Stereoselective synthesis of (*Z*)-α-halo-α,β-unsaturated esters, and amides from aldehydes and trihaloesters or amides promoted by manganese†

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Preliminary results of a Mn-promoted sequential process directed toward the stereoselective synthesis of different (*Z*)-α-halo-α,β-unsaturated compounds are described.

α-Halo-α,β-unsaturated esters are useful synthetic building blocks. Thus, these compounds have been used as starting materials to access important organic compounds, *inter alia*, trisubstituted alkenes with complete stereospecificity,[1] α-amino acids,[2] a variety of heterocycles including aziridines[2b,3] and natural or pharmaceutical products.[4] They can also serve as the functionalized vinyl halide in transition metal-mediated coupling reactions.[5] As a consequence of their importance, the most important classical methodologies to generate C–C double bonds (Wittig, Horner–Wadsworth–Emmons, Julia or Peterson olefination reactions) have been applied to their synthesis.[6] These methods often present some drawbacks. Thus, in some cases the former compounds are obtained in poor yields, low stereoselectivity, and the generality of other methods is scarce. Indeed, some reagents are expensive or the experimental work tedious.

Recently, a synthesis of (*Z*)-α-halo-α,β-unsaturated esters (chloro, bromo and fluoro) through a sequential reaction of trihaloacetates with various aldehydes promoted by $CrCl_2$ with total stereoselectivity and in high yields was described by Falck and Mioskowski *et al*.[7] A similar methodology was also applied to prepare two examples of (*Z*)-α-chloro-α,β-unsaturated amides,[8] but generality of the process was not demonstrated.[9] The main drawbacks of both syntheses could be the high price[10] and the relative toxicity of the chromium salts.

Later on, to overcome these drawbacks the same authors reported the preparation of (*Z*)-α-halo-α,β-unsaturated esters by using the cheaper and non-toxic Fe(0) instead of $CrCl_2$.[11] However, this objective was not completely attained due to: (a) in some cases the reaction was not completely stereoselective and *Z*–*E* mixtures of esters were obtained; and (b) when bromoacrylates were prepared, debrominated byproducts (ranging between 15%–20%) contaminated the corresponding α,β-unsaturated bromoester crude mixtures. In addition, only three examples of aliphatic α-halo-α,β-unsaturated esters by using $CrCl_2$ or Fe(0) were reported in the corresponding papers.[7,11]

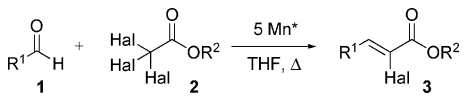
On the other hand, although the reduction potential of the $Mn^{+2}/Mn(0)$ system[12] is adequate to reduce an important number of organic functions, and the manganese is non-toxic and very cheap, it has been scarcely used in organic synthesis[13] possibly due to the inherent passivity exhibited by this metal, which is coated by an outer shell of oxide. This drawback could be overcome by using active manganese (Mn*), such as that reported by Cahiez *et al*.[14] Thus, very recently, we developed a Mn*-mediated sequential reaction of aldehydes with α,α-dihaloesters[15] or amides[16] to obtain (*E*)-α,β-unsaturated esters or amides, respectively, in high yields and with total *E*-stereoselectivity. These precedent results, prompted us to attempt the preparation of the scarcely reported aliphatic (*Z*)-α,β-unsaturated α-haloesters **3** and aliphatic or aromatic amides **5** by the Mn*-mediated reaction of aldehydes with different trihaloacetates or acetamides, and the transformation of amides derived from morpholine into (*Z*)-α,β-unsaturated α-haloketones **9** by reaction with organolithium compounds.[17] Thus, the obtained previous results are described in this communication.

Synthesis of aliphatic (*Z*)-α,β-unsaturated α-haloesters 3

The best results were obtained after the addition of 5 equiv. of the black slurry of active manganese to a solution of 1 equiv. of the corresponding aldehyde **1** and 1.1 equiv. of trichloroacetate **2** in THF at room temperature which afforded, after refluxing for 5 h, the corresponding aliphatic α,β-unsaturated α-haloester **3** with total stereoselectivity and in high yields (Table 1). The active manganese was readily prepared by using the method described by Cahiez.[14]‡

The reaction is general. Linear, branched or cyclic aliphatic aldehydes gave the corresponding 2-chloroalk-2-enoates **3** in high yields (>88%, after purification by column chromatography) and with complete *Z*-stereoselectivity as shown in Table 1 (entries 1–3). In contrast to other olefination reactions such as the Wittig reaction,[18] the yield and the stereoselectivity of the reaction was unaffected when a highly hindered trichloroacetate (Table 1, entry 3), was employed. All the starting materials were commercially (ethyl trichloro- or dibromofluoroacetate and aldehydes)

Table 1 Synthesis of aliphatic (*Z*)-α,β-unsaturated α-haloesters **3**



Entry	**3**	R^1	R^2	Hal	*Z*–*E*	Yield (%)[a]
1	**3a**	i-Bu	Et	Cl	>98 : 2	92
2	**3b**	Cy	Et	Cl	>98 : 2	95
3	**3c**	C_7H_{15}	i-Pr	Cl	>98 : 2	88
4	**3d**	C_7H_{15}	Et	Br	>98 : 2	71
5	**3e**	*s*-Bu	Et	F	>98 : 2	62

[a] Yield of the isolated product after column chromatography based on compound **1**.

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† Electronic supplementary information (ESI) available: General procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for compounds **3**, **5** and **9**. See DOI: 10.1039/b717513b

or readily (ethyl tribromoacetate from tribromoacetyl chloride) available compounds.

Under milder reaction conditions (room temperature, 12 h), bromo or fluoro derivatives could be also obtained in an efficient manner in which debrominated byproducts were not detected. Thus, the reaction of ethyl tribromoacetate or dibromofluoroacetate with the corresponding aldehyde afforded 2-bromoacrylate **3d** or 2-fluoroacrylate **3e** in good yields and with complete *Z*-stereoselectivity (Table 1, entries 4 and 5). The *Z*–*E* ratio of compounds **3** was determined on the crude reaction products by ^{1}H NMR spectroscopy (300 MHz) and/or GC-MS, showing the presence of a single stereoisomer. The *Z*-stereochemistry of the C–C double bond of α-halo-α,β-unsaturated esters **3** was established by NOESY experiments and by comparison with the NMR data previously described in the literature for compound **3c**.[19] The *trans* configuration of the fluoro derivative **3e** was established based on the value of the ^{1}H NMR coupling constant between the olefinic proton and the fluorine atom (J_{HF} = 34 Hz).[20] The configurations of other esters were established by analogy to the preceding determinations.

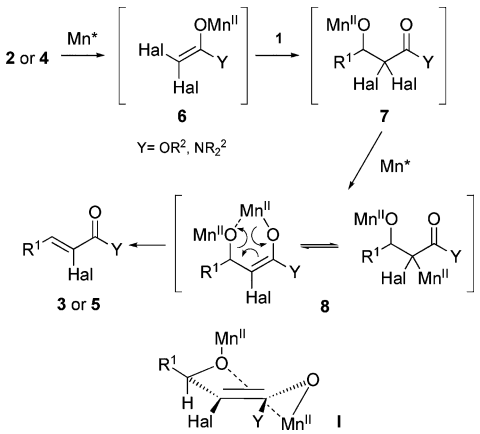
Synthesis of (*Z*)-α,β-unsaturated α-haloamides 5

After testing several reaction conditions, α,β-unsaturated α-haloamides were prepared by treatment of a solution of the corresponding aldehyde and trichloroacetamide in THF with 5 equiv. of Mn* at reflux for 5 hours. Hence, a range of amides, aliphatic (linear, branched or cyclic) and aromatic were obtained in high yields (>80%), after purification by column chromatography and with complete *Z*-diastereoselectivity (Table 2).

Similarly to esters **3**, the amides were obtained with complete *Z*-stereoselectivity (^{1}H NMR spectroscopy and GC-MS on the crude reaction products), the *Z* configuration of the C–C double bond of amides **5** being determined by performing NOESY experiments on compounds **5a**, **5b**, **5d**, and **5e**.

It is noteworthy that this process was not affected by the use of trichloroacetamides derived from different amines. In turn, the starting amides were readily obtained by reaction of trichloroacetyl chloride with the corresponding amine.

These obtained results could be explained by the same mechanism previously proposed to explain the synthesis of α,β-unsaturated esters[15] or amides[16] promoted by Mn*. Thus we assume that the synthesis of **3** or **5** took place through a sequential reaction in two steps (Scheme 1). Initially, a manganese enolate **6** was generated by metalation of one C–Hal bond of **2** or **4** with 2 equiv. of Mn*. Thus, a Reformatsky-type process takes place initially to afford the dihaloester or amide **7**. A metalation of a C–Hal of **7** afforded the manganese enolate **8**, which underwent a spontaneous 1,2-elimination reaction to give **3** or **5**.

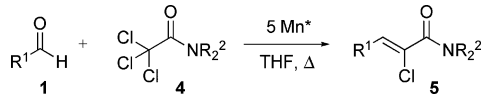


Scheme 1 Proposed mechanism.

This elimination could take place through a chelation-control model (Scheme 1), in which the Mn(II) center is coordinated with the oxygen atom of the alcoholate group in the enolate **8**, to produce a six-membered ring.[21] Tentatively we propose a chair transition state model **I** to justify the configuration of the alkene function on the obtained esters or amides **3** or **5**. Thus, in the more stable chair transition state, the R^1 group would adopt a pseudo-equatorial position to avoid 1,3-diaxial interactions. A 1,2-elimination reaction from **I** such as that depicted in **8**, would afford the *Z*-stereoisomer. An indirect support for this mechanism is given by the detection of the corresponding 2,2-dichloro-3-hydroxyester or amide (obtained by hydrolysis of the intermediates **7**) on the crude reaction of compounds **3b** and **5c**.

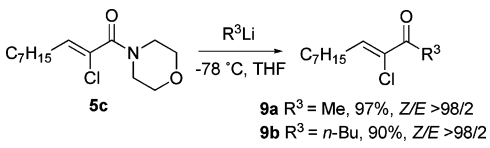
The synthesis of (*Z*)-α,β-unsaturated α-haloamides derived from morpholine are of special interest due to their synthetic applications.[22] Therefore, taking into account the important applications of α-haloenones in the preparation of different important substrates, and biologically active products,[23] the amide **5c** was readily transformed into ketones **9a** and **9b**, as shown in Scheme 2. Thus the reaction of **5c** with methyl- or butyllithium at −78 °C for 1 h afforded the corresponding ketone **9a** or **9b**. This transformation took place without loss of the diastereoisomeric purity of the C–C double bond (^{1}H NMR of the crude reaction products) and in nearly quantitative yields (97 and 90%, respectively). The *Z*-configuration of the alkene function was established by a NOESY experiment on ketone **9b**. Hence the assignment of the *Z*-stereochemistry of **9b** allowed the indirect determination of the

Table 2 Synthesis of (*Z*)-α,β-unsaturated α-haloamides **5**



Entry	**5**	R^1	R^2	*Z*–*E*	Yield (%)[a]
1	**5a**	i-Bu	Et	>98 : 2	82
2	**5b**	Cy	Et	>98 : 2	80
3	**5c**	C_7H_{15}	[b]	>98 : 2	84
4	**5d**	*p*-MeOC$_6$H$_4$	Et	>98 : 2	81
5	**5e**	*p*-MeOC$_6$H$_4$	i-Pr	>98 : 2	86

[a] Yield of the isolated product after column chromatography based on compound **1**. [b] From morpholine.



Scheme 2 Synthesis of (*Z*)-α,β-unsaturated α-chloroketones **9**.

Z-configuration of the starting α,β-unsaturated amide **5c**, which could not be established directly by a NOESY experiment. It is noteworthy that the prepared ketones **9a** and **9b** (R^3 = aliphatic) are difficult to achieve by using other reported methods.

In conclusion, an easy, straightforward and general sequential method has been developed to synthesize aliphatic α,β-unsaturated α-haloesters (bromo, chloro, and fluoro) **3** and chloroamides **5** with total *Z*-stereoselectivity, through a sequential process promoted by the non-toxic Mn*. The unsaturated amides **5** derived from morpholine were readily transformed into the corresponding ketones by reaction with organolithium compounds. Generalization of the reported synthesis is currently under investigation within our laboratory.

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Notes and references

‡ **Preparation of Rieke Manganese (Mn*)**: A mixture of lithium (26 mmol) and 2-phenylpyridine (4 mmol) in THF (20 mL) under a nitrogen atmosphere was stirred for 1 h. In a separate flask, a solution of the Li_2MnCl_4 complex was prepared by stirring a suspension of anhydrous $MnCl_2$ (13 mmol) and LiCl (26 mmol) in THF (20 mL) for 30 min. Then, this yellow solution was added at room temperature with a syringe to the 2-phenylpyridine–lithium solution previously prepared and was stirred, under a nitrogen atmosphere, at room temperature for 1 h. The black slurry was allowed to stir at room temperature for 3 h. **General procedure for the synthesis of α,β-unsaturated compounds 3 or 5**: The slurry of Mn* (2.5 mmol, 8.5 mL) in THF was added to a stirred solution of the trihaloester or amide (0.6 mmol) **2**, or **4**, respectively and the corresponding aldehyde (0.5 mmol) **1** in THF (2 mL) under an inert atmosphere. The mixture was heated at reflux for 5 h before it was quenched with HCl 3 M. The organic material was extracted with diethyl ether (3 × 20 mL), the combined organic extracts were washed sequentially with HCl 3 M (2 × 10 mL), saturated $NaHCO_3$ (2 × 20 mL), and water (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed *in vacuo*. Purification by flash column chromatography on silica gel (compounds **3**: hexane–EtOAc 10 : 1; compounds **5**: hexane–EtOAc 3 : 1) provided pure compounds **3** and **5**.

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