Cobalt-Mediated Aldol-Type Reactions

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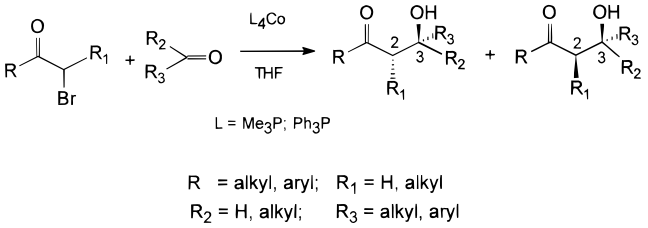
We have already reported that a Co(0)−trimethylphosphine complex is an efficient mediator for one-pot Reformatsky-type reactions of halogen derivatives with carbonyl compounds to give secondary and tertiary alcohols.[1] The investigation was extended to other low-oxidation-state cobalt complexes, which have also proven effective, with several advantages over the classical zinc-mediated Reformatsky reaction,[2] the most notable being the milder conditions and the higher yields of addition products.[3]

We have now found that α-halo ketones react with carbonyl compounds (ketones and aldehydes) in the presence of low-oxidation-state cobalt complexes with phosphines to yield aldols as shown in Scheme 1.

Scheme 1



Results and Discussion

Two series of experiments were carried out. In the first, several combinations of α-halo ketones and carbonyl compounds (ketone or aldehyde) were simultaneously added via a "one pot" procedure to tetrakis(trimethylphosphine)cobalt(0), $Co[P(CH_3)_3]_4$, in equimolar amounts. The $Co[P(CH_3)_3]_4$ was selected first because it is a well-identified complex[4] obtained by reducing a mixture of anhydrous Co(II) chloride and trimethylphosphine (1:4 mole ratio) with magnesium metal in tetrahydrofuran. Furthermore, it may be expected, by analogy with the Reformatsky-type reactions,[1] to undergo oxidative addition with α-halo ketones yielding intermediate species capable of functioning as nucleophiles.

In the second series of experiments, most of the reactions performed with $Co[P(CH_3)_3]_4$ were investigated by substituting trimethylphosphine with triphenylphosphine as a ligand-to-cobalt. This investigation had two objectives: one was to explore if the properties of the ligand could influence the effectiveness of the cobalt complex in promoting aldol reactions. The other and more specific objective was to find a ligand less toxic and easier to handle with respect to trimethylphosphine.

The results obtained, summarized in Table 1, illustrate some general features of this cobalt-mediated aldol reaction.

Addition of α-bromo ketones to carbonyl compounds in the presence of $Co[P(CH_3)_3]_4$ resulted in the formation of aldol products in high yields at a reaction temperature (0 °C) convenient for preparative work. α,β-Unsaturated aldehydes as cinnamaldehyde gave only 1,2-addition product. Nonselective condensations (autocondensation of the halo ketone or of the carbonyl electrophile) were not observed, not even when aldehydes such as acetaldehyde or phenyl acetaldehyde were used. Aldols were formed at the original site of the bromine atom and with moderate to good diastereoselectivity, depending on both the electrophile and on the bromo compound.

No appreciable differences have been observed when trimethylphosphine is substituted with triphenylphosphine as a ligand-to-cobalt.[5] The latter, more convenient to use, had the added advantage that it could be recovered at the end of the reaction.

The tested α-chloro ketones gave sluggish reactions and significant amounts of the common side products that plague typical aldol condensations such as polycondensation products. This problem, however, was overcome by "in situ" conversion of chlorides to the corresponding iodides in the presence of potassium iodide. Iodides gave generally high yields of aldols.

Under the experimental conditions tested, threo selectivity was generally observed with both bromo and iodo ketones.[6] The regioselectivity of this aldol reaction was demonstrated by treatment of 3-iodobutan-2-one (prepared in situ from 3-chlorobutan-2-one) with benzaldehyde to afford the expected β-hydroxy ketone without any contamination of the regioisomer.

In order to improve the diastereoisomeric ratio and to test a possible dependence from the reaction time, the reaction between phenylacetaldehyde and α-bromo propiophenone was investigated at long reaction time and gave a higher yield of the threo aldol (Table 1, entry 10).

A time/diastereoisomeric ratio dependence was also verified in the reaction between α-bromo propiophenone and pivalaldehyde (Table 1, entry 7).

For one model system (α-bromopropiohenone and benzaldehyde), the reaction was also carried out at different temperatures (Table 2). In each case, the aldol was obtained in good yield. Temperature, however, had a significant effect on the diastereoselectivity of the reaction, which proceeded smootly at low temperature (−78 °C) to give the erythro aldol as the major diastereoisomer.

The reactions also proceeded cleanly when carried out with a 10/1 mole ratio of the organic reagents to cobalt, in the presence of magnesium metal (Table 3). The fact that the reaction can be carried out with a substoichio-

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(1) Orsini, F.; Pelizzoni F.; Pulici, M.; Vallarino, L. M. *J. Org. Chem.* **1994**, *59*, 1−3.

(2) Orsini, F.; Pulici, M.; Vallarino. L. M. *J. Organomet. Chem.* **1995**, *495*, C1−C5.

(3) Orsini, F.; Pulici, M. Highlights on Recent Advancement on Reformatsky-Type Reactions: the Cobalt Approach. In *Trends in Organometallic Chemistry*; Research Trends Ed.; Trivandrum, India, 1994; Vol. 1, pp 625−667.

(4) (a) Klein, H. F. *Angew. Chem.* **1971**, *83*, 363. (b) Klein, H. F.; Karsch, H. H. *Chem Ber.* **1975**, *108*, 944−955.

(5) The species formed from Co(II) by reduction with magnesium metal in the presence of 4 equiv of triphenylphosphine was not isolated. The course of the reduction with magnesium and of the addition to carbonyl compounds suggests the formation of a Co(0) species. However, for correcteness, we will refer to it as a low-state-oxidation complex.

(6) The stereochemical assignment was based on the ^1H NMR vicinal coupling constant $J_{2,3}$ [$J_{2,3}$ (threo) > $J_{2,3}$ (erythro)][14] and on the ^{13}C NMR[15] resonances of C_2, C_3, R_1, assuming hydrogen-bonded structures in a chair conformation with the maximum number of R substituents equatorial. In the reaction between α-bromopropiophenone and pivalaldehyde the stereochemical assignment based on NMR data can be misleading as the favored conformation in the threo isomer would place the bulky *tert*-butyl group and the methyl group apart with, as a consequence, a small $H_2-C-C-H_3$ angle.

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Table 1. Cobalt-Mediated Nucleophilic Addition of α-Halo Ketones to Carbonyl Compounds[a]

		carbonyl compd		L = Me_3P			L = Ph_3P		
entry	α-halo ketone	R_2	R_3	yield (%)	threo/erythro[b]	time (min)	yield (%)	threo/erythro[b]	time (min)
1	α-bromoacetophenone	H	C_6H_5	59[c]		90	57[c]		90
2	4-methoxy-α-bromoacetophenone	H	C_6H_5	85		90	85		120
3	4-methoxy-α-bromoacetophenone	H	$C_6H_5CH{=}CH$	81[d]		90	83		120
4	4-methoxy-α-bromoacetophenone		$-(CH_2)_5-$	78		120	82		90
5	α-bromopropiophenone	H	C_6H_5	84	91/9	60	86	91/9	90
6	α-bromopropiophenone	H	$C_6H_5CH{=}CH$	78	88/12	120	81	87/13	120
7	α-bromopropiophenone	H	$(CH_3)_3C$	83[e]		30	81[e]		50
8	α-bromopropiophenone		$-(CH_2)_5-$				88		60
9	α-bromopropiophenone	H	CH_3	87	80/20	120	87	80/20	120
10	α-bromopropiophenone	H	CH_2Ph	90	88/12	480	90	70/30	60
								90/10	480
11	1-bromo-3,3-dimethyl-butan-2-one	H	C_6H_5	85		120	83		120
12	α-chloroacetophenone	H	C_6H_5	mixture[i]		480			
				54[d,f,j,l]		180			
13	2-chlorocyclohexanone	H	C_6H_5	25 [14][g−i,k]	90/10	480			
				85[f,j,l]	75/25	120			
14	2-chlorocyclopentanone	H	C_6H_5	20 [10][g−i,k]	77/23	480			
				50 [25][f,g,j,l]	79/21	180			
15	3-chlorobutan-2-one	H	C_6H_5	mixture[i]		480			
				86[f,j,l]	65/35	180			

[a] The reactions were performed at 0 °C, if not otherwise stated. [b] The stereochemistry was assigned from the coupling constant $J_{2,3}$ in the ^1H NMR spectrum[14] and from the ^{13}C NMR resonance of C_2, C_3.[15] [c] Low recovery of crude material was observed. [d] Yield determined by ^1H NMR. [e] Two diastereoisomers were obtained in 91/9 ratio. A longer reaction time (3 h) gave a 72/28 diastereoisomeric ratio. In this case the stereochemical assigment is doubtful since the $J_{2,3}$ are very similar (2.0 and 3.5 Hz, respectively).[6] [f] The reaction was performed in the previous "in situ" formation of the corresponding iodo ketone in the presence of KI. [g] Yields in brackets refer to the product formed by water elimination from the hydroxilic function. [h] Bis-adducts, from condensation on both α positions of the halo ketone, were observed (~20%).[14] [i] The reaction was performed at 25 °C. [j] Reaction performed in the presence of dimethylformamide. [k] Starting benzaldehyde (33%) and dihydrobenzoin (meso and racemate, 30%) were recovered. [l] Yield determined from α-chloro ketone.

Table 2. Influence of the Temperature on the Reaction between α-Bromopropiophenone and Benzaldehyde[a]

T (°C)	time (h)	yield (%)	threo/erythro
0	1	84	91/9
−30	3	84	88/12
−78	5	82	30/70

[a] The reactions were carried out under stoichiometric conditions with a 1/1 reagent-to-cobalt molar ratio.

metric amount of the Co-phosphine complex offsets the disadvantage inherent in the use of trimethylphosphine. In most cases $Co[P(CH_3)_3]_4$ was therefore used to avoid purification of the aldol from the phosphine at the end of the reaction. In few cases, however, triphenylphosphine was also tested as a ligand-to-cobalt and gave essentially the same results obtained with trimethylphosphine. The course and the end point of the reaction were easily monitored by the alternation of the yellow-brown color of the Co(0) complex and the deep purple-blue color of the Co(II) complex during the addition of the α-halo ketone/carbonyl compound reagents. The high yield of the aldol was obtained when the reaction was worked up as soon as the organic reagents were added, and the yellow-brown color of Co(0) complex persisted for few minutes. Prolonged reaction times served only to degrade the initially formed aldol to form byproducts.

To investigate whether an organomagnesium compound might be involved,[7] parallel experiments were performed adding the α-bromo ketones and the carbonyl compounds reported in Table 3 to magnesium alone in tetrahydrofuran. The amounts of bromo ketone, aldehyde, and magnesium were the same in both series of experiments, and so were the other experimental conditions (temperature, time of reaction, speed of stirring). The reactions in the absence of cobalt were generally slower, less reproducible, and required a variable period of induction. Once started, the reactions afforded the expected aldol, in variable amounts depending on the organic reagents and on the speed of the reaction, accompanied by several byproducts (detected in the ^1H NMR spectrum of the crude reaction mixture) and occasionally by starting organic reagents. In one case, when 1-bromo-3,3-dimethylbutan-2-one was used, no reaction was observed.

These results indicate that, in the absence of Co−complex, magnesium alone is capable of giving *β*-hydroxy ketones from carbonyl compounds and α-bromo ketones, but a different composition of the reaction mixture is generally observed under the same experimental conditions. One more piece of evidence that might prove the actual involvement of cobalt also under substoichiometric conditions is the color of the solution that continuosly and swiftly changes from yellow-brown (Co(0) complex) to deep purple-blue (Co(II) complex) during the addition of the organic reagents and that allows a timely visualization of the end point of the reaction with minimization of the byproducts. It is therefore reasonable to assume that, as far as the reduction Co(II)/Co(0) is faster than the reaction of magnesium with the α-halo ketone, the soluble Co(0)−phosphine complex reacts with the α-halo ketone before magnesium, which must work in the heterogeneous phase. A cobalt species is no doubt involved in the substoichiometric reaction of 1-bromo-3,3-dimethylbutan-2-one with benzaldehyde.

As observed for Co-mediated Reformatsky-type reactions, the obtained results and the stoichiometry of the reaction (1/1/1 ratio reagents/Co-complex)[8] suggest a mechanism involving the oxidative addition of the α-halo ketone to the Co(0) complex to give a Co(II) intermediate species. This is also supported, as mentioned above, by

(7) Preparation of the magnesium enolate from various 2-bromo-2-alkyl-5,5′-dimethylcyclopentanones and α-bromo-α′-*tert*-butyl ketones in ether-benzene solutions at reflux, followed by condensation with carbonyl compounds was reported: Fellmann, P; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349−1357.

(8) A 1:1:0.5 organic reagents/Co ratio was also tested and produced a ~ 50% recovery of starting product.

Table 3. Cobalt (Substoichiometric Conditions) and Magnesium-Mediated Addition of α-Bromo Ketones to Carbonyl Compounds

		carbonyl compd					
entry	α-halo ketone	R_2	R_3	yield (%)	threo/erythro[a]	procedure[b]	time (min)
1	4-methoxy-α-bromoacetophenone	H	C_6H_5	80[c]		A	40
2	4-methoxy-α-bromoacetophenone	H	C_6H_5	35[d,e]		B	40
3	α-bromopropiophenone	H	C_6H_5	84[f]	88/12	A	40
4	α-bromopropiophenone	H	C_6H_5	27[g]	90/10	A	150
5	α-bromopropiophenone	H	C_6H_5	66[h]	82/18	B	40
6	α-bromopropiophenone	H	$(CH_3)_3C$	85[c,i]		A	20
7	α-bromopropiophenone	H	$(CH_3)_3C$	40[j,k]		B	20
8	α-bromopropiophenone		$-(CH_2)_5-$	80[l]		A	35
9	α-bromopropiophenone		$-(CH_2)_5-$	75		B	35
10	α-bromopropiophenone	H	CH_2Ph	95[c]	70/30	A	30
		H	CH_2Ph	92[c,l]	70/30	A	35
11	α-bromopropiophenone	H	CH_2Ph	62[m]	75/25	B	35
12	1-bromo-3,3-dimethyl-butan-2-one	H	C_6H_5	83[n]		A	30
				83[l]		A	50

[a] The stereochemistry was assigned from the coupling constant $J_{2,3}$ in the ^{1}H NMR spectrum[14] and from the ^{13}C NMR resonance of C_2,C_3.[15] [b] Procedure A (substoichiometric in Co(0) complex): the halo ketone and the carbonyl compound were added to the Co complex in a 10/10/1 molar ratio at 0 °C, if not otherwise stated. Procedure B: the reaction was performed in the presence of magnesium alone at 0 °C, if not otherwise stated. [c] Yield determined by ^{1}H NMR. [d] Yield of isolated products. [e] Benzyl alcohol (10%), dihydrobenzoin (meso and racemate, 10%), starting reagents (30%), and other unidentified compounds were observed in the ^{1}H NMR spectrum of the crude product. [f] 1,3-Diphenyl-2-methyl-1,3-propanediol (4%) was obtained as a byproduct. [g] Several byproducts were observed. One of them was identified as 1,3-diphenyl-2-methyl-1,3-propanediol (15%). [h] Starting reagents (31%) were recovered. [i] Two diastereoisomers were obtained in 91/9 ratio. In this case the stereochemical assigment is doubtful since the $J_{2,3}$ are very similar (2.0 and 3.5 Hz, respectively).[6] [j] Starting bromo ketone was observed in the ^{1}H NMR spectrum. [k] Two diastereoisomers were obtained in 91/9 ratio. A longer reaction time (90 min) gave 65% yield of aldol (75/25 diastereoisomeric ratio). [l] Triphenylphosphine was used as a ligand-to-cobalt. [m] Several unidentified products were detected in the ^{1}H NMR spectrum. [n] No reaction was observed in the presence of magnesium alone.

the typical purple-blue color of the tetrahedral Co(II)−phosphine complex, which appears in the solution of substoichiometric reactions.

The intermediate Co(II)-species could not be isolated under the conditions of the reactions. Therefore, its identity (C-metalated species or enolate) cannot be determined with certainty.

However, the stereochemical outcome of the reactions and the trends of the diastereoselection, similar for the cobalt-mediated and for the magnesium-mediated reactions,[9] would suggest the involvement of a Co−enolate and a chairlike six-membered transition state with the metal bonded to the oxygen atoms of the enolate and the carbonyl compound.

Conclusion

The aldol condensation is one of the most important tools for C−C bond formation, and several methods were developed to overcome the problems connected with this fundamental reaction. The use of a preformed enolate or enol ether of one of the components has been the most successful.[10] The former usually requires strictly anhydrous conditions, cosolvent (such as HMPT), bases, and, in some cases, multistep procedures to achieve a good stereoselectivity; the latter require Lewis acids to form aldols. The most common method for generating a metal−enolate is based on metal−hydrogen exchange. Occasionally, oxidative metalations have been used:[11] generally, in these cases activation of the metal was essential for the success of the reaction.

The cobalt-mediated aldol reaction proceeds cleanly and smoothly,[12] requires no additives (acids or bases) and no cosolvents, and does not need freshly distilled and dried solvents.[13] The fact that the solid, air-stable triphenylphosphine can be used as a ligand-to-cobalt and that the reactions can be carried out with a 10/1 molar ratio of reagents-to-cobalt are added advantages. Finally, with respect to other methods that involve oxidative metalation, the use of a soluble Co(0) complex offsets the disadvantages of heterogeneous reactions and activation of the metal.

In conclusion, this new procedure represents a valid supplement to the existing procedures.

Experimental Section

General Methods. Trimethylphosphine (1 M solution in tetrahydrofuran), triphenylphosphine, tetrahydrofuran (THF), anhydrous, and tetrahydrofuran, ACS reagent, were purchased from Aldrich and used as received. Anhydrous cobalt(II) chloride was heated at 120−150 °C for 2 h prior to use. Magnesium metal (as turnings) was activated by treatment with a solution of 1,2-dichloroethane in THF, followed by washing with THF. α-Chloro- and α-bromo ketones and carbonyl compounds were purchased from Aldrich and used as received. α-Iodo ketones were prepared from the corresponding α-chloro ketones by reaction with KI in tetrahydrofuran−dimethylformamide and directly used. Proton nuclear magnetic resonence (^{1}H NMR) spectra were obtained with Varian XL-200 and Bruker AC-300 instruments. Thin layer chromatography (TLC) was carried out

(9) The enolate structure was unambigously assigned for some magnesium derivatives: Fellmann, P; Dubois, J. E. *Tetrahedron Lett.* **1977**, 247−250.

(10) Mukayama, T. *Org. React.* **1982**, *28*, 203−331.

(11) For aldol-type reactions based on oxidative metalation of the halo carbonyl compounds, see the following for examples. (a) Titanium: Ishihara, T.; Yamanaka, T.; Ando, T. *Chem. Lett.* **1984**, 1165−1168. (b) Chromium: Dubois, J. E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* **1985**, *26*, 4371−4372. (c) Boron: Nozaki, K.; Oshima K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041−1044. (d) Aluminum: Matsubara, S.; Tsuboriwa, N; Morizava, Y.; Oshima K.; Nozaki, H. *Bull. Soc. Chim. Jpn.* **1984**, *57*, 3243−3246. (e) Tin: Mukaiyama, T.; Harada, T. *Chem. Lett.* **1982**, 161−164; Kato, J. I.; Mukaiyama, T. *Chem. Lett.* **1983**, 1727−1728. (f) Antimony: Huang, Y. Z.; Chen C.; Shen, Y. *J. Chem. Soc., Perkin Trans.* **1988**, *1*, 2855−2859. (g) Cerium: Fukuzawa, S.; Sumimoto, N.; Fijinama, T.; Sakai, S. *J. Org. Chem.* **1990**, *55*, 1628−1631.

(12) Complexes of Co(II) acetate with 2,2′-bipyridine were reported to promote aldol condensation of aldehydes with ketones in DMF at 80 °C for several hours to give α,β-unsaturated ketones: Irie, K; Watanabe K. I. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1366−1371.

(13) In one run the reaction of α-bromopropiophenone and benzaldehyde was performed in absolute tetrahydrofuran (0 °C, 1 h) and afforded 86% of the expected aldol (91/9 threo/erythro diastereoisomeric ratio).

on silica gel plates (60 F254, Merk); zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol/H_2SO_4 9:1 followed by heating at 100 °C.

All reactions were carried out at 25 °C in a dry nitrogen atmosphere.

The tetrakis(trimethylphosphine)cobalt(0), $Co[P(CH_3)_3]_4$, was prepared as previously reported[1,4]

Preparation of the Low-Valent Cobalt−Triphenylphosphine Complex. Activated magnesium turnings (500 mg), anhydrous cobalt(II) chloride (130 mg, 1 mmol), and triphenylphosphine (1.05 g, 4 mmol) were added to THF (4.0 mL). The mixture was stirred until the original blue color turned to yellow-brown. The clear supernatant was transferred by syringe to another flask immediately before use.

Typical Procedure for the Cobalt-Mediated Stoichiometric Reactions. The filtered solution of the Co−phosphine complex (1 mmol) was treated dropwise with a solution containing α-bromopropiophenone (1 mmol) and benzaldehyde (1 mmol) in tetrahydrofuran (4 mL) at 0 °C. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane 20/80). When the organic reagents were no longer present, the solution was diluted with ethyl acetate, poured into crushed ice/0.1 N HCl, and extracted with ethyl acetate (3 × 15 mL). The combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude material was flash chromatographed over silica gel (ethyl acetate/*n*-hexane 15/85) and yielded 84% of 1-phenyl-2-methyl-3-hydroxy-3-phenylpropan-1-one (91/9 threo/erythro ratio).

Threo: IR 1480, 1545, 1590, 1673, 3482, 3598 cm^{-1}; ^1H NMR δ 1.05 (3 H, d, J = 7.5 Hz), 3.84 (1 H, dq, J = 7.5, 7.5, 7.5, 7.5 Hz), 3.86 (1H, s, disappears with D_2O), 4.98 (1 H, d, J = 7.5 Hz), 7.17−7.78 (8 H, m), 7.98 d (2 H, d, J = 8.0 Hz); ^{13}C NMR: 16.27 (q), 48.67 (d), 77.45 (d), 127.43 (d), 128.53 (d), 4 × 129.10 (d), 2 × 129.24 (d), 2 × 133.86 (d), 137.62 (s), 143.01 (s), 205.51 (s); MS m/z 240 (M^+), 222 ($M^+ - H_2O$), 207 ($M^+ - CH_3$), 105 (C_6H_5CO).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.51; H, 6.24.

Erythro (detected in the ^1H NMR and ^{13}C NMR spectra of the threo/erythro mixture): ^1H NMR δ 1.21 (3 H, d, J = 7.5 Hz), 3.71 (1 H, dq, J = 4.0, 7.5, 7.5, 7.5 Hz), 3.86 (1 H, s, disappears with D_2O), 5.21 (1 H, d, J = 4.0 Hz), 7.17−7.78 (8 H, m), 7.91 (2 H, d, J = 8.0 Hz); ^{13}C NMR 12.10 (q), 47.93 (d), 73.96 (d), 126.77 (d), 127.96 (d), 4 × 129.10 (d), 2 × 129.24 (d), 2 × 133.86 (d), 136.50 (s), 143.01 (s), 205.90 d (s).

Typical Procedure for the Cobalt-Mediated Substoichiometric Reactions. Triphenylphoshine (524 mg, 2 mmol) was added to a mixture of activated magnesium turnings (300 mg) and anhydrous $CoCl_2$ (65 mg, 0.5 mmol) in tetrahydrofuran (4 mL). The reaction was stirred at room temperature until the yellow-brown color of the low-oxidation-state cobalt complex developed. The mixture was then cooled at 0 °C, and a tetrahydrofuran solution (6 mL) of α-bromopropiophenone (5 mmol) and benzaldehyde (5 mmol) was added dropwise at 0 °C: the speed of addition was modulated so as to preserve the original brown color and reduce to a minimum the time of development of the blue color (Co(II)-complex). At the end of the reaction (40 min), indicated by the persistence for few minutes of the yellow-brown color of the low-oxidation-state Co complex, the reaction mixture was diluted with ethyl acetate, poured into crushed ice/0.1 N HCl, and extracted three times with ethyl acetate. The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude 1-phenyl-2-methyl-3-hydroxy-3-phenyl-propan-1-one did not require further purification (84% yield, 88/12 threo/erythro ratio by 1H NMR analysis). In one run a longer reaction time (3 h) afforded the aldol (27% yield) accompanied by several byproducts: one of them was identified as 1,3-diphenyl-2-methyl-1,3-propandiol (15% yield).

1,3-Diphenyl-2-methyl-1,3-propanediol: ^1H NMR (main diastereoisomer) δ 1.25 (3 H, d, J = 7.5 Hz), 2.18 (1 H, ddq, J = 4.2, 7.0, 7.5, 7.5, 7.5 Hz), 4.70 (1 H, d, J = 7.0 Hz), 5.02 (1H, d, J = 4.2 Hz), 7.2 - 7.4 (10 H); ^{13}C NMR: 11.22 (q), 45.80 (d), 74.26 (d), 74.27 (d), 2 × 125.97 (d), 2 × 126.21 (d), 126.91 (d), 127.52 (d), 2 × 127.95 (d), 2 × 128.38 (d), 2 × 143.49 (s); MS m/z 242 (M^+), 224 ($M^+ - H_2O$), 209 ($M^+ - H_2O$, $- CH_3$). Minor diastereoisomer (detected in the ^1H NMR spectrum): δ 1.22 (3 H, d, J = 7.5 Hz), 2.45 (1 H, dq, J = 7.0, 7.5, 7.5 7.5 Hz), 4.05 (1 H, d, J = 7.0 Hz), 5.65 (1H, s), 7.2−7.4 (10 H).

Typical Procedure for the Magnesium-Mediated Reactions. To activated magnesium turnings (300 mg) in tetrahydrofuran (4 mL) was added a tetrahydrofuran solution (6 mL) of α-bromopropiophenone (5 mmol) and benzaldehyde (5 mmol) dropwise under stirring at 0 °C. The progress of the reaction was monitored by TLC and compared with the reaction performed in the presence of cobalt. After 40 min, the reaction mixture was diluted with ethyl acetate, poured into crushed ice/aqueous HCl, and extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude material was flash-chromatographed (silica gel, ethyl acetate/*n*-hexane 20/80) and afforded 1-phenyl-2-methyl-3-hydroxy-3-phenylpropan-1-one (66%, 82/18 threo/erythro ratio) accompanied by starting bromo ketone (31%). In one run a longer reaction time (3 h) afforded aldol (60%), starting bromo ketone (20%), 1,3-diphenyl-2-methyl-1,3-propanediol (10%), and dihydrobenzoin (meso and racemate 10%, identified by TLC and ^1H NMR analysis).

1-Phenyl-3-hydroxy-3-phenylpropan-1-one (entry 1, Table 1): colorless solid: mp = 48−50 °C (diisopropyl ether) (lit.[14] mp = 50−53 °C); IR 1541, 1599, 1674, 3525, 3676 cm^{-1}; ^1H NMR δ 3.28 (1 H, s, disappears with D_2O), 3.38 (2 H, d, J = 6.5 Hz), 5.33 (1 H, dd, J = 6.5, 6.5 Hz), 7.2−7.6 (8 H, m), 7.95 (2 H, dd, J = 8.6, 2.2 Hz); ^{13}C NMR 48.07 (t), 70.71 (d), 126.42 (d), 128.32 (d), 2 × 128.82 (d), 2 × 129.24 (d), 2 × 129.32 (d), 129.62 (d), 134.30 (d), 136.50 (s), 143.67 (s), 200.79 (s); MS m/z 226 (M^+), 208 ($M^+ - H_2O$), 120 ($C_6H_5C(OH)=CH_2$), 105 (C_6H_5CO).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.77; H, 6.25.

1-(4′-Methoxyphenyl)-3-hydroxy-3-phenylpropanone (entry 2, Table 1): colorless amorphous solid; IR 1515, 1578, 1602, 1670, 3510, 3666 cm^{-1}; ^1H NMR δ 3.29 (2 H, d, J = 4.5 Hz), 3.5 (1 H, s, disappears with D_2O, OH), 5.30 (1 H, t, J = 4.5 Hz), 6.90 d (2 H, d, J = 8.8 Hz), 7.15−7.5 (5 H, m), 7.90 (2 H, d, J = 8.8 Hz); ^{13}C NMR 46.93 (t), 55.43 (q), 70.27 (d), 2 × 113.50 (d), 2 × 127.4 (d), 128.49 (d), 2 × 128.49 (d), 2 × 130.77 (d), 130.01 (s), 143.36 (s), 164.04 (s), 198.57 (s); MS m/z 256 (M^+), 238 ($M^+ - H_2O$), 150 ($CH_3OC_6H_5C(OH)=CH_2$), 135 (150 − CH_3).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.56; H, 6.34.

1-(4′-Methoxyphenyl)-3-hydroxy-5-phenylpent-4-en-1-one (entry 3, Table 1): colorless solid: mp 76−78 °C (diisopropyl ether/ethyl acetate); IR 1512, 1576, 1603, 1668, 3517, 3673 cm^{-1}; ^1H NMR δ 3.12 and 3.20 (2 H, AB system, J_{AB} = 18.0, J_{AX} = 5.5, J_{BX} = 4.0 Hz), 3.61 (1 H, s, disappears with D_2O), 3.86 (3 H, s), 4.93 (1 H, ddd, J = 6.9, 5.5, 4.0 Hz), 6.32 (1 H, dd, J = 15.4, 6.9 Hz), 6.71 (1 H, d, J = 15.4 Hz), 6.95 (2 H, d, J = 8.8 Hz), 7.20−7.40 (5H, m), 7.95 (2 H, d, J = 8.8 Hz); ^{13}C NMR 53.74 (t), 64.38 (d), 77.71 (q), 2 × 122.84 (d), 2 × 135.45 (d), 136.55 (d), 2 × 137.47 (d), 138.87 (s), 139.22 (d), 2 × 139.46 (d), 139.66 (d), 145.71 (s), 172.92 (s), 207.41 (s); MS m/z 282 (M^+), 264 ($M^+ - H_2O$), 150 ($CH_3OC_6H_5C(OH)=CH_2$), 135 (150 − CH_3).

Anal Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.77; H, 6.45.

1-(4′-Methoxyphenyl)-3-(1"-hydroxycyclohexyl)propan-1-one (entry 4, Table 1): colorless prisms; mp 67−69 °C (diisopropyl ether−ethyl acetate); IR 1500, 1545, 1590, 1670, 3483, 3679 cm^{-1}; ^1H NMR δ 1.25 (2 H, m), 1.45 (4 H, m), 1.75 (4 H, m), 3.05 (2 H, s), 3.85 (3 H, s), 3.85 (1 H, s, disappears with D_2O), 6.92 (2 H, d, J = 9.5 Hz), 7.92 (2 H, d, J = 9.5 Hz); ^{13}C NMR 22.12 (t), 2 × 25.92 (t), 2 × 37.96 (t), 47.25 (t), 55.60 (q), 71.01 (s), 2 × 113.93 (d), 2 × 130.61 (d), 130.61 (s), 164.02 (s), 200.53 (s). MS m/z 248 (M^+), 230 ($M^+ - H_2O$), 150 ($CH_3OC_6H_5C(OH)=CH_2$), 135 (150 − CH_3), 107 ($CH_3OC_6H_5$).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.36; H, 8.00.

1-Phenyl-2-methyl-3-hydroxy-5-(4′-methoxyphenyl)pent-1-en-5-one (entry 6, Table 1). *Threo*: IR 1676, 1711, 3505 cm^{-1}; ^1H NMR δ 1.27 (3 H, d, J = 7.3 Hz), 3.0 (1 H, s, disappears with D_2O), 3.71 (1 H, qd, J = 7.3, 7.3, 7.3, 7.3 Hz), 4.60 (1 H, dd, J = 7.3, 7.3 Hz), 6.28 (1 H, dd, J = 17.4, 7.3 Hz), 6.68 (1 H, d,

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J = 17.4 Hz), 7.20−7.65 (8 H, m), 8.00 (2 H, d, J = 8.7 Hz); ^{13}C NMR 15.97 (q), 47.00 (d), 75.88 (d), 2 × 127.16 (d), 3 × 129.10 (d), 3 × 129.30 (d), 129.31 (d), 130.37 (d), 132.69 (d), 133.94 (d), 137.00 (s), 137.10 (s), 205.02 (s); MS m/z 266 (M^+), 248 ($M^+ - H_2O$), 233 (248 − CH_3), 134 ($C_6H_5C(OH)$═$CHCH_3$), 105 (C_6H_5CO).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.41; H, 6.74.

Erythro (detected in the ^{1}H NMR and ^{13}C NMR spectra of the threo/erythro mixture): ^{1}H NMR δ 1.32 (3H, d, J = 7.3 Hz), 3.0 (1 H, s, disappears with D_2O), 3.80 (1 H, m), 4.70 (1 H, m), 6.23 (1 H, dd, J = 17.4, 7.3 Hz), 6.70 (1 H, d, J = 17.4 Hz), 7.20−7.65 d (8 H, m), 7.80 (2 H, d, J = 8.7 Hz); ^{13}C NMR 12.44 (q), 46.12 (d), 72.91 (d), 127.16 (d), 127.18 (d), 128.38 (d), 3 × 129.10 (d), 2 × 129.30 (d), 129.31 (d), 130.37 (d), 132.69 (d), 133.94 (d), 137.00 (s), 137.10 (s), 205.02 (s).

1-Phenyl-2,4,4-trimethyl-3-hydroxypentan-1-one (entry 7, Table 1). Major diastereoisomer: colorless thick oil; IR 1579, 1597, 1660, 3451 cm^{-1}; ^{1}H NMR δ 0.88 (9 H, s), 1.44 (3 H, d, J = 7.5 Hz), 3.45 (1 H, d, J = 2.0 Hz), 3.80 (1 H, dq, J = 7.5, 7.5, 7.5, 2.0 Hz), 5.75 (1 H, s, disappears with D_2O), 7.55 (2H, dd, J = 8.1, 8.1 Hz), 7.55 (1H, dd, J = 8.1, 8.1 Hz), 7.95 (2 H, d, J = 8.1 Hz); ^{13}C NMR: 19.71 (q), 3 × 27.58 (q), 37.05 (s), 38.44 (d), 85.75 (d), 2 × 128.94 (d), 129.11 (d), 2 × 133.55 (d), 134.36 (s), 208.90 (s); MS m/z 220 (M^+), 203 ($M^+ - H_2O$), 205 ($M^+ - CH_3$), 203, 163 ($M^+ - C(CH_3)_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.12; H, 9.12.

Minor diastereoisomer: colorless needles; mp = 58−60 °C (diisopropyl ether); IR 1579, 1597, 1660, 3451 cm^{-1}; ^{1}H NMR δ 0.99 (9 H, s), 1.25 (3 H, d, J = 7.5 Hz), 3.73 (1 H, d, J = 3.5 Hz), 3.72 (1 H, dq, J = 7.5, 7.5, 7.5, 3.5 Hz), 5.75 (1 H, s, disappears with D_2O), 7.48 (2 H, d, J = 8.1 Hz), 7.55 (1 H, d, J = 8.1 Hz), 7.95 (2 H, d, J = 8.1 Hz); ^{13}C NMR 15.25 (q), 3 × 26.91 (q), 35.70 (s), 41.05 (d), 77.58 (d), 2 × 128.46 (d), 2 × 128.77 (d), 133.26 (d), 133.80 (s), 205.65 (s); MS m/z 220 (M^+), 205 ($M^+ - CH_3$), 163 ($M^+ - C(CH_3)_3$), 134 ($C_6H_5C(OH)$═$CHCH_3$), 105 (C_6H_5CO).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.22; H, 9.12.

1-Phenyl-3-(1′-hydroxycyclohexyl)-2-methylpropan-1-one (entry 8, Table 1): ^{1}H NMR δ 1.25 (3 H, d, J = 7.5 Hz), 1.2−1.7 (10 H, m), 3.52 (1 H, q, J = 7.5, 7.5, 7.5, 7.5 Hz), 7.45 (2 H, dd, J = 8.0, 8.0 Hz), 7.55 (1 H, dd, J = 8.0, 8.0 Hz), 7.96 (2 H, dd, J = 8.0, 8.0 Hz); ^{13}C NMR 10.0 (q), 19.16 (t), 19.50 (t), 23.37 (t), 32.32 (t), 34.80 (t), 44.57 (d), 70.03 (s), 125.84 (d), 2 × 126.31 (d), 129.51 (d), 131.10 (d), 134.57 (s), 205.39 (s); MS m/z 232 (M^+), 214 ($M^+ - H_2O$), 134 ($C_6H_5C(OH)$═$CHCH_3$), 105 (C_6H_5CO).

1-Phenyl-2-methyl-3-hydroxybutan-1-one (entry 9, Table 1). *Threo*: ^{1}H NMR δ 1.22 (3 H, d, J = 7.9 Hz), 1.28 (3 H, d, J = 7.9 Hz), 2.70 d (1 H, s, disappears with D_2O), 3.40 (1 H, dq, J = 7.9, 7.9, 7.9, 7.9 Hz), 4.08 (1 H, dq, J = 7.9, 7.9, 7.9, 7.9 Hz), 7.22- 7.60 (3 H, m), 7.90 (2 H, d, J = 9.8 Hz); ^{13} C NMR 15.60 (q), 21.28 (q), 48.44 (d), 70.30 (d), 3 × 129.04 (d), 2 × 133.86 (d), 137.44 (s), 205.91 (s); MS m/z 178 (M^+), 160 ($M^+ - H_2O$), 145 (160 − CH3), 105 (C_6H_5CO).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.10; H, 7.89.

Erythro (detected in the ^{1}H NMR and ^{13}C NMR spectra of the threo/erythro mixture): ^{1}H NMR δ 1.21 (3 H, d, J = 6.8 Hz), 1.27 (3 H, d, J = 6.8 Hz), 2.70 (1 H, s, disappears with D_2O), 3.42 (1 H, dq, J = 6.8, 6.8, 6.8, 3.4 Hz), 4.22 (1 H, dq, J = 6.8, 6.8, 6.8, 3.4 Hz), 7.22−7.60 (3 H, m), 7.92 (2 H, d, J = 9.8 Hz); ^{13}C NMR 12.02 (q), 20.97 (q), 46.69 (d), 68.18 (d), 3 × 129.30 (d), 2 × 133.97 (d), 136.84 (s), 205.91 (s).

1-Phenyl-2-methyl-3-hydroxy-4-phenylbutan-1-one (Entry 10, Table 1). *Threo*: ^{1}H NMR δ 1.32 (3 H, d, J = 7.0 Hz), 2.75 (1 H, s, disappears with D_2O), 2.82 and 2.86 (2 H, ABX system, J_{AB} = 13.5 Hz, J_{AX} = 7.2 Hz, J_{BX} = 6.0 Hz), 3.58 (1 H, dq, J = 7.0, 7.0, 7.0, 7.0 Hz), 4.19 (1 H, ddd, J = 7.2, 7.0, 6.0 Hz), 7.15−7.30 (5 H, m), 7.40−7.60 (3H, m), 7.90−8.0 (2H, m); ^{13}C NMR: 15.07 (q), 41.24 (t), 44.32 (d), 75.04 (d), 126.21 (d), 2 × 128.23 (d), 2 × 128.46 (d), 2 × 129.19 (d), 131.78 (d), 133.15 (d), 136.46 (s), 138.28 (s), 205.70 (s); MS m/z 254 (M^+), 236 ($M^+ - H_2O$), 221 (236 − CH_3), 163 ($M^+ - C_6H_5CH_2$), 134 ($C_6H_5C(OH)$═$CHCH_3$), 120 ($C_6H_5CH_2CHO$), 105 (C_6H_5CO).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.15; H, 7.12.

Erythro (detected in the ^{1}H NMR and ^{13}C NMR mixture): ^{1}H NMR δ 1.36 (3 H, d, J = 7.0 Hz), 2.75 (1 H, s, disappears with D_2O), 2.78 and 2.84 (2 H, ABX system, J_{AB} = 13.9 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.8 Hz), 3.46 (1 H, dq, J = 7.0, 7.0, 7.0, 3.7 Hz), 4.32 (1 H, ddd, J = 7.4, 6.8, 3.7 Hz), 7.15−7.35 (5 H, m), 7.40−7.65 (3H, m), 7.85−7.95 (2H, m); ^{13}C NMR 12.07 (q), 41.37 (t), 44.31 (d), 73.32 (d), 127.19 (d), 2 × 127.09 (d), 2 × 129.22 (d), 2 × 129.34 (d), 129.36 (d), 129.95 (d), 134.02 (d), 138.94 (s), 138.95 (s), 205.77 (s).

1-*tert*-Butyl-3-hydroxy-3-phenylpropan-1-one (entry 11, Table 1): Colorless thick oil (lit.[14] mp = 22−23 °C); IR 1693, 3523 cm^{-1}; ^{1}H NMR δ 1.14 (9 H, s), 2.88 (2 H, d, J = 8.4 Hz), 3.55 (1 H, s, disappears with D_2O), 5.15 (1 H, dd, J = 8.4, 8.4 Hz), 7.25−7.40 d (5 H, m); ^{13}C NMR 3 × 26.61 (q), 44.85 (s), 46.06 (t), 70.49 (d), 126.23 (d), 126.24 (d) 128.00 (d), 2 × 128.94 (d), 143.85 (s), 216.88 (s); MS m/z 206 (M^+), 189 (M^+ − OH), 149 ($M^+ - C(CH_3)_3$), 131 (149 − H_2O), 107 (149 − CH_2CO).

Anal. Calcd for $C_{13}H_{18}O_2$ C, 75.69; H, 8.80. Found: C, 75.57; H, 8.78.

2-(1′-Phenyl-1′-hydroxymethyl)cyclohexan-1-one[14] (entry 13, Table 1). *Threo*: IR 1496, 1602, 1699, 3529, 3648 cm^{-1}; ^{1}H NMR δ 1.28 (2 H, m), 1.56 (2 H, m), 2.10 (2 H, m), 2.38 (2 H, m), 2.61 (1 H, ddd, J = 14.0, 8.4, 6.0 Hz), 3.45 (1 H, d, J = 2.6 Hz, disappears with D_2O), 4.70 (1 H, d, J = 8.4 Hz), 7.15−7.45 (5 H, m); MS m/z 204 (M^+), 186 ($M^+ - H_2O$), 105 (C_6H_5CHO), 98 ($(CH_2)_5CO$).

Erythro (detected in the ^{1}H NMR spectra of the threo/erythro mixture): ^{1}H NMR δ 1.28−2.8 (9H, m), 3.45 (1H, s, disappears with D_2O), 5.30 (1H, d, J = 3.2 Hz), 7.0−7.5 (5H, m).

2-(1′-Phenyl-1′-hydroxymethyl)cyclopentan-1-one[14] (entry 14, Table 1). *Threo*: IR 1734, 3446, 3606 cm^{-1}; ^{1}H NMR δ 1.4−2.3 d (6 H, m), 2.48 (1 H, m) 2.70 (1H, s, disappears with D_2O), 4.70 (1 H, d, J = 8.0 Hz), 7.2−7.4 (5 H, m); ^{13}C NMR 23.28 (t), 27.40 (t), 38.27 (t), 55.90 (d), 75.60 (d), 127.17 (d), 128.53 (d), 128.87 (d), 129.87 (d), 132.89 (d), 143.59 (s), 220.99 (s); MS m/z 190 (M^+), 172 ($M^+ - H_2O$), 130 (172 − CHCO), 107 (C_6H_5-CHOH), 84 ($(CH_2)_4CO$).

Erythro (detected in the ^{1}H NMR and ^{13}C NMR spectra of the threo/erythro mixture): ^{1}H NMR δ 1.4−2.3 (6 H, m), 2.48 (1 H, m), 2.70 (1H, s, disappears with D_2O), 5.30 (1 H, d, J = 4.0 Hz), 7.2−7.4 (5 H, m); ^{13}C NMR 21.05 (t), 29.87 (t), 39.76 (t), 56.71 (d), 71.95 (d), 126.16 (d), 127.75 (d), 128.87 (d), 129.23(d), 131.06 (d), 143.59 (s), 220.99 (s).

4-Phenyl-4-hydroxy-3-methylbutan-2-one (Entry 15, Table 1). *Threo*: ^{1}H NMR δ 0.80 (3 H, d, J = 7.9 Hz), 2.15 (3 H, s), 2.80 (1 H, dq, J = 9.5, 7.9, 7.9, 7.9 Hz), 3.6 (1 H, s, disappears with D_2O), 4.15 (1 H, d, J = 9.5 Hz), 7.15 - 7.25 (5 H, m); ^{13}C NMR 14.59 (q), 30.56 (q), 54.39 (d), 77.03 (d), 2 × 127.32 (d), 128.48 (d), 2 × 129.01 (d), 142.75 (s), 213.97 (s); MS m/z 178 (M^+), 160 ($M^+ - H_2O$), 117 (160 − CH_3CO), 107 (C_6H_5-CHOH).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.0; H, 7.90.

Erythro (detected in the ^{1}H NMR and ^{13}C NMR spectra of the threo/erythro mixture): ^{1}H NMR δ 1.00 (3 H, d, J = 7.9 Hz), 2.05 (3 H, s), 2.80 (1 H, dq, J = 7.9, 7.9, 7.9, 4.2 Hz), 3.6 (1 H, s, disappears with D_2O), 4.35 (1 H, d, J = 4.2 Hz), 7.15−7.25 (5 H, m); ^{13}C NMR 11.08 (q), 30.06 (q), 54.13 (d), 73.84 (d), 2 × 126.60 (d), 127.91 (d), 2 × 128.84 (d), 142.75 (s), 213.97 (s).

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