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An Efficient Cobalt(I)-Catalysed Reformatsky Reaction using α-Chloro Esters

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Dedicated to Professor Vincenzo Balzani on the occasion of his 70th birthday.

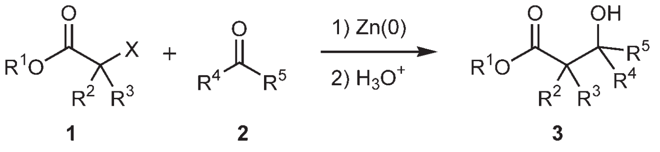
Abstract: An efficient cobalt(I)-catalysed Reformatsky reaction using α-chloro esters has been developed. The catalyst is prepared by reducing the cobalt(II) chloride (5%)/1,2-bis(diphenylphosphino)ethane (dppe)(5%)/zinc iodide (10%) system with zinc metal in acetonitrile in the presence of both the α-chloro ester and the carbonyl compound; good to excellent conversions to β-hydroxy esters are obtained at room temperature in 2.5 h.

Keywords: catalysis; α-chloro esters; cobalt(I); β-hydroxy esters; Reformatsky reaction

Introduction

The Reformatsky reaction is the zinc-promoted addition of α-halo esters **1** to carbonyl compounds **2** to give β-hydroxy esters **3** (Scheme 1).[1]

Despite its usefulness as a complement of the Grignard reaction, which cannot be applied to α-halo esters, nitriles, amides, etc., since its discovery in 1887[2] the Reformatsky reaction presented several problems in terms of yields, reproducibility, and competing reactions, such as ester or aldehyde self-condensation or adduct dehydration. The metal was early identified as the main factor responsible for the somewhat erratic performance of Reformatsky reactions which, when carried out with partially passivated zinc, required long heating in aromatic solvents with a variable induction time, while the adoption of activation techniques on the zinc surface resulted in clean reactions at or below room temperature. Several of the techniques to activate the zinc surface proposed so far have been recently reviewed;[1] they include i) the chemical activation of commercial zinc powder with acidic or oxidising agents, ii) the physical activation of the metal by means of ultrasound and microwaves, iii) the *in situ* production of highly reactive metal species by the reduction of zinc halides with alkali metals or potassium-graphite, iv) and the use of electrochemical techniques. Other low-valent metals have been also exploited in the Reformatsky reaction instead of zinc; Orsini proposed cobalt(0)-phosphine complexes to achieve Reformatsky-like reactions,[3] while a very recent example based on the use of the $FeBr_2$/Mn couple was reported by Périchon.[4]



Scheme 1.

Alternatively, a low-valent metal was used to perform the oxidative addition of the α-halo ester to first afford a metal enolate that reacted with a zinc(II) species (e.g., zinc halide or dialkylzinc) to produce a zinc enolate through an alternative reaction channel.[5]

Following this approach, here we report a very efficient Reformastsky reaction protocol, catalysed by an *in situ* formed cobalt(I) species and using α-chloro esters, without appreciable side-product formation.

Results and Discussion

The chemistry of Co(I) directed to the construction of carbon-carbon bonds is recently enjoying an interesting revival.

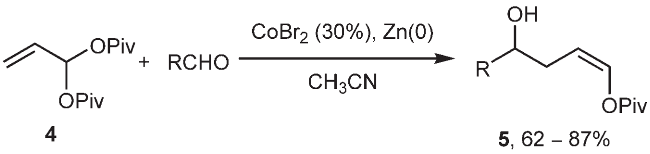
Significant examples were proposed by Hilt who exploited the Co[1,2-bis-(diphenylphosphino)ethane (dppe)]Br_2 (1.5%)/Bu_4NBH_4/ZnI_2 system in a 1:1:3 ratio to catalyse the [4+2] homo-Diels–Alder cycloaddition of acyclic 1,3-dienes with alkynes in CH_2Cl_2[6] and the redox system Co(dppe)Br_2 (10%)/Zn(0)/ZnI_2

in the 1:5:5 ratio to catalyse the Diels–Alder reaction of propargylic amines with butadienes in CH_2Cl_2,[7] as well as the cyclotrimerisation of alkynes to polysubstituted benzenes.[8] Snyder exploited an analogous route to Co(I) using the CoI_2 (5%)/dppe/Zn(0)/ZnI_2 system in the 1:1:1:3 ratio to catalyse the [4+2+2] homo-Diels–Alder cycloaddition of substituted norbornadienes with butadiene at room temperature in CH_2Cl_2.[9]

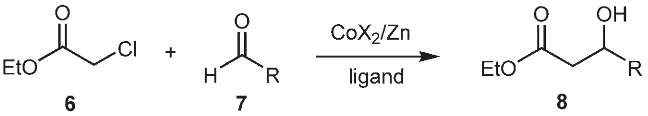
Recent studies by Périchon and Gosmini[10] demonstrated that Co(I) species, generated in acetonitrile using the Co(II)/Zn(0) redox couple, insert into the carbon-halogen bond of aryl, vinyl and allyl halides; through the intermediacy of allyl- and arylzinc complexes, and useful carbon-carbon bond forming reaction protocols were developed. Exploiting the process developed by Gosmini on allyl acetate, we recently proposed a simple Co(I)-catalysed homoaldol reaction of allylidene dipivalate **4** with aldehydes leading to configurationally pure (*Z*)-4-hydroxy-alk-1-en-1-yl pivalates **5** (Scheme 2).[11]

Inspired by the foregoing cobalt chemistry, we started searching for a practical way to catalyse the otherwise very sluggish Reformatsky reaction of α-chloro esters, using an *in situ* prepared Co(I) species. An optimisation study was carried out on the ethyl α-chloroacetate (**6**)/benzaldehyde system (**7a**, R=Ph), and, after a number of combinations of experimental conditions had been tested (Scheme 3), we realised that the reaction occurred in more than 90% yield using the $CoCl_2$ (5%)/(dppe)/ZnI_2 system in the 1:1:2 ratio, and 1.5 equivalents of commercial zinc powder in CH_3CN. It is worth noticing that the reaction did not proceed at all in the absence of cobalt salts.

Among all the experiments performed in the optimisation stage, Table 1 and Table 2 collect those aiming at verifying the importance of ZnI_2 and of supplementary ligands for cobalt, respectively. In all the runs of Table 1 and Table 2 temperature and reaction time were set at 20°C and 2.5 h, respectively. The role of ZnI_2 in favouring the catalyst formation is apparent (Table 1); the interaction of CoX_2 with ZnX_2 is known to give the ion pair $[Co^{2+}][ZnX_4]^{2-}$,[10a] much more easily reduced by Zn metal to a transient Co(I), whose lifetime is increased by the presence of ZnX_2 and of supplementary ligands, such as the acetonitrile itself, as well as phosphines, diimines, etc.



Scheme 2.



Scheme 3.

Table 1. The role of ZnI_2 in the reaction of **6** and benzaldehyde.[a]

Run	ZnI_2 (%)	**8a**, Yield [%][b]
1	0	10
2	5	75
3	10	93

[a] $CoCl_2$ (5%)/dppe (5%)/Zn(0) (1.5 equivs.) in CH_3CN at 20°C for 2.5 h.

[b] Isolated yields after purification by flash chromatography on silica.

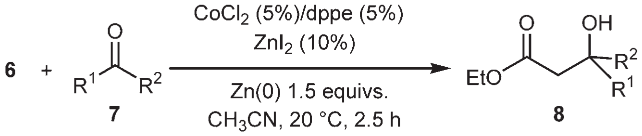
Table 2. Effect of different ligands in the Co(I)-catalysed Reformatsky reaction of **6** with benzaldehyde.[a]

Run	Ligand (5%)	**8a**, Yield [%][b]
1	-	17
2	2,2′-bipyridyl	<5
3	dppe	93
4	dppp[c]	95

[a] $CoCl_2$ (5%)/ligand (5%)/ZnI_2 (10%)/Zn(0) (1.5 equivs.) in CH_3CN at 20°C for 2.5 h.

[b] Isolated yields after purification by flash chromatography on silica.

[c] 1,3-Bis(diphenylphosphino)propane.



Scheme 4.

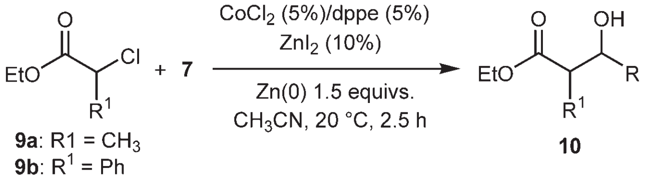
The dramatic effect of a supplementary diphosphine was unambiguously confirmed by results shown in Table 2. 1,4-Bis(diphenylphosphino)butane (dppb) was also tested, but being insoluble in CH_3CN, the same result as for run 1 was observed.

Once having established the optimum conditions for the coupling of ethyl chloroacetate (**6**) and benzaldehyde, we checked the same reaction protocol with a series of representative aromatic and aliphatic aldehydes and ketones (Scheme 4). In the results collected in Table 3, half of the runs presented chemical yields ≥90%. The lowest yield (run 8) was due to pivalaldehyde; α,β-unsaturated aldehydes (runs 9 and 10) afforded yields in the 70–75% range. In all the experiments, dehydration was the only side reaction, however its extent was variable and always limited to less

Table 3. Co(I)-catalysed Reformatsky reaction of ethyl chloroacetate and carbonyl compounds, using $CoCl_2$ (5%)/dppe (5%)/ZnI_2 (10%)/Zn(0) (1.5 equivs.) in CH_3CN at 20 °C for 2.5 h.

Run	$R^1R^2C{=}O$	**8**, Yield [%][a]
1	Benzaldehyde	**8a**, 93
2	4-Chlorobenzaldehyde	**8b**, 98
3	4-Methoxybenzaldehyde	**8c**, 90
4	4-Fluorobenzaldehyde	**8d**, 79
5	2-Naphthaldeyde	**8e**, 66
6	Cyclohexanecarboxaldehyde	**8f**, 94
7	Octanal	**8g**, 93
8	Pivalaldehyde	**8h**, 59
9	(*E*)-Crotonaldehyde	**8i**, 69
10	(*E*)-Cinnamaldehyde	**8j**, 76
11	Cyclohexanone	**8j**, 85
12	Acetophenone	**8k**, 95

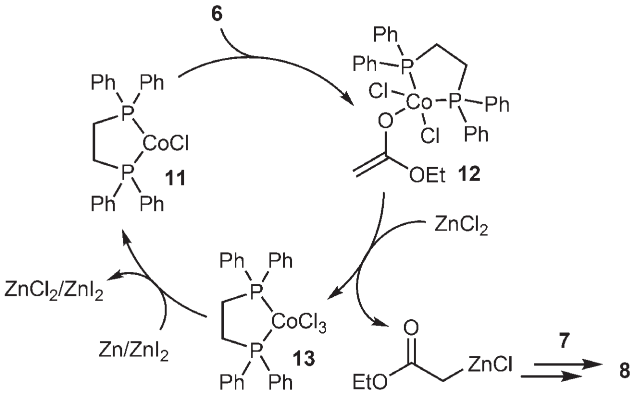
[a] Isolated yields after purification by flash chromatography on silica.



Scheme 5.

than 5%. Pinacol coupling products of the carbonyl compounds were never observed, while using metals with a higher reduction potential (e.g., manganese) pinacolisation intereferes with the Reformatsky reaction.[4]

The reaction was then applied to α-chloro esters **9a** and **9b** with model aldehydes under the same reaction conditions applied in Table 3 (Scheme 5 and Table 4). Good to excellent yields were again observed, while, as generally observed in Reformatsky reactions, zinc enolates do not display interesting diastereoselectivities when a prochiral enolate reacts with a prochiral carbonyl compound.



Scheme 6.

A plausible synthetic reaction mechanism is shown in Scheme 6. Complex **11** is a simplified picture of the catalytically active Co(I) species – acetonitrile molecules complete the coordination shell of Co – which insert into the carbon-chlorine bond of **6** to give the Co(III) enolate **12**. Transmetallation by the zinc halides present in the reaction mixture frees a classical Reformatsky reagent and the catalyst precursor **13** which, finally, is reduced to **11** by zinc. Actually, we cannot rule out a slightly modified catalytic cycle where the Co(III) enolate **12** undergoes reduction to a Co(II) enolate in the presence of zinc, leaving after the transmetallation step a Co(II) precatalyst species analogous to **13**.

Conclusions

We have reported a cobalt-catalysed modification of the Reformatsky reaction, affording an efficient cross coupling of α-chloro esters and carbonyl compounds to give β-hydroxy esters in high isolated yields. Making α-chloro esters competitive to α-bromo esters in Reformatsky reactions is advantageous both under economic (the prices of α-chloro esters are from 50% to two-fold lower than those of their brominated counterparts) and toxicological terms. α-Bromo esters are, indeed, classified as much more toxic and can-

Table 4. Co(I)-catalysed Reformatsky with substituted α-chloro esters, using $CoCl_2$ (5%)/dppe (5%)/ZnI_2 (10%)/Zn(0) (1.5 equivs.) in CH_3CN at 20 °C for 2.5 h.

Run	**9**	RCHO	**10**, Yield [%][a]	**10**, *syn*/*anti*
1	**9a**	Benzaldehyde	**10a**, 95	56:44
2	**9a**	Cyclohexanecarboxaldehyde	**10b**, 80	55:45
3	**9b**	Benzaldehyde	**10c**, 96	60:40
4	**9b**	Cyclohexanecarboxaldehyde	**10d**, 98	51:49

[a] Isolated yields after purification by flash chromatography on silica.

cerogenic agents than their chloro counterparts owing to their higher reactivity as alkylating agents.

Experimental Section

Synthesis of Ethyl 3-Hydroxy-3-phenylpropanoate (8a, Table 1, Entry 1); General Procedure

Commercial $CoCl_2 \cdot 6H_2O$ (0.012 g, 0.05 mmol) is flamed under a positive argon pressure until the colour turns from pink to bright blue. Anhydrous ZnI_2 (0.032 g, 0.10 mmol) is added and again the flask is flamed under a positive argon pressure. The salts are dissolved in freshly distilled acetonitrile (2 mL) and to this solution dppe (0.020 g, 0.05 mmol), ethyl chloroacetate **6** (0.127 mL, 1.2 mmol) and benzaldehyde (0.102 mL, 1 mmol) are added. The temperature is set at 20 °C with a thermostated bath, and commercial zinc powder (0.98 g, 1.5 mmol) is added. The reaction mixture is vigorously stirred at the same temperature for 2.5 h, quenched with saturated NH_4Cl aqueous solution (1 mL) and filtered on a short pad of Celite®. The filtered solution is dried on Na_2SO_4, evaporated under reduced pressure and the residue is purified by flash-chromatography on silica eluting with cyclohexane/ethyl acetate 8:2 to afford pure **8a** as an oil; yield: 0.181 g (93%).

Acknowledgements

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