# Development and Scope of the Phenolic Aldol Reaction of 2-Formylpyridines

Matthew Whiting,* Mark C. Wilkinson, Kathy Harwood[1]

Synthetic Chemistry, Chemical Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK
Fax +44(1438)764869; E-mail: matthew.p.whiting@gsk.com

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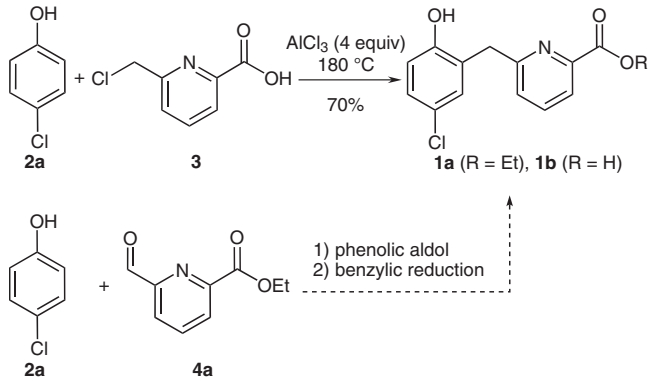
**Abstract:** 2-Formylpyridines have been shown to be suitable electrophiles for the magnesium-promoted phenolic aldol reaction. Exceptionally mild reaction conditions have been developed and a brief survey of the reaction scope has been conducted. This process gives straightforward access to a range of functionalised 2-hydroxyphenyl-2-pyridylmethanols and 2-hydroxyphenyl-2-pyridylmethanes via their subsequent reduction.

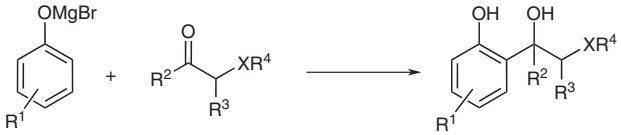
**Key words:** phenolic aldol reaction, arylation, magnesium phenoxides, 2-formylpyridines, 2-hydroxyphenyl-2-pyridylmethanols

A cheap and scalable synthesis of diarylmethane **1a** or **1b** was required as part of a program towards the development of novel EP1 antagonists.[2] Initial work revealed that a direct Friedel–Crafts alkylation could be accomplished, however, the electron-deficient nature of both coupling partners necessitated the use of extreme conditions (a melt consisting of 4 equiv $AlCl_3$ at 180 °C for 6 h). These conditions were not considered suitable for further scale-up, leading us to investigate alternative options, including the phenolic aldol reaction[3] of 2-formylpyridine (**4a**) with 4-chlorophenol (**2a**), followed by reduction of the initially formed diarylmethanol to the desired diarylmethane **1a** (Scheme 1).




**Scheme 1** Friedel–Crafts and proposed phenolic aldol–reduction route to diarylmethanes **1a** and **1b**

Magnesium phenoxides are known to undergo selective reaction at the *ortho* position with a wide range of electrophiles to provide a variety of *ortho*-substituted phenol derivatives,[4] presumably via an initial coordination complex.[5] Phenolic aldol-type reaction with aldehydes or ketones generally occurs under quite forcing conditions, initially providing *ortho*-hydroxyalkylated products, which then often react further under the reaction conditions to produce a variety of products dependent upon the nature of the reaction partners.[4,6] A number of aldehydic and ketonic compounds containing α-coordinating functionalities, including α-alkoxy aldehydes,[3b,d] suitably protected α-amino aldehydes,[3b,c,g,h] glyoxal,[3a] and isatins[3f] have been shown to undergo the corresponding reaction under much milder conditions enabling selective formation of the initial *ortho*-hydroxyalkylated phenol products (Scheme 2).




$R^1$, $R^2$, $R^3$ = various
$XR^4$ = O-alkyl, N-Boc or =O

**Scheme 2** Phenolic aldol reaction of magnesium phenoxides

We postulated that the pyridyl nitrogen of 2-formylpyridines could act as a suitable α-coordinating substituent, thereby facilitating the desired reaction. The only example we were able to find in the literature was the reaction of 2-methylphenoxymagnesium bromide with 2-formylpyridine itself. This reaction was said to proceed in only 8% yield, though the precise reaction conditions were not given.[7]

Given this limited precedent we were pleased to find that 4-chlorophenoxymagnesium bromide, generated by addition of one equivalent of EtMgBr in $Et_2O$ to a solution of 4-chlorophenol in $CH_2Cl_2$, underwent rapid phenolic aldol reaction upon addition of aldehyde **4a** at room temperature to give 50% conversion to the desired diarylmethanol **5a** (Table 1, entry 1). Use of 2.2 equivalents of the magnesium phenoxide enabled the reaction to progress to completion, presumably as one equivalent is required to deprotonate the relatively acidic product (Table 1, entry 2). Use of a 1 M MTBE solution of the Grignard reagent[8] still gave high conversion albeit at a slightly reduced rate (Table 1, entry 3), though using a 1 M THF solution gave a much reduced reaction rate and lower product formation due to competing side reactions (Table 1, entry 4). Use of EtMgCl (Table 1, entry 5) gave identical conversion compared to the bromide. A number of metal alkoxide bases gave only low conversion to prod-

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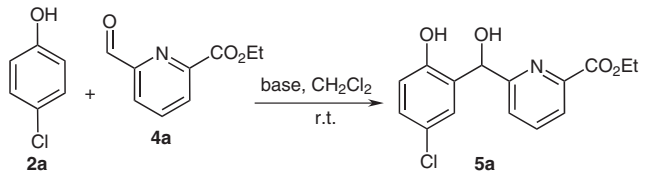
uct (Table 1, entries 6–9). Importantly, generation of the magnesium phenoxide using $Et_3N$ in the presence of $MgCl_2$[9] also gave efficient product formation; in the absence of $MgCl_2$ no reaction was observed (Table 1, entries 10 and 11).

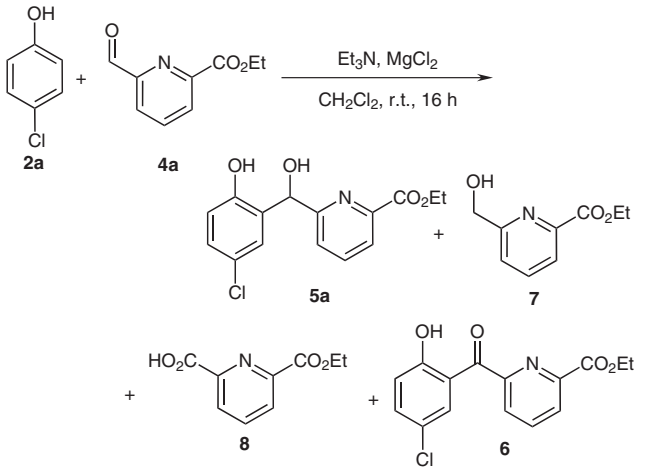
**Table 1** Phenolic Aldol Reaction Using Various Bases[a]




| Entry | Base | Time (h) | Conversion to **5a** (%)[b] |
|---|---|---|---|
| 1[c] | EtMgBr[d] | 2 | 50 |
| 2 | EtMgBr[d] | 1 | 98 (95) |
| 3 | EtMgBr[e] | 2 | 97 |
| 4 | EtMgBr[f] | 16 | 62 |
| 5 | EtMgCl[g] | 2 | 97 |
| 6 | $Mg(OEt)_2$ | 16 | 14 |
| 7 | $Al(OEt)_3$ | 16 | 8 |
| 8 | $Ti(O\textit{i}\text{-}Pr)_4$ | 16 | 4 |
| 9 | $Ca(O\textit{i}\text{-}Pr)_2$ | 16 | 8 |
| 10 | $Et_3N/MgCl_2$ | 16 | 68 |
| 11 | $Et_3N$ | 16 | 0 |

[a] **2a** (2.5 equiv) and base (2.2 equiv) were stirred in $CH_2Cl_2$ for 30 min, **4a** (1 equiv) was then added as a solution in $CH_2Cl_2$.
[b] Determined by LC-UV analysis; isolated yield after chromatography is given in parentheses.
[c] 1 equiv of **2a** and base used.
[d] 3 M soln in $Et_2O$.
[e] 1 M soln in MTBE.
[f] 1 M soln in THF.
[g] 2 M soln in $Et_2O$.

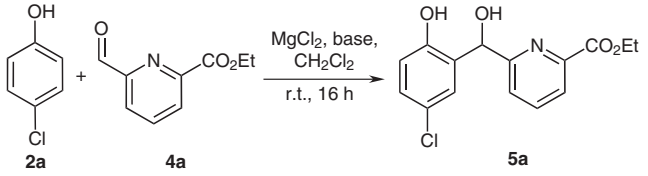
Phenolic aldol-type reactions have generally been conducted by formation of the magnesium phenoxide in an ethereal solvent followed by removal of the ether and replacement with a nondonating solvent, typically benzene or $CH_2Cl_2$, to promote the required complexation.[3a–d,3f–h,5] Our finding in the current example that reactions proceed readily in a mixture of $CH_2Cl_2$ and MTBE was already a large step forward, enabling us to scale the chemistry without serious issues. The necessity for a large amount of the expensive and reactive Grignard reagent, however, prompted us to further investigate phenoxide generation using simple bases in combination with cheap magnesium salts. Analysis of the $Et_3N/MgCl_2$ promoted reaction (Table 1 entry 10) showed the observed yield reduction was due to competing redox reactions (Scheme 3) along with the presence of residual starting aldehyde which we postulate could be trapped under the reaction conditions as an unreactive acetal.




**Scheme 3** Byproducts arising from the $Et_3N/MgCl_2$ process

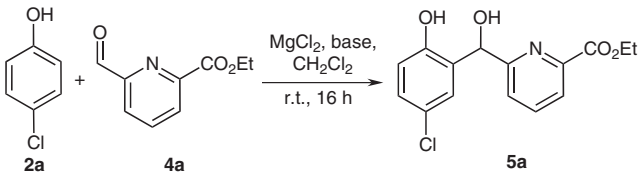
Ketone **6** is formed by magnesium promoted Oppenauer oxidation of the initial product using the starting aldehyde as the oxidant, concomitantly generating alcohol **7**. Acid **8** and alcohol **7** are also generated by a mild $MgCl_2/Et_3N$ promoted Cannizzarro-type disproportionation.[10] To try and improve the reaction selectivity we investigated use of a range of alternative bases (Table 2).

**Table 2** $MgCl_2$-Promoted Phenolic Aldol Reaction Base Screen[a]




| Entry | Base | Conversion to **5a** (%)[b] |
|---|---|---|
| 1 | $Et_3N$ | 67 |
| 2 | $K_2CO_3$ | 27 |
| 3 | $NaHCO_3$ | 20 |
| 4 | DIPEA | 67 |
| 6 | 4-methylmorpholine | 78 |
| 7 | *N*-methylpiperidine | 72 |
| 8 | *N*-ethylmorpholine | 62 |
| 9 | 4-ethyliperidine | 64 |
| **10** | **$Me_2NEt$** | **80** |
| 11 | DABCO | 0 |
| 12 | $Bu_2NH$ | 0 |
| 13 | 2,6-lutidine | 1 |
| 14 | TMEDA | 33 |
| 15 | triethanolamine | 0 |
| 16 | tetramethylguanidine | 58 |

**Table 2** $MgCl_2$-Promoted Phenolic Aldol Reaction Base Screen[a]

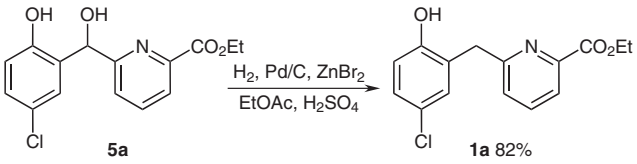



| Entry | Base | Conversion to **5a** (%)[b] |
|---|---|---|

[a] Compound **2a** (2.5 equiv), $MgCl_2$ (3 equiv), and base (3 equiv) were stirred in $CH_2Cl_2$ for 30 min, **4a** (1 equiv) was then added as a solution in $CH_2Cl_2$.
[b] Determined by LC-UV analysis.

Use of inorganic bases gave greatly reduced reactivity (Table 2, entries 2 and 3); however, use of alternative trialkylamines maintained high conversion. Diisopropylethylamine (Table 2, entry 4) behaved similarly to $Et_3N$, use of 4-methylmorpholine or *N*-methylpiperidine gave slightly improved selectivity (Table 2, entries 6 and 7), whereas use of their ethyl derivatives gave slightly lower yields (Table 2, entries 8 and 9). *N*,*N*-Dimethylethylamine ($Me_2NEt$) gave the highest observed selectivity (Table 2, entry 10), and a range of alternative organic bases gave lower or no reactivity (Table 2, entries 11–16). It therefore appears that for efficient conversion a trialkylamine is required as base, with smaller (and also less basic) derivatives seemingly giving higher selectivities for reasons which are not currently fully understood. Investigation of a range of alternative solvents gave no improvement.[11] Use of strongly donating or protic solvents had an adverse effect on the reactivity, whereas ethers and a number of other hydrocarbon solvents were not sufficiently polar to solubilise the reaction intermediates. After optimisation of the $Me_2NEt$ process we briefly surveyed the scope of the reaction (Table 3 and Table 4).

A range of functionalised phenols was well tolerated (Table 3, entries 1–4). Under the optimised conditions (increased $MgCl_2$, reduced base, and slow addition of the aldehyde), 4-chlorophenol (**2a**) gave 92% solution yield, and **5a** was isolated in 86% yield after chromatography; alternatively, isolation by crystallisation from 1:1 EtOH–$H_2O$ gave 78% yield (cf. 83% for the Grignard-promoted process; Table 3, entry 1). The highly electron-deficient 4-nitrophenol (**2e**) only gave poor conversion (Table 3, entry 5), however, the reasonably electron-deficient ethyl-4-hydroxybenzoate (**2d**) still furnished the desired product **5d** in good yield (Table 3, entry 4).



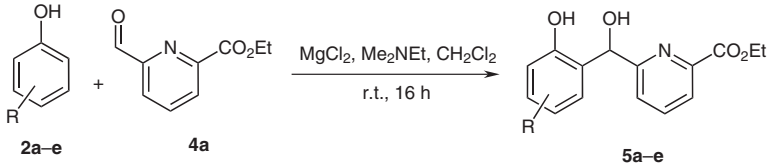

**Scheme 4** Reduction to give diarylmethane **1a**

Whilst the parent 2-formylpyridine (**4b**) underwent efficient reaction with chloromagnesium phenoxide generated from phenol, $MgCl_2$, and $Me_2NEt$ (Table 4, entry 1), replacement of the 2-pyridyl group with either a benzene ring or a 3-pyridyl substituent gave no conversion under the reaction conditions (Table 4, entries 2 and 3). This supports the hypothesis that the 2-pyridyl nitrogen is required for efficient chelation of the magnesium centre prior to reaction. A range of further substituted 2-formylpyridines (**4e**–**h**) all underwent smooth conversion to provide **5i**–**l** (Table 4, entries 4–7).

Reduction of diarylmethanol **5a** to the desired diarylmethane **1a** was readily achieved by palladium-catalysed hydrogenolysis. Conducting the reaction in ethyl acetate with catalytic $ZnBr_2$ proved key to controlling competitive reduction of the aryl chloride (Scheme 4).[12]

In summary, 2-formylpyridines have been demonstrated to be suitable substrates for the magnesium-promoted phenolic aldol reaction. This enables a very mild and

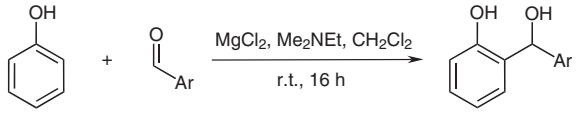
**Table 3** Scope of Phenol Component[a]




| Entry | Phenol | | Conversion to **5** (%)[b] |
|---|---|---|---|
| 1 | **2a**, R = 4-Cl | **5a** | 92 (86) |
| 2 | **2b**, R = H | **5b** | 96 (85) |
| 3 | **2c**, R = 2-Cl | **5c** | 93 |
| 4 | **2d**, R = 4-$CO_2$Et | **5d** | 87 (81) |
| 5 | **2e**, R = 4-$NO_2$ | **5e** | 26 |

[a] Phenol (2.5 equiv), $MgCl_2$ (4 equiv), and $Me_2NEt$ (2.2 equiv) were stirred in $CH_2Cl_2$ for 30 min, **4a** (1 equiv) was then added as a solution in $CH_2Cl_2$ over 3 h.
[b] Determined by LC-UV analysis; isolated yield after chromatography is given in parentheses.

**Table 4** Scope of Aldehyde Component[a]




**2b** **4b–h** **5f–l**

| Entry | Aldehyde | | Conversion to **5** (%)[b] |
|---|---|---|---|
| 1 | **4b** | **5f** | 94 (50)[c] |
| 2 | **4c** | **5g** | 0 |
| 3 | **4d** | **5h** | 0 |
| 4 | **4e** | **5i** | 93 |
| 5 | **4f** | **5j** | 97 (81) |
| 6 | **4g** | **5k** | 93 |
| 7 | **4h** | **5l** | 86 |

[a] Compound **2b** (2.5 equiv), $MgCl_2$ (4 equiv), and $Me_2NEt$ (2.2 equiv) were stirred in $CH_2Cl_2$ for 30 min, aldehyde (1 equiv) was then added as a solution in $CH_2Cl_2$ over 3 h.
[b] Determined by LC-UV analysis; isolated yield after chromatography is given in parentheses.
[c] Isolated by precipitation from $CH_2Cl_2$–phosphate buffer (pH= 7).

straightforward synthesis of a range of 2-hydroxyphenyl-2-pyridylmethanols, the more functionalised and electron deficient of which would be problematic or impossible to synthesise by more conventional Friedel–Crafts/Fries-type chemistry. Reduction of the initially formed benzylic alcohols enables access to the corresponding diarylmethanes. In addition, new conditions for this reaction have been developed which facilitate reaction scale-up by removing the necessity to use expensive and reactive Grignard reagents.

**Procedure for the Preparation of 5a**

$CH_2Cl_2$ (40 mL) was added to 4-chlorophenol (**2a**, 8.9 g, 69 mmol) and $MgCl_2$ (10.6 g, 111 mmol). $Me_2NEt$ (6.7 mL, 61 mmol) was cautiously added to the resultant suspension at a rate which maintained the internal temperature below 30 °C (caution, 2-stage exotherm observed). The reaction mixture was equilibrated to 23 °C, and a soln of the aldehyde **4a** (5 g, 28 mmol) in $CH_2Cl_2$ (10 mL) was added over 4 h. The resulting orange suspension was stirred at r.t. for 15 h before being cooled to 0 °C and cautiously quenched by addition of HCl (30 mL of a 2 M aq soln, 60 mmol) followed by $KHSO_4$ (18 mL of a 0.54 M aq soln, 9.7 mmol). The organic phase was separated and the aqueous phase back extracted with $CH_2Cl_2$ (5 mL). The combined organics were washed with $H_2O$ (20 mL) and the aqueous phase again back extracted with $CH_2Cl_2$ (5 mL). The combined organic phases were concentrated to 15 mL by atmospheric pressure distillation before EtOH (50 mL) was added, and the soln further concentrated to 35 mL. $H_2O$ (35 mL) was slowly added at reflux. The solution was cooled to 70 °C, seeded with **5a**, held for 1 h, and then cooled to 0 °C over 2 h. The resultant slurry was held for 1 h before the product was collected by filtration and washed with EtOH–$H_2O$ (1:1, 3 × 10 mL) at 0 °C. The fluffy white solid was dried overnight under vacuum at 40 °C to furnish **5a** (6.7 g, 78%, >99.9% a/a purity by LC-UV). $^1$H NMR (400 MHz, $CDCl_3$): δ = 10.34 (br s, 1 H), 8.01 (d, *J* = 7.5 Hz, 1 H), 7.91 (t, *J* = 7.5 Hz, 1 H), 7.75 (d, *J* = 7.5 Hz, 1 H), 7.37 (d, *J* = 2.5 Hz, 1 H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 6.10 (s, 1 H), 4.45 (q, *J* = 7.0 Hz, 2 H), 3.98 (br s, 1 H), 1.44 (t, *J* = 7.0 Hz, 3 H). ESI-HRMS: *m/z* calcd for $C_{15}H_{15}NO_4{}^{35}Cl$ [$MH^+$]: 308.0684; found: 308.0691.

**Procedure for the Preparation of 1a**

Compound **5a** (70 g, 1 equiv) and Pd/C (5.25 g of JM type 487 10 wt% Pd on activated carbon, dry powder, 2.2 mol% Pd) were charged to a hydrogenation vessel. EtOAc (525 mL) was added, and further EtOAc (525 mL) was used to wash in $ZnBr_2$ (1.4 g, 2.7 mol%), after which $H_2SO_4$ (70 mL, concd) was cautiously added with vigorous stirring. The vessel was flushed with $N_2$ followed by $H_2$ at 1 atm (above atmospheric pressure) and the reaction was heated to 65 °C for 6 h. The reaction was cooled to r.t. and filtered through a short plug of Celite, washing with EtOAc (3 × 70 mL). The combined filtrates were added into $H_2O$ (700 mL). The aqueous phase was separated and diluted with further $H_2O$ (980 mL) before being back extracted with EtOAc (350 mL). The combined organic phases were washed with $Na_2SO_4$ (2 × 420 mL of a 10% w/w solution) followed by $H_2O$ (420 mL). The organic phase was concentrated to 350 mL by atmospheric pressure distillation, diluted with 2-PrOH (1.4 L), and further concentrated to 490 mL. The resultant solution was cooled to 55 °C, seeded with **1a**, then cooled to 0 °C over 2 h, and held for a further 1 h before the product was collected by filtration and washed with cold 2-PrOH (140 mL). The white solid was dried overnight under vacuum at 40 °C to furnish **1a** (54.6 g, 82%, >99% a/a purity by LC-UV). $^1$H NMR (400 MHz, $CDCl_3$): δ = 11.21 (br s, 1 H), 8.01 (d, *J* = 7.5 Hz, 1 H), 7.86 (t, *J* = 7.5 Hz, 1 H), 7.50 (d, *J* = 7.5 Hz, 1 H), 7.13 (d, *J* = 2.5 Hz, 1 H), 7.09 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 4.46 (q, *J* = 7.0 Hz, 2 H), 4.11 (s, 2 H), 1.47 (t, *J* = 7.0 Hz, 3 H). ESI-HRMS: *m/z* calcd for $C_{15}H_{15}NO_3{}^{35}Cl$ [$MH^+$]: 292.0735; found: 292.0738.

## Acknowledgment

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## References and Notes

(1) Current address: Peakdale Molecular Ltd, Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith SK23 0PG, UK.

(2) For leading references, see: (a) Hall, A.; Billinton, A.; Giblin, G. M. P. *Curr. Opin. Drug Discovery Devel.* **2007**, *10*, 597. (b) Giblin, G. M. P.; Hall, A.; Hurst, D. N.; Rawlings, D. A.; Scoccitti, T. WO 2006066968, **2006**; *Chem. Abstr.* **2006**, 145, 83231.

(3) (a) Casiraghi, G.; Salerno, G.; Sartori, G. *Synthesis* **1975**, 186. (b) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919. (c) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G.; Bocelli, G. *Tetrahedron Lett.* **1989**, *30*, 1121. (d) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869. (e) Saimoto, H.; Yoshida, K.; Tetsuya, M.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768. (f) Hewawasam, P.; Erway, M. *Tetrahedron Lett.* **1998**, *39*, 3981. (g) Rondot, C.; Retailleau, P.; Zhu, J. *Org. Lett.* **2007**, *9*, 247. (h) Chen, X.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 3962.

(4) For a review, see: Casnati, G.; Casiraghi, G.; Pochini, A.; Sartori, G.; Ungaro, R. *Pure Appl. Chem.* **1983**, *55*, 1677.

(5) For leading references, see: Bocelli, G.; Cantoni, A.; Sartori, G.; Maggi, R.; Bigi, F. *Chem. Eur. J.* **1997**, *3*, 1269.

(6) For selected examples, see: (a) Casiraghi, G.; Casnati, G.; Cornia, M.; Sartori, G.; Ungaro, R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 2077. (b) Casnati, G.; Colli, M.; Pochini, A.; Ungaro, R. *Chim. Ind. (Milan)* **1977**, *59*, 764. (c) Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, M.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 318. (d) Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803. (e) Casiraghi, G.; Casnati, G.; Dradi, E.; Messori, R.; Sartori, G. *Tetrahedron* **1979**, *35*, 2061. (f) Casiraghi, G.; Casnati, G.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 805. (g) Mibu, N.; Sumoto, K. *Chem. Pharm. Bull.* **2000**, *48*, 1810.

(7) Sartori, G.; Maggi, R.; Bigi, F.; Arienti, A.; Porta, C.; Predieri, G. *Tetrahedron* **1994**, *50*, 10587.

(8) Use of $Et_2O$ on scale is complicated by its high volatility and flammability, MTBE is a much preferred alternative.

(9) For the use of $Et_3N/MgCl_2$ to promote selective ortho-formylation of phenols, see: (a) Hofslokken, N. U.; Skattebol, L. *Acta Chem. Scand.* **1999**, *53*, 258. (b) Hansen, T. V.; Skattebol, L. *Org. Synth.* **2005**, *82*, 64.

(10) This becomes the main reaction pathway if phenol is omitted from the reaction mixture. For a recent report of a similar process, see: Abaee, M. S.; Sharifi, R.; Mojtahedi, M. M. *Org. Lett.* **2005**, *7*, 5893.

(11) Solvents investigated; acetone, MeCN, MTBE, chlorobenzene, cyclopentyl methyl ether, $CH_2Cl_2$, EtOH, EtOAc, *i*-PrOAc, 2-methyltetrahydrofuran, THF, α,α,α-trifluorotoluene, and sulfolane.

(12) This reaction will be described in more detail in a future report. Addition of $ZnBr_2$ does not have a significant effect on the rate of the desired reduction but greatly reduces the rate of competitive dechlorination. For a report on the use of zinc halides to modulate the activity of hydrogenation catalysts, see: Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. *Synthesis* **2003**, 1657.