reactions



using a stoichiometric amount of $TiCl_2Cp_2$ (yield of **3a**: 9%), $ZrCl_2Cp_2$(6%), VCl_2Cp_2 (19%), $NbCl_5$ (3%), $TaCl_5$ (7%), $MoCl_3$ (0%), or $NbCl_2Cp_2$ (0%) as a mediator were slow or did not take place. This $CrCl_3$-mediated method (method A) was successfully applied to other functionalized arylaldehydes **2b**−**f** or arylzinc compound **1b** to yield the corresponding 3-aryl-1(3*H*)-isobenzofuranones **3a**−**f** in good yields (Table 1). A catalytic amount of $CrCl_3$ was sufficient for proceeding of the reaction but took longer reaction time (run 6).

When method A was applied to *ortho*-fluorinated arylzinc compound **1c**, ketone **5a** (12%) and 4-(hydroxymethyl)benzenecarbonitrile (10%) were obtained together with the desired benzhydrol **4a** as shown in eq 2. To

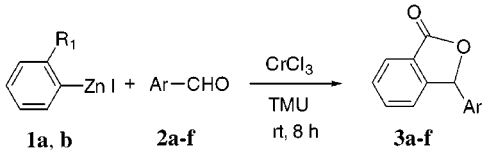


prevent the Oppenauer-type oxidation of the initially formed adducts (vide infra), the reaction was carried out in the presence of TMSCl.[7] Following this procedure (method B), benzhydrol **4a** was obtained in a better yield and the formation of **5a** was suppressed below 5% yield. This method was also readily applied to other arylzinc compounds **1d**−**h** or arylaldehydes **2a**,**b**,**g** to yield the corresponding benzhydrols **4b**−**f** in good yields (Table 2).

Next, the Cr^{3+}-mediated reaction of arylzinc compound **1a** with alkylaldehyde **6a** or **6b** was examined by method

(7) For the reaction of alkoxychromium intermediates with TMSCl, see for example: Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533.

Table 1. $CrCl_3$-Mediated Synthesis of 3-Aryl-3-hydroisobenzofuran-1-one[a]

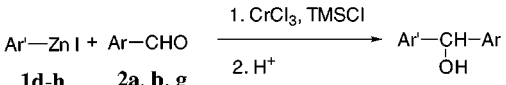


1a, b **2a-f** **3a-f**

Run	R_1	1	Ar	2	3	Yield (%)[b]
1	CH_3O_2C-	**1a**	NC-	**2b**	**3b**	68
2		**1a**	CH_3O_2C-	**2c**	**3c**	78
3		**1a**	CH_3CO_2-	**2d**	**3d**	63
4		**1a**	CH_3O-, OCH_3, OCH_3	**2e**	**3e**	83
5		**1a**	Br-thienyl-S	**2f**	**3f**	73
6[c]		**1a**		**2a**	**3a**	68
7	NC-	**1b**		**2a**	**3a**	68

[a] Method A (molar ratio: **1**/**2**/$CrCl_3$ = 1/1/1). [b] Isolated yields. [c] Reaction run with 0.25 equiv of $CrCl_3$ for 70 h.

Table 2. $CrCl_3$-Mediated Synthesis of Benzhydrols[a]

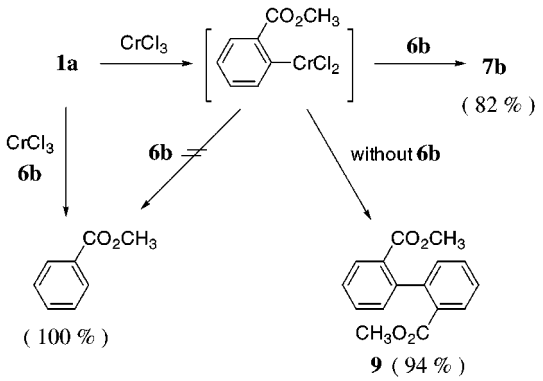


1d-h **2a, b, g** **4b-f**

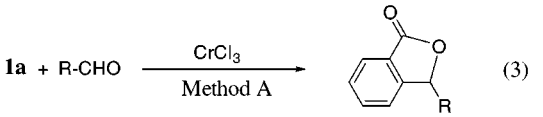
Run	Ar'	1	Ar	2	4	Yield (%)[b]
1	Br-	**1d**	O_2N-	**2g**	**4b**	68
2	Cl-	**1e**	NC-	**2b**	**4c**	87
3	CH_3O_2C-	**1f**		**2b**	**4d**	82
4	CH_3O_2C-	**1g**		**2b**	**4e**	81
5	O, C	**1h**		**2a**	**4f**	88

[a] Method B (molar ratio:**1**/**2**/$CrCl_3$/TMSCl = 1/1/1.1/3). The mixture of **1**, **2**, and $CrCl_3$ was stirred at room temperature for 8 h. [b] Isolated yields.

Scheme 2



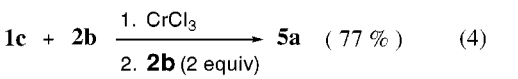
A. As a result, the reaction of **1a** with **6a** gave the desired product **7a** in a good yield, whereas one with **6b** did not give the desired adduct **7b** as shown in eq 3. In the latter



6a: R = $C(CH_3)_3$ **7a**: R = $C(CH_3)_3$ (82 %)
6b: R = $CH(CH_3)_2$ **7b**: R = $CH(CH_3)_2$ (0 %)

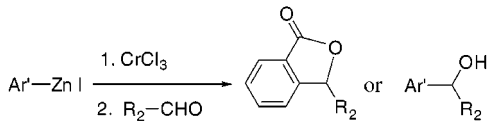
reaction, protodezincation of **1a** with **6b** proceeded quickly to afford methyl benzoate in a quantitative yield (see also Scheme 2). Accordingly, to avoid the contact of **1a** with the enolizable aldehyde, a TMU solution of **1a** was treated with $CrCl_3$ to make the arylchromium(III) species. The aldehyde **6b** was then added to the resulting solution. Following this procedure (method C), **7b** was obtained in a good yield (Table 3, run 1). Similarly, a variety of 3-alkyl-1(3*H*)-isobenzofuranones **7c**−**f** or α-substituted benzyl alcohols **8a**−**c** were obtained in moderate to good yields (Table 3, runs 2−8). In these runs, oxidation leading to ketones did not take place at all even in the absence of TMSCl; however, the presence of TMSCl exerted beneficial effects on the proceeding of the nucleophilic addition of arylzinc compounds to aldehydes (runs 8 and 9).[8]

Taking advantage of the incidental formation of diaryl ketone **5a** in eq 2, we next examined the novel Cr^{3+}-mediated one-pot synthesis of diaryl ketones from arylzinc compounds and arylaldehydes. The ketone **5a** is most probably formed through the Oppenauer-type oxidation of initially formed adduct (alkoxychromium(III) intermediate) with aldehyde **2b**, since the prolonged reaction time of the above run did not increase the yield of **5a**.[9] Then the aldehyde **2b** (2 equiv) was added as an oxidant to the resulting solution. This procedure provided diaryl ketone **5a** in 77% yield as shown in eq 4. As the

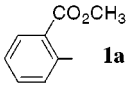
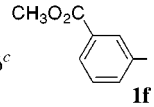
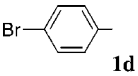


oxidant, benzaldehyde (**2a**), the most ordinary arylaldehyde, worked well, which makes this one-pot procedure attractive from the practical point of view (method D). This method was successfully applied for the synthesis of various diaryl ketones (Table 4). Curiously, if excess amount of **2b** (**1c**/**2b** = 1/3) was used at the beginning of the procedure, the yield of **5a** was decreased (run 6). As

Table 3. $CrCl_3$-Mediated Synthesis of Benzyl Alcohols or 3-Alkyl-3-hydroisobenzofuran-1-ones[a]



1a, d, f **6b-g** **7b-f** **8a-d**

Run	Ar'	1	R_2	6	7, 8	Yield (%)[b]
1		**1a**	$(CH_3)_2CH$–	**6b**	**7b**	77
2		**1a**	CH_3CH_2–	**6c**	**7c**	82
3		**1a**	*c*-C_6H_{11}–	**6d**	**7d**	73
4		**1a**	Ph–CH(–CH_3)–	**6e**	**7e**	81
5		**1a**	C_2H_5–CH(–CH_3)–	**6f**	**7f**	72
6[c]		**1f**		**6c**	**8a**	82
7[c]		**1f**		**6b**	**8b**	72
8[c]		**1d**		**6f**	**8c**	53
9		**1d**		**6f**	**8c**	42

[a] Method C (molar ratio: **1**/**6**/$CrCl_3$ = 1/2/1 for runs 1−5 or 1/1/1 for runs 6−9). The mixture of $CrCl_3$ and TMU solution of **1** was stirred at room temperature for 6 h (**1a**) or 10 °C for 8 h (**1d** or **1f**). To the resulting solution was added **6** and stirred overnight at room temperature. [b] Isolated yields. [c] With TMSCl (2 equiv).

the oxidant, benzaldehyde worked more effectively than alkylaldehydes (run 7).

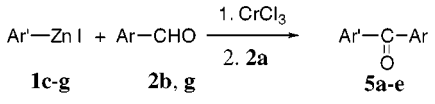
In our $CrCl_3$-mediated reaction between arylzinc compounds and aldehydes, arylchromium(III) species were probably generated in situ and acted as active intermediates. The chemical evidence summarized in Scheme 2 might support the idea for the intermediary of arylchromium(III) species: $CrCl_3$, a pink solid, gradually dissolved into a TMU solution of **1a** to give a green solution after stirring for 6 h.[10] In the solution, **1a** no longer existed, since the addition of alkylaldehyde **6b** to this solution afforded **7b** in a good yield (Table 3, run 1)

(8) For the beneficial effect of TMSCl on enhancing the reactivities of aldehydes, see for example: (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Tamaru, Y.; Nakamura, T.; Sakaguchi, M.; Ochiai, H.; Yoshida, Z. *J. Chem. Soc., Chem. Commun.* **1988**, 610. (c) Gosmini, C.; Rollin, Y.; Gebehenne, C.; Lojou, E.; Ratovelomanana, V.; Perichon, J. *Tetrahedron Lett.* **1994**, *35*, 5637.

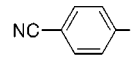
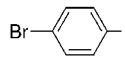
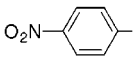
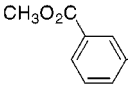
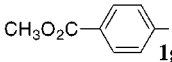
(9) This result suggests that the alkoxychromium intermediate does not undergo the spontaneous β-elimination reaction under the reaction conditions. However, see also: Ito, T.; Ono, T.; Maruyama, K.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2212.

(10) NMR spectroscopy was attempted by employing the mixture of the green solution and DMF-d_7 or CD_3CN. However, clear ^1H NMR spectra were not observed, which probably suggests the existence of paramagnetic arylchromium(III) species in the green solution. At present, we have no experimental proof to ascertain whether the arylchromium(III) species is $ArCrX_2$, $[ArCrX_3]ZnX$, or others.

Table 4. $CrCl_3$-Mediated Synthesis of Diaryl Ketones[a]



1c-g **2b, g** **5a-e**

Run	Ar'	1	Ar	2	5	Yield (%)[b]
1		**1c**		**2b**	**5a**	77
2		**1d**		**2g**	**5b**	79
3		**1e**		**2b**	**5c**	79
4		**1f**		**2b**	**5d**	82
5		**1g**		**2b**	**5e**	79
6[c]		**1c**		**2b**	**5a**	54
7[d]		**1c**		**2b**	**5a**	30

[a] Method D (molar ratio: **1**/**2**/**2a**/$CrCl_3$ = 1/1.2/3/1). The mixture of **1**, **2**, and $CrCl_3$ was stirred at room temperature for 8 h. To the resulting solution was added **2a** and stirred overnight at the same temperature. [b] Isolated yields. [c] **2b** was used in excess (**1c**/**2b** = 1/3) at the beginning of the reaction. [d] **6a** was used in place of **2a**.

instead of methyl benzoate, the expected product of the reaction between **1a** and **6b** (eq 3). There are several precedents where the nucleophilic addition of arylchromium(III) intermediates derived from not our arylzinc compounds but other compounds such as aryl halides or diaryliodonium salts to aldehydes was reported.[11,12] If the stirring was continued without the addition of **6b**, biaryl **9** was obtained in a high yield. Homo-coupling is a prevailing reaction in organo-transition metal chemistry including arylchromium(III) complexes.[13] It would be worth noting that a catalytic amount of $CrCl_3$ can sufficiently mediate the nucleophilic addition (Table 1, run 6). These results probably indicate that direct reaction of arylchromium(III) intermediates with aldehydes proceed to yield the addition products.

In conclusion, we developed the new utility of arylzinc compounds as a reactive nucleophilic reagents to aldehydes by making use of a novel transmetalation into Cr^{3+} compounds. The present reaction possesses the availability of starting materials and proceeds in good to high yield by simple experimental procedures. Therefore it provides an efficient synthetic methods of highly functionalized benzhydrols, 1(3*H*)-isobenzofuranones, benzyl alcohols, or diaryl ketones.

Experimental Section

General. Zn powder and $CrCl_3$ were purchased from Kanto Chemical and Mitsuwa Chemical and used without further purification. TMU was distilled under nitrogen and stored over Molecular Sieves 3A. Ultrasonic cleaner, Branson 1200, or ultrasonic liquid processor, Astrason XL2020, was used for the application of ultrasound.

Synthesis of Arylzinc Compounds. Arylzinc compounds were prepared by the reaction of aryl iodides with zinc powder in TMU under the irradiation of ultrasound, following the reported procedure.[4d] The aliquots of the resulting solutions were used in the reaction with aldehydes, after the concentration of arylzinc compounds was determined by quenching the aliquot of the solutions with iodine, followed by the GLC analysis of the amount of aryl iodides reformed.

Procedure. Four procedures were employed in the reaction of arylzinc compounds with aldehydes. A typical example of each is described below.

Method A. $CrCl_3$ (130 mg, 1.0 mmol) was dried by air-gun heating for 5 min under vacuum (1 mmHg). To the solid, 0.8 M TMU solution of **1a** (1.25 mL, 1.0 mmol) and **2a** (0.10 mL, 1.0 mmol) were successively added at room temperature under nitrogen and stirred for 8 h at the temperature. The resulting mixture was quenched by addition of aqueous HCl. Workup by extraction with ether, washing with water, drying with $MgSO_4$, and evaporation of the solvent afforded a crude product, which was chromatographed on silica gel with hexane/ethyl acetate as eluent to afford 164 mg of 3-phenyl-1(3*H*)-isobenzofuranone, **3a** (78%): mp 118−118.5 °C (lit.[14] 117 °C).

4-(3-Oxohydroisobenzofuranyl)benzenecarbonitrile (3b): mp 153−154 °C; IR ($CDCl_3$) 1773, 2230 cm^{-1}; ^1H NMR δ 6.5 (s, 1H), 7.3−7.5 (m, 1H), 7.4 (d, J = 9 Hz, 2H), 7.6−7.7 (m, 2H), 7.7 (d, J = 9 Hz, 2H), 7.9−8.0 (m, 1H); ^{13}C NMR δ 81.2, 113.3, 118.1, 122.6, 125.3, 126.1, 127.4, 129.9, 132.8, 134.7, 141.7, 148.5, 169.8. Anal. Calcd for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.83; H, 3.88; N, 6.06.

Methyl 4-(3-oxohydroisobenzofuranyl)benzoate (3c): mp 133−134 °C; IR ($CDCl_3$) 1721, 1765 cm^{-1}; ^1H NMR δ 3.9 (s, 3H), 6.4 (s, 1H), 7.3−7.4 (m, 1H), 7.4 (d, J = 9 Hz, 2H), 7.5−7.7 (m, 2H), 7.9−8.1 (m, 1H), 8.0 (d, J = 9 Hz, 2H); ^{13}C NMR δ 52.2, 81.8, 122.7, 125.4, 125.9, 126.7, 129.6, 130.3, 131.1, 134.5, 141.4, 149.1, 166.4, 170.3. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.50; H, 4.47.

4-(3-Oxohydroisobenzofuranyl)phenyl acetate (3d): mp 124−125 °C; IR ($CDCl_3$) 1767 cm^{-1}; ^1H NMR δ 2.3 (s, 3H), 6.4 (s, 1H), 7.1 (d, J = 9 Hz, 2H), 7.3 (d, J = 9 Hz, 2H), 7.1−7.3 (m, 1H), 7.5−7.7 (m, 2H), 7.9−8.0 (m, 1H); ^{13}C NMR δ 21.0, 82.1, 122.2, 123.0, 125.6, 128.2, 129.5, 133.9, 134.4, 149.4, 151.4, 169.1, 170.3. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.34; H, 4.73.

3-(2,4,6-Trimethoxyphenyl)-1(3*H*)-isobenzofuranone (3e): mp 204−205 °C (lit.[15] mp 200 °C); IR ($CDCl_3$) 1756 cm^{-1}; ^1H NMR δ 3.6 (s, 6H), 3.8 (s, 3H), 6.1 (s, 2H), 7.0 (s, 1H), 7.1−7.3 (m, 1H), 7.4−7.6 (m, 2H), 7,8−7.9 (m, 1H); ^{13}C NMR δ 55.3, 55.8, 65.2, 91.2, 104.5, 121.5, 124.7, 127.2, 128.0, 133.2, 151.2, 160.3, 162.4, 169.7.

3-(4-Bromo-2-thienyl)-1(3*H*)-isobenzofuranone (3f): mp 120−121 °C; IR ($CDCl_3$) 1770 cm^{-1}; ^1H NMR δ 6.6 (s, 1H), 6.8

(11) Nucleophilic addition of arylchromium(III) intermediates to aldehydes is reported in Mn-mediated and $CrCl_2$- and Ni^{2+}-catalyzed reaction of aryl iodides with aldehydes,[11b,c] $CrCl_2$- and Pd^{2+}-catalyzed electrochemical reaction of aryl halides with arylaldehydes,[11d] $CrCl_2$-mediated reaction of aryl halides with aldehydes,[11e] or $CrCl_2$-mediated and Ni^{2+}-catalyzed reaction of diaryliodonium salts with aldehydes.[11f] As the synthetic methods of benzhydrols or benzyl alcohols, these reactions suffered disadvantages of the use of air-sensitive $CrCl_2$[11b−f] in excess (4−6 equiv),[11e,f] or available aldehydes owing to the facile pinacol coupling leading to diols as major products.[11b,c] (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (d) Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1997**, *38*, 6307. (e) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (f) Chen, D.; Takai, K.; Ochiai, M. *Tetrahedron Lett.* **1997**, *38*, 8211.

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(d, J = 4 Hz, 1H), 6.9 (d, J = 4 Hz, 1H), 7.4−7.9 (m, 4H); ^{13}C NMR δ 76.6, 113.8, 122.1, 124.9, 127.4, 129.0, 129.1, 133.5, 139.6, 147.0, 168.3. Anal. Calcd for $C_{12}H_7BrO_2S$: C, 48.83; H, 2.39. Found: C, 48.53; H, 2.72.

Method B. $CrCl_3$ (143 mg, 1.1 mmol) was dried by air-gun heating for 5 min under vacuum (1 mmHg). To the solid were successively added **2b** (131 mg, 1.0 mmol), a 0.75 M TMU solution of **1c** (1.33 mL, 1.0 mmol), and TMSCl (0.38 mL, 3.0 mmol) at room temperature under nitrogen and stirred for 8 h at the temperature. The resulting mixture was quenched by addition of aqueous HCl. Workup by extraction with ether, washing with water, drying with $MgSO_4$, and evaporation of the solvent afforded a crude product, which was chromatographed on silica gel with hexane/ethyl acetate (19/1) as eluent to afford 184 mg of 4-[(2-fluorophenyl)hydroxymethyl]benzenecarbonitrile, **4a** (81%): oil; IR ($CDCl_3$) 2228, 3606 cm^{-1}; ^{1}H NMR δ 3.1 (s, 1H), 6.1 (s, 1H), 6.9−7.5 (m, 8H); ^{13}C NMR δ 69.1 (d, J = 3 Hz), 111.1, 115.6 (d, J = 21 Hz), 118.7, 124.6 (d, J = 3 Hz), 127.0 (d, J = 2 Hz), 127.7 (d, J = 4 Hz), 129.7 (d, J = 8 Hz), 130.1 (d, J = 13 Hz), 132.2, 148.2, 159.7 (d, J = 247 Hz). Anal. Calcd for $C_{14}H_{10}FNO$: C, 74.00; H, 4.44; N, 6.16. Found: C, 74.12; H, 4.54; N, 6.31.

(4-Bromophenyl)(4-nitrophenyl)methan-1-ol (4b): mp 158−159 °C; IR (Nujol) 1341, 1505, 3492 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.9 (d, J = 4 Hz, 1H), 6.3 (d, J = 4 Hz, 1H), 7.4 (d, J = 9 Hz, 2H), 7.5 (d, J = 9 Hz, 2H), 7.7 (d, J = 9 Hz, 2H), 8.2 (d, J = 9 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 72.9, 120.4, 123.6, 127.4, 128.7, 131.3, 144.0, 146.6, 152.8. Anal. Calcd for $C_{13}H_{10}BrO_3$: C, 50.67; H, 3.27; N, 4.55. Found: C, 50.72; H, 3.20; N, 4.74.

4-[(3-Chlorophenyl)hydroxymethyl]benzenecarbonitrile (4c): mp 74−75 °C; IR ($CDCl_3$) 2240, 3460 cm^{-1}; ^{1}H NMR δ 2.9 (s, 1H), 5.8 (s, 1H), 7.2−7.7 (m, 8H); ^{13}C NMR δ 75.0, 111.5, 118.7, 124.8, 126.8, 127.1, 128.4, 130.1, 132.4, 134.8, 144.8, 148.3. Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.85; H, 4.13; N, 5.77.

Methyl 3-[(4-cyanophenyl)hydroxymethyl]benzoate (4d): mp 105−106 °C; IR ($CDCl_3$) 1720, 2228, 3602 cm^{-1}; ^{1}H NMR δ 3.3 (d, J = 3 Hz, 1H), 3.9 (s, 3H), 5.9 (d, J = 3 Hz, 1H), 7.3−8.0 (m, 8H); ^{13}C NMR δ 52.3, 75.1, 111.3, 118.7, 127.1, 127.7, 128.9, 129.2, 130.6, 131.1, 132.3, 143.4, 148.6, 166.8. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90 H; 4.90; N, 5.24. Found: C, 71.53; H, 4.90; N, 5.20.

Methyl 4-[(4-cyanophenyl)hydroxymethyl]benzoate (4e): mp 152−153 °C; IR (Nujol) 1718, 2225, 3532 cm^{-1}; ^{1}H NMR δ 3.1 (d, J = 3 Hz, 1H), 3.9 (s, 3H), 5.9 (d, J = 3 Hz, 1H), 7.4 (d, J = 9 Hz, 2H), 7.5 (d, J = 6 Hz, 2H), 7.6 (d, J = 6 Hz, 2H), 8.0 (d, J = 9 Hz, 2H); ^{13}C NMR δ 52.2, 75.2, 111.5, 118.7, 126.5, 127.2, 129.8, 130.1, 132.4, 147.7, 148.4, 166.8. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.85; H, 4.88; N, 5.31.

4-(Hydroxyphenyl)methylphenyl phenyl ketone (4f): oil; IR ($CDCl_3$) 1659, 3610 cm^{-1}; ^{1}H NMR δ 2.8 (s, 1H), 5.8 (s, 1H), 7.2−7.8 (m, 14H); ^{13}C NMR δ 75.8, 126.2, 126.6, 127.8, 128.2, 128.6, 129.9, 130.2, 132.3, 136.5, 137.6, 143.3, 148.4, 196.4; HRFAB-MS calcd for $C_{20}H_{17}O_2$ 289.1229, found (M + H)$^+$ 289.1236.

Method C. $CrCl_3$ (130 mg, 1.0 mmol) was dried by air-gun heating for 5 min under vacuum (1 mmHg). To the solid was added a 0.8 M TMU solution of **1a** (1.25 mL, 1.0 mmol) at room temperature under nitrogen and stirred for 6 h at the temperature. To the resulting solution was added **6b** (0.182 mL, 2.0 mmol) and stirred overnight at the same temperature. The resulting mixture was quenched by addition of aqueous HCl. Workup by extraction with ether, washing with water, drying with $MgSO_4$, and evaporation of the solvent afforded a crude product, which was chromatographed on silica gel with hexane/ethyl acetate (19/1) as eluent to afford 271 mg of 3-(methylethyl)-1(3*H*)-isobenzofuranone, **7b** (77%): oil (lit.[16] mp 36 °C); IR ($CDCl_3$) 1760 cm^{-1}; ^{1}H NMR δ 0.81 (d, J = 7 Hz, 3H), 1.2 (d, J = 7 Hz, 3H), 2.1−2.5 (m, 1H), 5.4 (d, J = 4 Hz, 1H), 7.4−7.9 (m, 4H); ^{13}C NMR δ 15.8, 18.7, 32.5, 85.7, 122.2, 125.8, 126.9, 129.1, 133.9, 149.0, 176.1.

3-(*tert*-Butyl)-1(3*H*)-isobenzofuranone (7a): oil;[17] IR ($CDCl_3$) 1766 cm^{-1}; ^{1}H NMR δ 1.0 (s, 9H), 5.6 (s, 1H), 7.6−7.9 (m, 4H); ^{13}C NMR δ 25.5, 35.7, 88.6, 123.4, 125.6, 127.2, 129.0, 133.4, 148.0, 170.5.

3-Ethyl-1(3*H*)-isobenzofuranone (7c): oil;[16] IR ($CDCl_3$) 1760 cm^{-1}; ^{1}H NMR δ 1.0 (t, J = 8 Hz, 3H), 1.7−2.2 (m, 2H), 5.4 (dd, J = 7 and 5 Hz, 1H), 7.4−7.9 (m, 4H); ^{13}C NMR δ 8.9, 27.8, 82.3, 121.8, 125.8, 126.4, 129.1, 134.0, 149.8, 170.6.

3-Cyclohexyl-1(3*H*)-isobenzofuranone (7d): mp 98−99 °C (lit.[18] mp 98−99 °C); IR ($CDCl_3$) 1760 cm^{-1}; ^{1}H NMR δ 1.1−1.9 (m, 11H), 5.3 (d, J = 4 Hz, 1H), 7.4−7.9 (m, 4H); ^{13}C NMR δ 25.9, 26.1, 26.2, 29.2, 42.2, 85.3, 122.2, 125.6, 126.8, 129.0, 133.8, 148.8, 170.7.

3-(Phenylethyl)-1(3*H*)-isobenzofuranone (7e) (∼1/1 diastereomers): mp 79−80 °C; IR ($CDCl_3$) 1760 cm^{-1}; ^{1}H NMR δ 1.4 (d, J = 7 Hz, 3H), 3.1 (quint, J = 7 Hz, 1H), 5.6 (d, J = 7 Hz, 1H), 6.6−6.7 (m, 1H), 7.3−7.5 (m, 7H), 7.8−7.9 (m, 1H); ^{13}C NMR δ 17.4, 45.2, 84.9, 122.8, 125.6, 126.5, 127.4, 128.2, 128.8, 129.2, 133.6, 141.8, 148.7, 170.5. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.42; H, 5.89. mp 106.5−107 °C; IR ($CDCl_3$) 1762 cm^{-1}; ^{1}H NMR δ 1.4 (d, J = 7 Hz, 3H), 3.4−3.7 (m, 1H), 5.7 (d, J = 4 Hz, 1H), 7.0−7.8 (m, 9H); ^{13}C NMR δ 15.5, 43.0, 84.8, 122.7, 125.5, 127.0, 127.2, 128.4, 128.4, 129.1, 133.4, 139.1, 147.9, 170.4. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.60; H, 5.99.

3-(Methylpropyl)-1(3*H*)-isobenzofuranone (∼4/5: diastereomeric mixture) **(7f):** oil; IR ($CDCl_3$) 1760 cm^{-1}; ^{1}H NMR δ 0.6−2.0 (m, 9H), 5.4−5.5 (m, 1H), 7.4−7.9 (m, 4H); ^{13}C NMR δ 11.7, 11.8, 12.3, 14.9, 23.5, 26.3, 38.9, 84.1, 85.2, 121.9, 122.4, 125.6, 125.6, 126.7, 127.0, 129.0, 129.0, 133.8, 133.9, 148.7, 149.3, 170.7, 170.9; HRFAB-MS calcd for $C_{12}H_{15}O_2$ 191.1072, found (M + H)$^+$ 191.1058.

Method C with TMSCl. $CrCl_3$ (130 mg, 1.0 mmol) was dried by air-gun heating for 5 min under vacuum (1 mmHg). To the solid was added 0.60 M TMU solution of **1f** (1.67 mL, 1.0 mmol) at 10 °C under nitrogen and stirred for 8 h at the temperature. To the resulting solution were successively added **6c** (0.072 mL, 1.0 mmol) and TMSCl (0.25 mL, 2.0 mmol) at room temperature and stirred overnight at the temperature. The resulting mixture was quenched by addition of aqueous HCl. Workup by extraction with ether, washing with water, drying with $MgSO_4$, and evaporation of the solvent afforded a crude product, which was chromatographed on silica gel with hexane/ethyl acetate (19/1) as eluent to afford 160 mg of methyl 3-(1-hydroxypropyl)benzoate, **8a** (82%): oil; IR ($CDCl_3$) 1718, 3614 cm^{-1}; ^{1}H NMR δ 0.9 (t, J = 7 Hz, 3H), 1.7 (quint, J = 7 Hz, 2H), 3.0 (s, 1H), 3.9 (s, 3H), 4.6 (t, J = 7 Hz, 1H), 7.3−8.0 (m, 4H); ^{13}C NMR δ 9.9, 31.9, 52.0, 75.3, 127.1, 128.3, 128.5, 130.1, 130.5, 145.2, 167.1; HRFAB-MS calcd for $C_{11}H_{15}O_3$ 195.1021, found (M + H)$^+$ 195.1036.

Methyl 3-(1-hydroxy-2-methylpropyl)benzoate (8b): oil; IR ($CDCl_3$) 1720, 3610 cm^{-1}; ^{1}H NMR δ 0.8 (d, J = 7 Hz, 3H), 1.0 (d, J = 7 Hz, 3H), 1.6−2.2 (m, 2H), 3.9 (s, 3H), 4.5 (d, J = 7 Hz, 1H), 7.3−7.6 (m, 2H), 7.9−8.0 (m, 2H); ^{13}C NMR δ 18.0, 19.1, 35.4, 52.2, 79.5, 127.8, 128.3, 128.7, 130.2, 131.1, 144,2, 167.2; HRFAB-MS calcd for $C_{12}H_{17}O_3$ 209.1178, found (M + H)$^+$ 209.1137.

1-(4-Bromophenyl)-2-methyl-1-butanol (∼3/5: diastereomeric mixture) **(8c):** oil; IR ($CDCl_3$) 3614 cm^{-1}; ^{1}H NMR δ 0.7−1.8 (m, 9H), 2.0 (s, 1H), 4.4 (t, J = 7 Hz, 1H), 7.2 (d, J = 8 Hz, 2H), 7.4 (d, J = 8 Hz, 2H); ^{13}C NMR δ 11.4, 11.7, 13.8, 15.1, 24.8, 25.9, 41.8, 42.1, 77.3, 78.2, 121.0, 121.2, 128.2, 128.5, 131.3, 141.6, 143.0. Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.34; H, 6.22. Found: C, 54.33; H, 6.16.

Method D. $CrCl_3$ (130 mg, 1.0 mmol) was dried by air-gun heating for 5 min under vacuum (1 mmHg). To the solid were successively added **2b** (157 mg, 1.2 mmol) and a 0.75 M TMU solution of **1c** (1.33 mL, 1.0 mmol) at room temperature under nitrogen and stirred for 8 h at the temperature. After **2a** (0.31

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mL, 3 mmol) was added to the reaction mixture, the whole mixture was stirred overnight at room temperature. The resulting mixture was quenched by addition of aqueous HCl. Workup by extraction with ether, washing with water, drying with $MgSO_4$, and evaporation of the solvent afforded a crude product, which was chromatographed on silica gel with hexane/ethyl acetate (19/1) as eluent to afford 173 mg of 4-[(2-fluorophenyl)carbonyl]benzenecarbonitrile, **5a** (77%). mp 74−75 °C; IR (Nujol) 1660, 2229 cm^{-1}; ^1H NMR δ 7.1−8.0 (m, 8H); ^{13}C NMR δ 116.1, 116.3 (d, J = 21 Hz), 117.7, 124.5 (d, J = 4 Hz), 125.5 (d, J = 14 Hz), 129.7 (d, J = 2 Hz), 130.8 (d, J = 2 Hz), 132.1, 134.0 (d, J = 9 Hz), 140.6, 160.0 (J = 254 Hz), 191.6. Anal. Calcd for $C_{14}H_8FNO$: C, 74.66; H, 3.58; N, 6.22. Found: C, 74.62; H, 3.76; N, 6.38.

4-Bromophenyl 4-nitrophenyl ketone (5b): mp 109−110 °C; IR ($CDCl_3$) 1353, 1530, 1668 cm^{-1}; ^1H NMR δ 7.7 (s, 4H), 7.9 (d, J = 9 Hz, 2H), 8.4 (d, J = 9 Hz, 2H); ^{13}C NMR δ 123.7, 128.9, 130.7, 131.6, 132.1, 135.1, 142.5, 154.6, 193.5. Anal. Calcd for $C_{13}H_8BrNO_3$: C, 51.01; H, 2.63; N, 4.58. Found: C, 51.10; H, 2.78; N, 4.49.

4-[(3-Chlorophenyl)carbonyl]benzenecarbonitrile (5c): mp 111−112 °C; IR (Nujol) 1660, 2226 cm^{-1}; ^1H NMR δ 7.4−7.8 (m, 8H); ^{13}C NMR δ 116.2, 117.9, 128.1, 129.9, 130.0, 130.2, 132.4, 133.3, 135.1, 138.1, 140.6, 193.6. Anal. Calcd for $C_{14}H_8ClNO$: C, 69.58; H, 3.34; N, 5.80. Found: C, 69.43; H, 3.51; N, 5.90.

Methyl 3-[(4-cyanophenyl)carbonyl]benzoate (5d): mp 121−122 °C; IR ($CDCl_3$) 1668, 1725, 2228 cm^{-1}; ^1H NMR δ 4.0 (s, 3H), 7.5−8.4 (m, 8H); ^{13}C NMR δ 52.6, 116.2, 117.9, 129.1, 130.3, 130.9, 131.0, 132.4, 134.0, 134.1, 136.8, 140.7, 166.0, 194.1. Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.36; H, 4.19; N, 5.19.

Methyl 4-[(4-cyanophenyl)carbonyl]benzoate (5e): mp 138−139 °C; IR (Nujol) 1648, 1720, 2238 cm^{-1}; ^1H NMR δ 4.0 (s, 3H), 7.8−8.0 (m, 6H), 8.2 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 52.6, 116.3, 117.9, 129.8, 130.3, 132.4, 134.2, 140.0, 140.6, 166.1, 194.4. Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.51; H, 4.31; N, 5.07.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **4f**, **7f**, **8a**, and **8b**. This material is availabe free of charge via the Internet at http://pubs.acs.org.

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