Ortho-Coordinated Acylation on Phenol Systems

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The ortho-coordinated acylation of phenol salts reported in recent synthetic applications has been extensively investigated. The data obtained support the hypothesis that formation of an organized complex between the phenol salts and the acylating agents may strongly influence the reaction pathway, depending on the nature of the specific cation, phenol, and acyl chloride involved in the process. The structural factors which control the formation of the reacting complex **3** have been extensively investigated; the results obtained allow us to discuss the possibilities and limitations of this methodology in selective *o*-acylphenol synthesis. The present methodology is the procedure of choice for ortho-functionalization of phenols with electrophilic reagents such as phosgene, oxaloyl chlorides, polyunsaturated acid chlorides, phthalic dichlorides, and, in general, acid chlorides α-functionalized with an electron-withdrawing group.

Introduction

Regiochemical control over the electrophilic reaction of ambident systems such as phenols, enols, and enamines is a basic goal in both synthetic and theoretical organic chemistry. In our preceding studies in this area we exploited the "template-effect" of highly coordinating metal phenolates and obtained ortho-regioselective electrophilic substitutions with a large number of reagents.[1] For these reactions we indicated the complex **3** (Scheme I) as the intermediate responsible for the ortho-regioselective control.

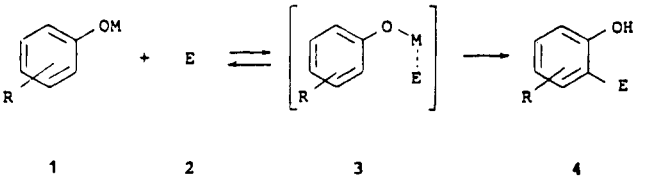
In the complex **3**, the cation assembles the reacting species into an ordered structure via coordinating interactions with the phenolic substrate, the electrophilic reagent, and the ligands. ^{1}H and ^{13}C NMR studies provided information which supports the formation of a complex like **3** in the reaction of magnesium phenolates with aliphatic and aromatic aldehydes.[2] In connection with these studies, we now present our results on regiochemical control in the reactions of metal phenolates with acyl chlorides.

The acylation of phenols **5** with acyl chlorides **6** results in the formation of both ortho and para ketones **7** and **8** (Scheme II). Generally, a prevalence of para attack has been observed, particularly in the case of the unsubstituted phenol.[3] However, we recently achieved ortho-selective acylation of phenol salts with specific acylating agents.[4] We have now examined the factors which control the reactivity of metal phenolates toward acyl chlorides in these processes.

Results and Discussion

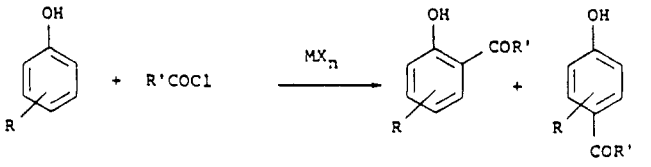
In the first stage, we analyzed the cation effect in order to gain information on the roles played by the Lewis acidity and the coordination power of the metal phenolates on the reactivity and the regiochemical control of the process (Table I). The 2-*tert*-butylphenolates **9** were chosen as model substrates in order to avoid heterogeneity, claimed by Kornblum and Curtin as the factor responsible for the ortho-carbon attack on the metal phenolates.[5] Reactions were carried out in dry toluene in light of our previous

Scheme I



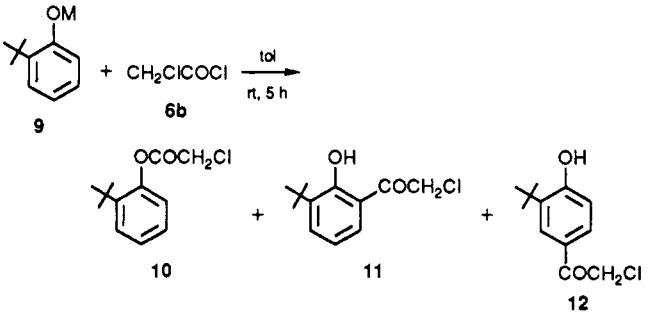
1 2 3 4

Scheme II



5 6 7 8

Table I. Cation Effect in the Reaction of Metal 2-*tert*-Butylphenolates with Monochloroacetyl Chloride



9 6b 10 11 12

entry	metal ion M	recovered phenol, %	10, %	11, %	12, %
a	Li[a]	38	100	–	–
b	Na[a]	15	100	–	–
c	K[a]	50	100	–	–
d	MgBr	20	71	29	–
e	$AlCl_2$	5	15	25	50[b]
f	BCl_2	97	–	–	–
g	$TiCl_3$	35	25	18	52
h	Al^{III}	28	2	98	–
i	B^{III}	98	–	–	–
l	Ti^{IV}	85	30	70	–

[a] Heterogeneous. [b] About 10% of de-*tert*-butylated derivatives was also recovered.

(1) Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677.
(2) Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1980**, *110*, 353.
(3) Gore, P. H. Aromatic Ketone Synthesis. In Olah G. A.; *Friedel-Crafts and Related Reactions*; Interscience Publishers: New York, 1964; Vol. III, Part 1, pp 1–381.
(4) (a) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2655. (b) Bigi, F.; Casiraghi, G.; Casnati, G.; Marchesi, S.; Sartori, G. *Tetrahedron* **1984**, *40*, 4081. (c) Sartori, G.; Casnati, G.; Bigi, F.; Robles, P. *Tetrahedron Lett.* **1987**, *28*, 1533. (d) Sartori, G.; Casnati, G.; Bigi, F.; Bonini, G. *Synthesis* **1988**, 763.

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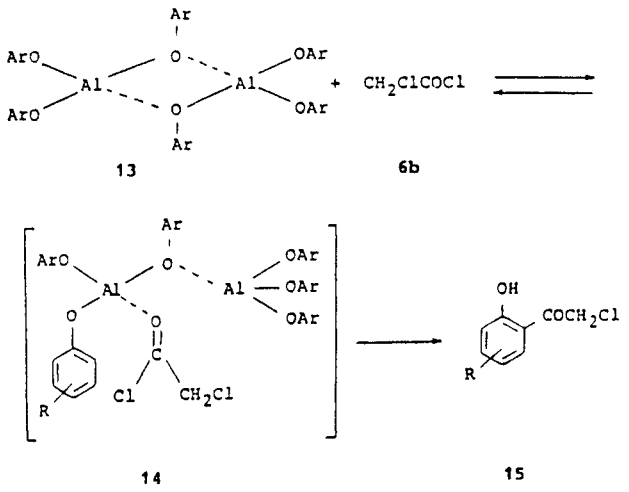
Scheme III



considerations on the conditions required for the formation of the donor–acceptor complex **3**.[2] Monochloroacetyl chloride **6b** was employed as a moderately activated electrophilic reagent (see below, Table III).

Analyzing the results from Table I we can discern the following general trends: (a) Poorly coordinating alkali metal ions (Li, Na, K) give attack at the oxygen atom, exclusively. (b) Highly coordinating metal ions (MgBr, Al(III)) give good to excellent ortho-regioselective control. (c) Hard Lewis acid promoters ($AlCl_2$, $TiCl_3$) give unselective reactions. (d) Boron phenolates give no reaction.

The high coordinating ability of the cations[6] can aid in promoting the formation of an organized reacting complex involving the phenolic substrate and the acyl chloride.

The aluminum triphenolate exists in nonpolar solvents as a mixture of dimeric and trimeric aggregates in which the aluminum coordinates four oxygen atoms.[6,7]

The electronic demand of the metal ion is balanced by the coordination of the bridged phenolate. The donor reagent $CH_2ClCOCl$ can interact with the aluminum, breaking the oxygen bridge and giving rise to the donor–acceptor complex **14** (Scheme III). Subsequent electrophilic attack at the aromatic ring is directed to the proximate ortho position (Table I, entry h).

The same hypothesis can be advanced to account for the reactivity of the bromomagnesium phenolates. In this case, the basic center at the phenol oxygen competes with the ortho carbon in the reaction with acyl chloride **6b** (Table I, entry d).

In the case of aluminum triphenolate (Table I, entry h) the reaction centers become increasingly crowded as the reaction proceeds. It is interesting to note that these structural modifications have no effect on the selectivity of the process, as **9h** is converted to **11** in about 72% yield.

Concerning the dichloroaluminum[7] and trichlorotitanium phenolates,[8] it is quite clear that the tendency of the metal ion to add a donor molecule is increased by the presence of electron-attracting groups on the metal. Consequently these systems give rise to a typical hard Lewis acid behavior and promote intracomplex template processes as well as extracomplex nontemplate and unselective reactions (Table I, entries e and g).

As far as the boron phenolates[9] are concerned, their very poor reactivity could stem from the marked p_π–p_π back bonding of the B–O bond, which reduces the electronic availability at both the phenolic oxygen and the aromatic ring[10] (Table I, entry i). Dichloroboron phenolates can give rise to the disproportionation[9] shown in Scheme IV.

Scheme IV

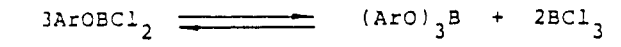
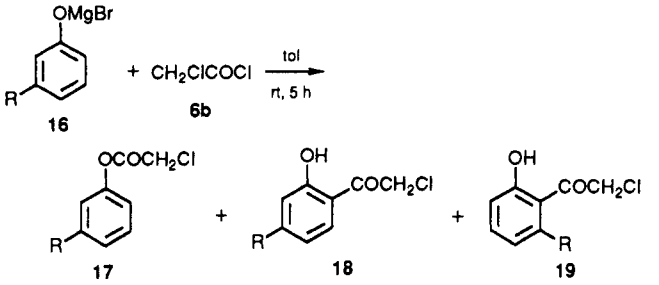
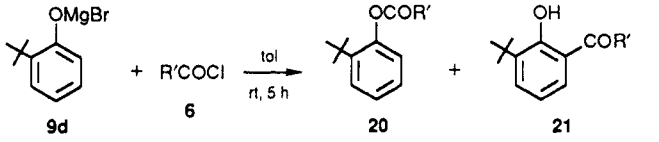


Table II. Electronic Effects in the Reaction of 3-Substituted Bromomagnesium Phenolates with Monochloroacetyl Chloride



entry	R	recovered phenol, %	17, %	18, %	19, %
a	H	20	73	17	–
b	OMe	16	6	84	10
c	$N(Me)_2$	18	8	92	–
d	Cl	22	99	–	–

Table III. R′ Electronegative Effects in the Reaction of Various Acyl Chlorides R′COCl 6 with Bromomagnesium 2-*tert*-Butylphenolate 9d



entry	R′	recovered phenol, %[a]	[21/20]	log [21/20]	$R'\sigma_I$[a]
a	CH_3	15	0.03	−1.52	−0.04
b	CH_2Cl	26	0.25	−0.60	0.15
c	$CHCl_2$	24	3.16	0.50	0.31
d	CCl_3	27	8.51	0.93	0.41
e	CF_3	26[b]	–	–	0.45
f	CH_2CH_2Ph	20	0.05	−1.30	0.01
g	CH=CHPh	27	0.70	−1.10	0.07
h	C≡CPh	24	0.63	−0.20	0.22

[a] Reference 12. [b] The compound **21e** was the sole reaction product.

For this reason, we also examined the reactions of **6b** with both 2-$Bu^tC_6H_4OH$·BCl_3 and (2-$Bu^tC_6H_4O)_3B$·$2BCl_3$ adducts. In both cases, the phenol was quantitatively recovered after standard workup (Table I, entry f).[11]

When poorly coordinating metal phenolates are used, the formation of the donor–acceptor complex is not favored and the acyl chloride reacts at the oxygen, as expected for a charge-controlled process (Table I, entries a, b, and c).

In order to study the electronic effect of the R substituent on the phenol ring, a series of experiments were conducted in which **6b** was allowed to react with variously 3-substituted bromomagnesium phenolates **16**. The ex-

(5) Kornblum, N.; Lurie, A. P. *J. Am. Chem. Soc.* **1959**, *81*, 2705.
(6) Malhotra, K. C.; Martin, R. L. *J. Organomet. Chem.* **1982**, *239*, 159.
(7) Starowieyski, B.; Pasynkiewiez, S.; Skowronska, M. D. *J. Organomet. Chem.* **1971**, *31*, 149.
(8) Crowe, R. W.; Caughlan, C. N. *J. Chem. Soc.* **1950**, 1694.
(9) Colclough, T.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1955**, 907.
(10) Fenwick, J. T.; Wilson, J. W. *J. Chem. Soc., Dalton Trans.* **1972**, 1324.
(11) Some ortho-acylation of activated boron phenolates have occasionally been reported in the synthetic literature: (a) Toyoda, T.; Sasakura, K.; Sugasawa, T. *J. Org. Chem.* **1981**, *46*, 189. (b) Piccolo, O.; Filippini, L.; Tinucci, L.; Valoti, E.; Citterio, A. *Tetrahedron* **1986**, *42*, 885.

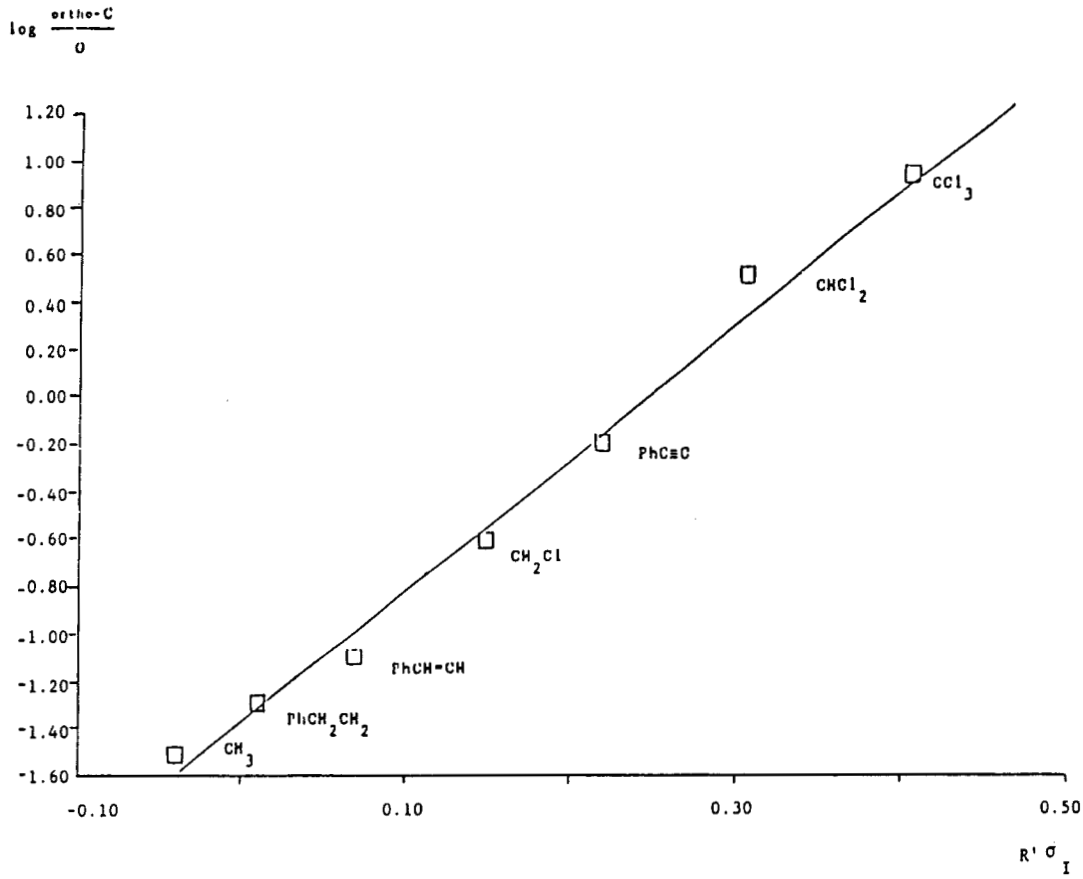


Figure 1.

perimental results are reported in Table II.

The R group in **16** has virtually no influence on the reactivity of the bromomagnesium phenolates (O plus ortho-C attack). On the other hand, the experimental results in Table II are in good agreement with a typical metal-coordinated ortho-regioselective electrophilic substitution process.

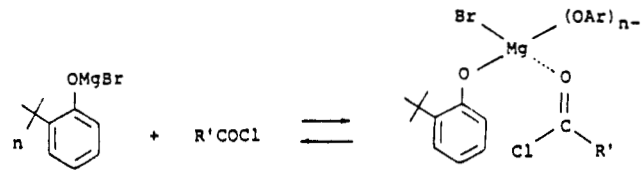
Next, a series of standard reactions were carried out in order to account for the role played by the electron-withdrawing ability of R′ in R′COCl in promoting the phenol ortho-regioselective acylation (Table III). To this end, the acylation of bromomagnesium 2-*tert*-butylphenolate **9d** was investigated. This particular cation was chosen for its balanced ortho-C/O reactivity ratio, observed in a preceding experiment (Table I, entry d).

An increase in the electronegativity of R′ results in a gradual increase in the ortho-C/O reactivity ratio. Again, it is interesting that this effect is observed in spite of the obvious increase in size and in the steric requirements of the reagents involved (see, for example, the series R = CH_3, CH_2Cl, $CHCl_2$, CCl_3; Table III, entries a–d). There is a reasonable correlation between the logarithm of the ortho-C/O reactivity ratio and the polar substituent constant σ_I, which is considered to be the true measure of the inductive effect of the substituent R′ group[12] (Figure 1).

These experimental data are consistent with initial formation of the acyl chloride → 2-Bu^{t}C$_6$H$_4$OMgBr adduct **22** (Scheme V).

The reaction products are the ester **20** and the ketone **21** (Table III). When R′ is an electron-donating group, the ligand reagent closely coordinates the metal ion $^+$MgBr, thus deshielding the phenolic oxygen and promoting the

Scheme V



9d **6** **22**

formation of the ester **20** as the main reaction product (Table III, entry a). As the electron-withdrawing power of the R′ group increases, the interaction of the ligand reagent with the metal ion $^+$MgBr becomes weaker; as a consequence, the metal ion strongly coordinates the phenolate, preventing competitive attack at the oxygen by coordinative protection (Table III, entry d).[13]

More information was obtained concerning the reagent–cation interaction in the complex **22** by carrying out the reaction in the presence of a specific ligand competitive with the acyl chloride in the complexation at the magnesium cation.[14] Indeed, the ortho-C/O reactivity ratio for the reaction of bromomagnesium 2-*tert*-butylphenolate **9d** with trichloroacetyl chloride **6d** is dramatically affected by increasing amounts of HMPA.

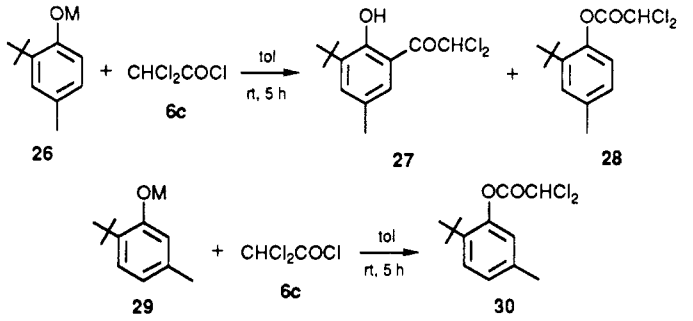
Increasing the HMPA/2-Bu^{t}C$_6$H$_4$OMgBr ratio resulted in a gradual shift of the acylation site from the ortho-carbon to the oxygen. The ester **20d** (Figure 3) was the

(12) Chapman, N. B.; Shorter, J. *Correlation Analysis in Chemistry*; Plenum Press: New York, 1978; pp 357–396.

(13) In the aliphatic series a similar Mg-promoted regioselective control was previously reported. Indeed, a high degree of C-regioselective acylation of ketones and β-dicarbonyl compounds was obtained via bromomagnesium chelates: Tirkpak, R. E.; Olsen, R. S.; Ratke, M. W. *J. Org. Chem.* **1985**, *50*, 4877 and references therein.

(14) Casnati, G.; Pochini, A.; Salerno, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1527.

Table IV. Steric Effects of the Phenol Ring Substituent in the "Metal-Template" Ortho-C Acylation



entry	M	phenol	recovered phenol, %	27, %	28, %	30, %
a	MgBr	**26**	22	78	22	–
b	MgBr	**29**	91	–	–	100
c	Al^{3+}	**26**	20	98	2	–
d	Al^{3+}	**29**	93	–	–	100

[a] The acid chloride **6c** was used due to its tendency to react at the ortho position (Table III, entry c).

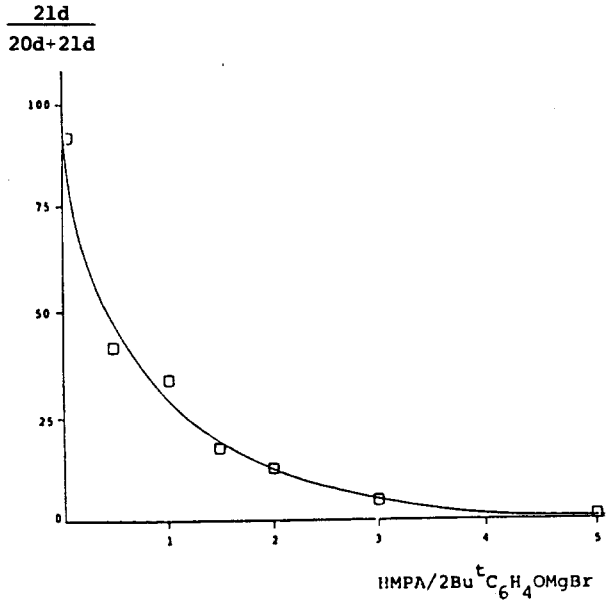
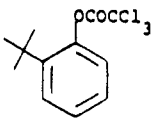


Figure 2. Plot of ortho-C selectivity vs HMPA concentration in the reaction of bromomagnesium 2-*tert*-butylphenolate with trichloroacetyl chloride.



20d

Figure 3.

sole reaction product when 5 mol of HMPA were used per mole of 2-Bu^{t}C$_6$H$_4$OMgBr.

Under these conditions, it is assumed that the basic ligand HMPA coordinates the metal ion $^+$MgBr, thus weakening the cation–phenolate interaction and promoting attack at the phenol oxygen.

Moreover, the role played by a specific ligand in inhibiting the complexation of the acylating agent was also investigated by comparing the reactivity of the isomeric methoxy phenolates **23** and **16b** with monochloroacetyl chloride **6b** (Scheme VI and Table II, Entry b).

When the metal center MgBr and the basic methoxy group are located in the proximate ortho position (Scheme VI) an "effective molarity" promoted interaction[15] produces

Scheme VI

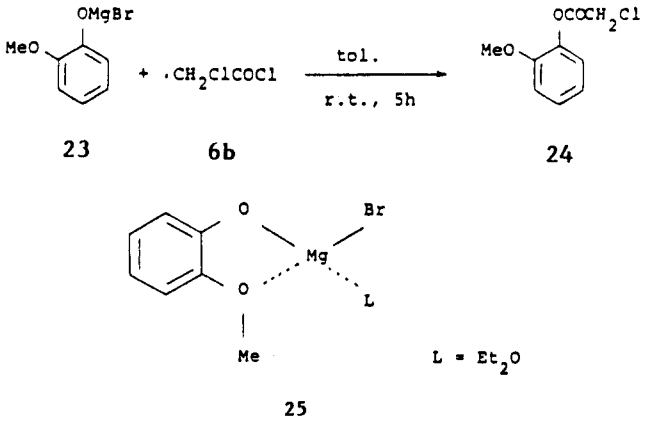


Figure 4.

the Lewis acid–base complex **25** (Figure 4).

The reaction of **25** with **6b** results in the exclusive formation of the ester **24** (83% yield), indicating that the interaction of the metal ion $^+$MgBr with the internal base OCH_3 completely blocks formation of the ortho-C reactive complex. Conversely, when the basic methoxy group is located in the meta position, ortho-coordinated acylation on the phenol substrate can occur, and the isomeric ortho ketones **18b** and **19b** are obtained in 94% total yield via the oriented complex promoted process (Table II, Entry b).

As previously noted, the results from Table III clearly show that the bulkiness of the acylating agent does not affect the ortho-regioselective attack.

In order to obtain further information on the sensitivity to steric effects of coordinative electrophilic reactions, the substituent group congestion proximate to the reactive site on the phenol ring was also analyzed. Bromomagnesium and aluminum derivatives of the variously substituted phenols **26** and **29** were allowed to react with dichloroacetyl chloride **6c** under similar experimental conditions. The results are reported in Table IV.

Comparison of the reactivity and isomer distribution in both bromomagnesium and aluminum derivatives of **26** and **29** reveals a dramatic steric effect. Whereas **26c** (entry c) reacts in 80% yield giving rise to the dichloro ketone **27** in 98% selectivity, only the ester **30** was recovered when the aluminum phenolate **29d** (entry d) was allowed to react

(15) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

with dichloroacetyl chloride **6c**. Using the bromomagnesium derivatives (entries a and b), the ortho-C/O reactivity ratio decreases only a little but the same great steric effect was observed. These results demonstrate that even the small methyl group in proximity to the reactive ortho-position is sufficient to prevent attack at the carbon, and reaction occurs only at the oxygen, and in very low yield. These data are in agreement with previous observations concerning "steric ortho-hindrance" in the Friedel–Crafts acylation of phenols, methoxy benzenes, alkylbenzenes, and halobenzenes.[16]

Summary

This study has demonstrated both the possibilities and limitations of the "ortho-coordinated acylation of phenol salts". In particular, in the course of the present research we have uncovered certain general aspects of the process.

These reactions require phenol salts with highly coordinating cations in aprotic apolar solvents. In this study, aluminum phenolates were the substrates of choice. These reactions involve attack only at the phenolic oxygen or at the carbon in the ortho position: no products of para attack were seen. The presence of an electron-donating group in the aromatic nucleus increases the ortho-C attack relative to ester formation.

High selectivity for ortho-functionalization of the phenol substrate is obtained with acylating agents characterized by the presence of electron-withdrawing groups in the α-position.

Phenols bearing ortho-substituent groups which are efficient at coordinating the counterion present in the phenol salt are not reactive in this process.

Steric factors connected with the structure of the acylating agent have no effect on the reaction course.

The features of the reaction studied in this report, as well as specific results obtained in previous synthetic applications, indicate that the ortho acylation of phenol substrates can be directly carried out on easily available and inexpensive phenol salts, such as aluminum phenolates, and does not involve the preparation or isolation of intermediates, as is required in the Fries rearrangement. Furthermore, the present methodology is the procedure of choice for a large series of α-functionalized acyl chlorides, particularly in the case of the acylation with halo acid chlorides, phosgene, oxaloyl chlorides, and unsaturated and polyunsaturated acyl chlorides. Generally, for these cases the Fries reaction gives negative results. Moreover, the mild reaction conditions and control of acidity in this methodology are particularly important in the case of phenols bearing substituent groups which are unstable under the usual Friedel–Crafts conditions; for example *tert*-alkylphenols give rise to dealkylation in the course of the Fries rearrangement.

Experimental Section

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. HPLC analyses were performed using a Model 6000A pump (Waters Associates Milford, MA), a U6K injector (Waters) and a Model 440 UV detector (Waters). ^{1}H NMR spectra were recorded on a Bruker CXP200 spectrometer at 200 MHz. Chemical shifts are expressed in ppm relative to TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Mass spectra were obtained on a Finnigan 1020 instrument at 70 eV. Microanalyses were carried out by Istituto di Chimica Generale ed Inorganica dell'Università di Parma, Italy. Chlorine content was determined by combustion in an oxygen filled flask.[17]

All reagents were of commercial quality from freshly opened containers. $AlCl_3$ was sublimed, and all acid chlorides were distilled before use. CF_3COCl,[18] $C_6H_5CH_2CH_2COCl$,[19] $C_6H_5CH{=}CHCOCl$,[20] $C_6H_5C{\equiv}CCOCl$[21] were prepared as described. Metal 2-*tert*-butylphenolates were prepared according to the methods previously reported for the metal phenolates (see below).

Metal Phenolates Preparation (General Procedures). Bromomagnesium 2-*tert*-Butylphenolate (9d). A solution of 2-*tert*-butylphenol (1.5 g, 0.01 mol) in anhydrous ethyl ether (100 mL) was added dropwise at room temperature with stirring, under nitrogen, to a solution of ethylmagnesium bromide (0.01 mol) in dry ether (100 mL). Most of the ether was removed by distillation under nitrogen, after which dry toluene (100 mL) was added. Distillation was continued until the temperature rose to 110 °C in order to completely remove the remaining ether. The final volume was adjusted to the selected value with dry toluene.

Aluminum 2-*tert*-Butylphenolate (9h).[7] To a solution of 2-*tert*-butylphenol (1.5 g, 0.01 mol) in dry toluene (100 mL) was added by syringe with stirring a 1 M hexane solution of Et_3Al (3.4 mL, 0.0034 mol) under nitrogen at 0 °C. Stirring was continued until the evolution of gas had ceased (about 10 min). The aluminum derivative **9h** was directly utilized.[22]

Dichloroaluminum 2-*tert*-Butylphenolate (9e).[7] Prepared as the preceding compound (**9h**) by using $EtAlCl_2$.

Boron 2-*tert*-Butylphenolate (9i). Boric acid (6.18 g, 0.10 mol) and 2-*tert*-butylphenol (46.56 g, 0.31 mol) were mixed in toluene (400 mL) with stirring. The mixture was distilled azeotropically for 12 h under a gentle stream of dry nitrogen. About 5.5 mL of water was separated. The reaction mixture was cooled (about 10 °C). The compound **9i** crystallized completely after 5 h. Crystals of **9i** (about 40 g) were filtered under nitrogen and washed with cold dry toluene (2 × 50 mL). The solid obtained was maintained at high vacuum for 8 h and stored under nitrogen.

Trichloro(2-*tert*-butylphenoxy)titanium (9g).[8] $TiCl_4$ (1.9 g, 0.01 mol) and 2-*tert*-butylphenol (1.5 g, 0.01 mol) were both diluted in a 20% mixture of dry petroleum ether and chloroform (50 mL). The solutions were mixed slowly in the cold. The solvent was distilled until dark red crystals began to separate, and the mixture was then cooled and filtered. The phenolate **9g** was carefully recrystallized (dry hexane/chloroform, 80:20), filtered, and utilized without further purification.

Titanium 2-*tert*-Butylphenolate (9l).[23] To a solution of titanium tetraethoxide (0.57 g, 0.0025 mol) in anhydrous toluene (50 mL) was added 2-*tert*-butylphenol (1.5 g, 0.01 mol) in toluene (50 mL) at room temperature under nitrogen. The resulting orange-red solution was refluxed for 30 min and then slowly distilled to completely remove the ethanol formed (about 2 h). The solution of **9l** obtained was directly utilized.[22]

Dichloro(2-*tert*-butylphenoxy)boron (9f).[9] To a solution of 2-*tert*-butylphenol (1.5 g, 0.01 mol) in dry toluene (100 mL) was added by syringe with stirring a 1 M hexane solution of BCl_3 (10 mL, 0.01 mol) under nitrogen at 0 °C. Stirring was continued for 10 min. The derivative **9f** was directly utilized.

Lithium, Sodium, and Potassium 2-*tert*-Butylphenolates (9a, 9b, and 9c). To a selected alkaline hydroxide (0.1 mol) dissolved in distilled water (10 mL) was added a solution of 2-*tert*-butylphenol (16.5 g, 0.11 mol) in toluene (300 mL). The mixture was distilled azeotropically for 10 h under dry nitrogen. About 12 mL of water was separated. The phenolate was filtered under nitrogen and washed with dry toluene (2 × 100 mL). The solid obtained was maintained at high vacuum for 5 h and stored under nitrogen.

Metal Phenolate Acylation. General Procedure. The

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selected acyl chloride (0.01 mol) in dry toluene (50 mL) was added dropwise to the phenolate (0.01 mol) in dry toluene (50 mL) with stirring under nitrogen. Stirring was continued for 5 h at room temperature; 10% aqueous NH_4Cl solution (100 mL) was rapidly added. The resulting mixture was extracted with ether (2 × 100 mL). The ethereal solution was dried (Na_2SO_4), the ether was distilled off, and the residue was chromatographed on silica gel plates with 2–15% hexane/EtOAc mixtures to give the products.

The reaction with CF_3COCl was carried out at 0 °C owing to the low boiling point of the acyl chloride (−27 °C (760 mm)).

Phenyl chloroacetate (17a): colorless oil; ^1H NMR ($CDCl_3$) δ 4.38 (s, 2 H, CH_2Cl), 6.7–7.6 (m, 5 H, H arom). Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.13; Cl, 20.78. Found: C, 56.20; H, 4.00; Cl, 20.48.

3-(*N*,*N*-Dimethylamino)phenyl monochloroacetate (17c): pink oil; IR (film) 2924, 1770, 1610, 1145, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (s, 6 H, $N(CH_3)_2$), 4.16 (s, 2 H, CH_2Cl), 6.0–7.3 (m, 4 H, H arom); MS *m/z* 213 (15), 136 (100), 121 (12), 108 (15), 94 (12). Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.30; H, 5.70; N, 6.48.

3-Chlorophenyl monochloroacetate (17d):[24] colorless oil; IR (film) 1780, 1590, 1468, 1197, 780, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.23 (s, 2 H, CH_2Cl), 6.8–7.3 (m, 3 H, H arom); MS *m/z* 204 (5), 128 (100), 111 (11), 99 (20). Anal. Calcd for $C_8H_6Cl_2O_2$: C, 46.86; H, 2.95; Cl, 34.58. Found: C, 46.98; H, 2.85; Cl, 34.40.

ω-Chloro-2-hydroxyacetophenone (18a): pale yellow crystals; mp 74–75 °C (lit.[11a] mp 75–76 °C); ^1H NMR ($CDCl_3$) δ 4.60 (s, 2 H, CH_2Cl), 6.90 (t, 1 H, H-5, *J* = 8.0 Hz), 7.63 (dd, 2 H, H-4 and H-6, *J* = 8.0 and 1.8 Hz), 12.20 (s, 1 H, OH). Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.13; Cl, 20.78. Found: C, 56.25; H, 4.28; Cl, 20.48.

ω-Chloro-2-hydroxy-4-methoxyacetophenone (18b): pale yellow crystals; mp 115–117 °C (lit.[11a] mp 117–118 °C); IR (KBr) 2963, 1640, 1625, 1220, 1135, 960, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3 H, OCH_3), 4.58 (s, 2 H, CH_2Cl), 6.3–6.6 (m, H-3 and H-5), 7.60 (d, 1 H, H-6, *J* = 8.0 Hz), 12.13 (s, 1 H, OH); MS *m/z* 200 (15), 151 (100), 137 (7), 108 (16), 95 (20). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52; Cl, 17.67. Found: C, 54.00; H, 4.45; Cl, 17.45.

ω-Chloro-2-hydroxy-4-(*N*,*N*-dimethylamino)acetophenone (18c): yellow crystals; mp 96–98 °C dec; IR (KBr) 2924, 1635, 1355, 1245, 1215, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (s, 6 H, $N(CH_3)_2$), 4.52 (s, 2 H, CH_2Cl), 6.10 (d, 1 H, H-3, *J* = 1.8 Hz), 6.20 (dd, 1 H, H-5, *J* = 8.0 and 1.8 Hz), 12.30 (s, 1 H, OH); MS *m/z* 213 (28), 164 (100), 150 (20), 136 (22), 120 (8), 108 (18). Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.40; H, 5.70; N, 6.40.

ω-Chloro-2-hydroxy-6-methoxyacetophenone (19b): pale yellow crystals; mp 105–109 °C; IR (KBr) 2963, 1640, 1625, 1220, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H, OCH_3), 4.90 (s, 2 H, CH_2Cl), 6.3–7.4 (m, 3 H, H arom), 12.10 (s, 1 H, OH). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52; C1, 17.67. Found: C, 53.95; H, 4.70; C1, 18.00.

2-*tert*-Butylphenyl acetate (20a): colorless oil; IR (film) 2960, 17.55, 12.20, 1176, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H, $(CH_3)_3C$), 2.33 (s, 3 H, CH_3), 6.8–7.5 (m, 4 H, H arom); MS *m/z* 192 (5), 150 (35), 135 (100), 107 (53), 91 (28). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.20.

2-*tert*-Butylphenyl chloroacetate (20b): yellow oil; IR (film) 2960, 1786, 1190, 1136, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 9 H, $(CH_3)_3C$), 4.30 (s, 2 H, CH_2Cl), 6.8–7.5 (m, 4 H, H arom); MS *m/z* 226 (8), 211 (8), 150 (30), 135 (100), 115 (3), 107 (50), 91 (60). Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.70; H, 6.50; Cl, 15.80.

2-*tert*-Butylphenyl dichloroacetate (20c): colorless oil; IR (film) 2975, 1770, 1250, 1176, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 6.13 (s, 1 H, $CHCl_2$) 6.7–7.6 (m, 4 H, H arom); MS *m/z* 260 (8), 245 (20), 227 (10), 135 (30), 107 (25), 91 (100). Anal. Calcd for $C_{12}H_{14}Cl_2O_2$: C, 55.19; H, 5.40; Cl, 27.15. Found: C, 55.00; H, 5.25; Cl, 27.28.

2-*tert*-Butylphenyl trichloroacetate (20d): pale yellow oil; IR (film) 2940, 1770, 1220, 810, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 6.8–7.5 (m, 4 H, H arom); MS *m/z* 294 (10), 279 (33), 261 (7), 115 (29), 91 (100). Anal. Calcd for $C_{12}H_{13}Cl_3O_2$: C, 48.75; H, 4.43; Cl, 35.98. Found: C, 48.90; H, 4.25; Cl, 35.80.

2-*tert*-Butylphenyl 3-phenylpropanoate (20f): white crystals; mp 58–60 °C; IR (KBr) 3000, 1680, 1500, 1460, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 9 H, $(CH_3)_3C$), 2.8–3.3 (m, 4 H, CH_2CH_2), 6.8–7.6 (m, 9 H, H arom); MS *m/z* 282 (20), 150 (95), 135 (100), 105 (90), 91 (96). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 90.00; H, 7.73.

2-*tert*-Butylphenyl 3-phenylpropenoate (20g): pale yellow crystals; mp 79–82 °C; IR (KBr) 2990, 1730, 1640, 1490, 1200, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, $(CH_3)_3C$), 6.69 (d, 1 H, CH=C, *J* = 15.90 Hz), 7.0–7.8 (m, 9 H, H arom), 7.89 (d, 1 H, COCH=C, *J* = 15.90 Hz); MS *m/z* 280 (10), 131 (100), 103 (26). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.25; H, 7.00.

2-*tert*-Butylphenyl 3-phenylpropynoate (20h): pale yellow crystals; mp 62–63 °C; IR (KBr) 2960, 2200, 1720, 1440, 1280, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, $(CH_3)_3C$), 7.0–7.8 (m, 9 H, H arom); MS *m/z* 278 (1), 221 (22), 129 (100). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.10; H, 6.48.

2-Hydroxy-3-*tert*-butylacetophenone (21a): yellow oil; IR (film) 2960, 1625, 1428, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 2.53 (s, 3 H, CH_3), 6.8–7.5 (m, 3 H, H arom), 12.10 (s, 1 H, OH); MS *m/z* 192 (25), 177 (100), 159 (42), 149 (25), 131 (39). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.90; H, 8.30.

ω-Chloro-2-hydroxy-3-*tert*-butylacetophenone (21b): yellow crystals; mp 52–53 °C; IR (KBr) 2976, 1640, 1430, 745, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 4.64 (s, 2 H, CH_2Cl), 6.77 (t, 1 H, H-5, *J* = 8.0 Hz), 7.47 (d, 2 H, H-4 and H-6, *J* = 8.0 Hz), 12.48 (s, 1 H, OH); MS *m/z* 226 (14), 211 (40), 177 (40), 165 (18), 150 (20), 115 (35). Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.60; H, 6.53; Cl, 15.55.

ω,ω-Dichloro-2-hydroxy-3-*tert*-butylacetophenone (21c): yellow oil; IR (film) 2958, 1640, 1600, 1410, 1250, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 6.77 (s, 1 H, $CHCl_2$), 6.79 (t, 1 H, H-5, *J* = 8.0 Hz), 7.50 (dd, 1 H, H-4, *J* = 8.0 Hz), 7.66 (d, 1 H, H-6, *J* = 8.0 Hz), 12.23 (s, 1 H, OH); MS *m/z* 260 (6), 245 (10), 177 (100), 161 (9), 105 (7), 91 (16). Anal. Calcd for $C_{12}H_{14}Cl_2O_2$: C, 55.19; H, 5.40; Cl, 27.15. Found: C, 55.30; H, 5.28; Cl, 26.98.

ω,ω,ω-Trichloro-2-hydroxy-3-*tert*-butylacetophenone (21d): yellow crystals; mp 54–58 °C; IR (KBr) 2960, 1650, 1600, 1422, 1190, 830, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 6.75 (t, 1 H, H-5, *J* = 8.0 Hz), 7.53 (dd, 1 H, H-4, *J* = 8.0 and 1.8 Hz), 8.17 (dd, 1 H, H-6, *J* = 8.0 and 1.8 Hz), 11.93 (s, 1 H, OH); MS *m/z* 294 (6), 177 (100), 161 (23), 133 (9), 115 (22), 105 (10). Anal. Calcd for $C_{12}H_{13}Cl_3O_2$: C, 48.75; H, 4.43; Cl, 35.98. Found: C, 48.86; H, 4.35; Cl, 35.90.

ω,ω,ω-Trifluoro-2-hydroxy-3-*tert*-butylacetophenone (21e): yellow oil; IR (film) 2940, 1670, 1613, 1428, 1190, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 9 H, $(CH_3)_3C$), 6.80 (t, 1 H, H-5, *J* = 8.0 Hz), 7.56 (d, 1 H, H-4, *J* = 8.0 Hz), 7.63 (d, 1 H, H-6, *J* = 8.0 Hz), 11.90 (s, 1 H, OH); MS *m/z* 246 (26), 231 (100), 203 (78), 177 (18), 161 (52), 133 (45), 115 (34). Anal. Cald for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32. Found: C, 58.60; H, 5.20.

1-(2-Hydroxy-3-*tert*-butylphenyl)-3-phenylpropan-1-one (21f): pale yellow crystals; mp 72–74 °C; IR (KBr) 2980, 1780, 1640, 1430, 1210, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H, $(CH_3)_3C$), 2.9–3.5 (m, 4 H, CH_2CH_2), 6.80 (t, 1 H, H-5, *J* = 7.8 Hz), 7.2–7.4 (m, 5 H, H arom), 7.47 (dd, 1 H, H-4, *J* = 7.8 and 1.6 Hz), 7.64 (dd, 1 H, H-6, *J* = 7.8 and 1.6 Hz), 13.15 (s, 1 H, OH); MS m/z 282 (80), 267 (70), 249 (18), 177 (74), 91 (100). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.68; H, 8.00.

1-(2-Hydroxy-3-*tert*-butylphenyl)-3-phenyl-2-propen-1-one (21g): yellow crystals; mp 79–82 °C; IR (KBr) 2990, 1730, 1640, 1450, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H, $(CH_3)_3C$), 6.69 (d, 1 H, CH=C, *J* = 15.90 Hz), 7.0–7.8 (m, 8 H, H arom), 7.89 (d, 1 H, COCH=C, *J* = 15.90 Hz); MS *m/z* 280 (10), 131 (100), 103 (26). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.23; H, 7.25.

1-(2-Hydroxy-3-*tert*-butylphenyl)-3-phenyl-2-propyn-1-one (21h): yellow crystals; mp 87–89 °C; IR (KBr) 2980, 2220, 1610, 1440, 1220, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9 H, $(CH_3)_3C$), 6.90 (t, 1 H, H-5, *J* = 7.8 Hz), 7.3–7.8 (m, 6 H, H arom), 8.02 (dd, 1 H, H-6, *J* = 7.8 and 1.5 Hz), 9.98 (s, 1 H, OH); MS *m/z* 278

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(80), 263 (85), 161 (100), 133 (20). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.84; H, 6.45.

3-Methoxyphenyl monochloroacetate (24): yellow oil; IR (film) 2980, 1780, 1620, 1490, 1280, 1160, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3 H, OCH_3), 4.34 (s, 2 H, CH_2Cl), 6.8–7.3 (m, 4 H, H arom); MS m/z 200 (18), 124 (100), 109 (72), 95 (18). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52; Cl, 17.67. Found: C, 53.80; H, 4.45; Cl, 17.52.

ω,ω-Dichloro-2-hydroxy-3-*tert*-butyl-5-methylacetophenone (27): yellow crystals; mp 55–59 °C; IR (KBr) 2980, 1640, 1440, 1280, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 2.32 (s, 3 H, CH_3), 6.63 (s, 1 H, $CHCl_2$), 7.39 (s, 1 H, H-4), 7.44 (s, 1 H, H-6), 12.14 (s, 1 H, OH); MS m/z 274 (30), 259 (50), 191 (100), 175 (8). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.62; H, 5.94; Cl, 25.92.

2-*tert*-Butyl-4-methylphenyl dichloroacetate (28): pale yellow oil; IR (film) 2980, 1770, 1500, 1190, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H, $(CH_3)_3C$), 2.35 (s, 3 H, CH_3), 6.17 (s, 1 H, $CHCl_2$), 6.89 (d, 1 H, H-6, J = 8.2 Hz), 7.04 (dd, 1 H, H-3, J = 1.8 Hz); MS m/z 274 (54), 259 (100), 241 (30), 164 (25), 149 (78). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.60; H, 5.70; Cl, 25.58.

2-*tert*-Butyl-5-methylphenyl dichloroacetate (30): pale yellow oil; IR (film) 2990, 1680, 1520, 1240, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H, $(CH_3)_3C$), 2.32 (s, 3 H, CH_3), 6.17 (s, 1 H, $CHCl_2$), 6.81 (d, 1 H, H-6, J = 1.8 Hz), 7.03 (dd, 1 H, H-4, J = 8.1 and 1.8 Hz), 7.30 (d, 1 H, H-3, J = 8.1 Hz); MS m/z 274 (34), 259 (100), 241 (20), 176 (14), 149 (26). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.68; H, 5.95; Cl, 25.88.

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Registry No. **5** (R = 2-Bu-*t*), 88-18-6; **6a**, 75-36-5; **6b**, 79-04-9; **6c**, 79-36-7; **6d**, 76-02-8; **6e**, 354-32-5; **6f**, 645-45-4; **6g**, 102-92-1; **6h**, 7299-58-3; **9a**, 114299-91-1; **9b**, 39068-23-0; **9c**, 41769-06-6; **9d**, 36359-98-5; **9e**, 127354-48-7; **9f**, 127354-30-7; **9g**, 127354-49-8; **9h**, 5797-27-3; **9i**, 127354-31-8; **9l**, 127354-50-1; **10**, 127354-32-9; **11**, 127354-33-0; **12**, 127354-34-1; **16a**, 35770-74-2; **16b**, 55960-09-3; **16c**, 127354-51-2; **16d**, 127354-52-3; **17a**, 620-73-5; **17b**, 119929-84-9; **17c**, 127354-35-2; **17d**, 63573-05-7; **18a**, 53074-73-0; **18b**, 60965-23-3; **18c**, 127354-36-3; **19b**, 75717-59-8; **20a**, 3245-25-8; **20c**, 127354-37-4; **20d**, 127354-39-6; **20f**, 40123-27-1; **20g**, 127354-41-0; **20h**, 127354-43-2; **21a**, 24242-55-5; **21c**, 127354-38-5; **21d**, 111422-36-7; **21e**, 111422-37-8; **21f**, 127354-40-9; **21g**, 127354-42-1; **21h**, 127354-44-3; **23**, 127354-55-6; **24**, 30287-15-1; **26a**, 118967-71-8; **26c**, 127354-53-4; **27**, 127354-45-4; **28**, 127354-46-5; **29b**, 53863-60-8; **29d**, 127354-54-5; **30**, 127354-47-6.

Stereoselective Reduction of Diketones by a Novel Carbonyl Reductase from *Candida parapsilosis*

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An NADPH-linked carbonyl reductase purified from *Candida parapsilosis* IFO 0708 can reduce a variety of diketone compounds such as analogues of 1*H*-indole-2,3-dione (**3**), dihydro-4,4-dimethyl-2,3-furandione (**1a**), and 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione (**2**). Electron-donating substituents at the 5 position on the ring of **3** increased the reduction velocity; however, a 1-methyl group had no effect on it. Analogues of **1a** carrying bulky substituents at the 4 or 5 position of the lactone ring were reduced at lower rates than that of **1a**, although they showed higher affinities for the enzyme. Ones carrying less bulky substituents were reduced at higher rates, but had lower K_m values. On reduction, 4,4-diethyldihydro-2,3-furandione (**1c**), (*R*)- and (*S*)-dihydro-4,4-dimethyl-5-(1-methylethyl)-2,3-furandione (**1e**), and (*R*)-(−)- and (S)-(+)-**2**, **3**, and 1-methyl-1*H*-indole-2,3-dione (**4**) all gave *R* alcohols.

The stereospecific reduction of prochiral α-diketones is of synthetic importance. Several enzymatic reactions have been shwon to be promising in giving good enantiomeric excesses of the reduction products. The reduction of dihydro-4,4-dimethyl-2,3-furandione (**1a**) has been reported to give (*R*)-(−)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone,[2] which is a key intermediate in the synthesis of (*R*)-*N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine (D-pantothenic acid), and the reduction of 2-(6-carbomethoxyhexyl)cyclopentane-1,3,4-trione gives important intermediates of (−)-prostaglandin E_1 and (−)-prostaglandin E_2.[3] Furthermore, this type of reduction is involved in the metabolism of C_{18}-steroid hormones such as in the reduction of 3-hydroxyestra-1,3,5(10)-triene-16,17-dione (16-oxoestrone).[4] Many kind of ketols exist in nature and play important physiological roles.[5] In a previous paper, we reported that a fungus, *Mucor ambiguus*, produces a new type of carbonyl reductase showing strict specificity for only conjugated polyketone compounds.[6] The following studies demonstrated that similar enzymes are widely distributed in a variety of microorganisms.[7] For example, the carbonyl reductases of *Candida parapsilosis* and *Saccharomyces cerevisiae* also exhibit broad substrate specificities toward only conjugated polyketones.[7b,c] These results suggest that they can be grouped into a new carbonyl reductase family, which has not been reported previously. However, the two yeast enzymes (i.e., *Candida*

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