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Stereoselective synthesis of (*Z*)-α-haloacrylic acid derivatives, and (*Z*)-haloallylic alcohols from aldehydes and trihaloesters or amides promoted by Rieke manganese†

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A Mn*-promoted sequential process directed toward the synthesis of (*Z*)-α-halo-α,β-unsaturated esters or amides is described. In both cases, the process takes place with complete *Z*-stereoselectivity. In addition, (*Z*)-α-chloro-α,β-unsaturated ketones and carboxylic acids, and (*Z*)-haloallylic alcohols were readily prepared from (*Z*)-α-halo-α,β-unsaturated amides derived from morpholine, or esters. A mechanism has been proposed to explain the sequential process and the stereoselectivity observed.

Introduction

(*Z*)-α-Halo-α,β-unsaturated acid derivatives are useful building blocks from a synthetic point of view. These compounds have been used as starting materials for the synthesis of important organic compounds such as trisubstituted alkenes with complete stereospecificity,[1] α-aminoacids,[2] a variety of heterocycles including aziridines,[2b,3] and natural or pharmaceutical products.[4] These compounds are also interesting since they can be employed as key intermediates in the preparation of other functionalities, *inter alia* (*Z*)-α-halo-α,β-unsaturated ketones[5] and carboxylic acids,[6] and (*Z*)-haloallylic alcohols.[7]

The most important well-known methods of generating C–C double bonds (Wittig, Horner-Wadsworth-Emmons, Julia or Peterson olefination reactions) have been applied to the synthesis of (*Z*)-α-halo-α,β-unsaturated acid derivatives.[8] Nevertheless these methods often present some of the following drawbacks: poor yields, low stereoselectivity, lack of generality, the employment of expensive reagents or tedious experimental work.

Recently, the synthesis of (*Z*)-α-halo-α,β-unsaturated compounds by the reaction of dihaloacid derivatives with aldehydes promoted by $CrCl_2$,[9] Fe,[10] and SmI_2[11] has been published.

As part of our interest in the development of new selective syntheses of unsaturated compounds, and motivated by our studies on the synthetic applications of metalation reactions using different active metals, we tested the possibility of using manganese to perform 1,2-elimination processes.

Although manganese has been scarcely used in organic synthesis, it is cheaper and less toxic than other metals. Therefore, we developed a novel and totally stereoselective β-elimination reaction of 2-bromo-3-hydroxyesters promoted by the Mn–TMSCl system to obtain (*E*)-α,β-unsaturated esters.[12] More recently our laboratory has demonstrated the utility of Rieke-Mn (Mn*) to promote the sequential reaction of aldehydes with α,α-dihaloesters[13] or amides,[14] yielding (*E*)-α,β-unsaturated esters or amides, respectively. Very recently we communicated our first examples of the stereoselective synthesis of (*Z*)-α-halo-α,β-unsaturated esters and amides.[15] The good results reported in this communication prompted us to study the generality and drawbacks of this method. Thus, we report herein full studies concerning the Mn*-promoted sequential process directed toward the stereoselective synthesis of (*Z*)-α-halo-α,β-unsaturated esters and amides, giving special attention to the generality and main limitations of this process. A mechanism is proposed to explain the experimental results obtained. Finally some synthetic applications of the obtained (*Z*)-α-halo-α,β-unsaturated esters and amides are demonstrated: the syntheses of various compounds, such as (*Z*)-α,β-unsaturated α-halo ketones and carboxylic acids, and (*Z*)-haloallylic alcohols are reported.

Results and discussion

Synthesis of (*Z*)-α-haloacrylates and α-chloroacrylamides

The active manganese was readily prepared using the method described by Cahiez *et al.*[16] Thus, treatment of Li_2MnCl_4 (13 mmol) (prepared from 1 equivalent of $MnCl_2$ and 2 equivalents of LiCl) with 26 mmol of lithium in the presence of catalytic amounts of 2-phenylpyridine (4 mmol) at room temperature for 3 h, afforded active manganese cheaply as a black slurry.[17]

To 5 equiv. of the black slurry of active manganese (Mn*), a solution of 1 equiv. of the corresponding aldehyde **1** and 1.1 equiv. of trichloroacetate **2** in THF was added and then stirred at reflux for 5 h. After that time, the corresponding α,β-unsaturated α-haloesters **3** were isolated with total stereoselectivity and in high yields (Table 1).

The reaction showed general tolerance towards a variety of substrates. Thus, linear, branched or cyclic aliphatic aldehydes gave the corresponding 2-chloroalk-2-enoates **3** in high yields (>85%, after purification by column chromatography) and with complete *Z*-stereoselectivity as shown in Table 1 (entries 1–7). The process was also tolerant of the presence of other double bonds in the aliphatic chain, as demonstrated by the synthesis of compound **3g**. Nevertheless, when aromatic aldehydes were used as starting

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† Electronic Supplementary Information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for all new compounds **3**, **5** and **9–11**. See DOI: 10.1039/b803449d

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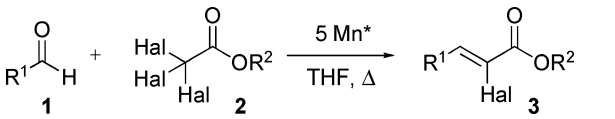
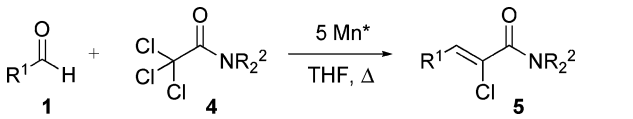
Table 1 Synthesis of aliphatic (*Z*)-α,β-unsaturated α-haloesters **3**



Entry	3	R^1	R^2	Hal	*Z* : *E*	Yield (%)[a]
1	**3a**	*n*-C_7H_{15}	Et	Cl	98 : 2	89
2	**3b**	*n*-C_7H_{15}	*i*-Pr	Cl	98 : 2	88
3	**3c**	Cy	Et	Cl	98 : 2	95
4	**3d**	Cy	*i*-Pr	Cl	98 : 2	89
5	**3e**	*i*-Bu	Et	Cl	98 : 2	92
6	**3f**	*s*-Bu	Et	Cl	98 : 2	85
7	**3g**	CH_2=$CH(CH_2)_8$	Et	Cl	98 : 2	87
8	**3h**	*p*-$MeOC_6H_4$	Et	Cl	98 : 2	48
9	**3i**	*n*-C_7H_{15}	Et	Br	98 : 2	71
10	**3j**	Cy	*i*-Pr	Br	98 : 2	74
11	**3k**	*i*-Bu	Et	Br	98 : 2	69
12	**3l**	Cy	Et	F	98 : 2	64
13	**3m**	*s*-Bu	Et	F	98 : 2	62

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

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



Entry	5	R^1	R^2	*Z* : *E*	Yield (%)[a]
1	**5a**	*n*-C_7H_{15}	Et	98 : 2	88
2	**5b**	*n*-C_7H_{15}	*i*-Pr	98 : 2	86
3	**5c**	*n*-C_7H_{15}	[b]	98 : 2	84
4	**5d**	Cy	Et	98 : 2	80
5	**5e**	Cy	[b]	98 : 2	75
6	**5f**	*i*-Bu	Et	98 : 2	82
7	**5g**	*i*-Bu	[b]	98 : 2	79
8	**5h**	*s*-Bu	Et	98 : 2	79
9	**5i**	CH_2=$CH(CH_2)_8$	Et	98 : 2	86
10	**5j**	$Ph(CH_3)CH$	Et	98 : 2	73
11	**5k**	*p*-$MeOC_6H_4$	Et	98 : 2	81
12	**5l**	*p*-$MeOC_6H_4$	*i*-Pr	98 : 2	86

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

materials, a complex mixture of products was obtained and no unsaturated compounds **3** or **5** were obtained except in the case of *p*-methoxybenzaldehyde in which the corresponding unsaturated ester **3** was obtained with complete stereoselectivity and in low yield (Table 1, entry 8).

When the same reaction conditions were used on trihaloacetates other than trichloroacetate (tribromoacetate or dibromofluoroacetate), completely dehalogenated compounds **3** were obtained. Nevertheless, when 5 equiv. of the black slurry of Mn*, 1 equiv. of the corresponding aldehyde **1** and 1.1 equiv. of the corresponding tribromo- or dibromofluoroacetate **2** in THF was stirred under milder reaction conditions (room temperature, 12 h), bromo or fluoro derivatives were obtained in an efficient manner. Thus, the reaction of tribromo or dibromofluoroacetates with the corresponding aldehyde afforded 2-bromoacrylates **3i–k** (Table 1, entries 9–11) or 2-fluoroacrylates **3l** and **3m** in good yields and with complete *Z*-stereoselectivity (Table 1, entries 12 and 13).

When this reaction was carried out employing ketones instead of aldehydes (acetophenone and 4-methyl-2-pentanone), no reaction took place and only unreacted ketone and byproducts from metalation of the trihaloesters or amides were isolated.

Based on the results of the syntheses of the (*Z*)-α-chloroacrylates, we tested the performance of the same reaction conditions in the synthesis of (*Z*)-α-chloroacrylamides. Hence, compounds **5** were obtained after stirring 5 equiv. of the black slurry of Mn*, 1 equiv. of the corresponding aldehyde **1** and 1.1 equiv. of the trichloroacetamide **4** in THF at reflux for 5 h.

The results are summarized in Table 2 and it can be observed that the method is general. Thus, a range of amides derived from aliphatic (linear, branched or cyclic, Table 2, entries 1–8), functionalized (entry 9), and readily enolizable aldehydes (entry 10) were obtained in high yields (ranging between 73–88%) and with complete *Z*-stereoselectivity (Table 2). When aromatic aldehydes were used as starting materials, the results obtained were similar to those observed in the synthesis of the esters. So, no acrylamides were obtained except in the case of *p*-methoxybenzaldehyde in which the corresponding product **5** was obtained in high yield and with complete stereoselectivity (Table 2, entries 11 and 12).

All attempts to access bromo- or fluoroacrylamides were unsuccessful. Thus, under milder reaction conditions (room temperature, 12 h), neither α-bromo- nor fluoroacrylamides were obtained and a mixture of debrominated byproducts or a complex mixture of compounds was afforded.

In contrast to other olefination methodologies such as the Wittig reaction,[18] it is noteworthy that no significant differences were observed in the stereoselectivity and/or yield of this process when hindered trihaloacetates **2** or trichloroacetamides **4** (Tables 1 and 2, respectively) were employed. Thus, no differences were observed between the reactions of ethyl and isopropyl trihaloacetates (Table 1, entries 1–2, 3–4 and 10) and ethyl and isopropyl trichloroacetamides (Table 2, entries 1–2, and 11–12).[19] In addition, acrylamides derived from morpholine were also available (Table 2, entries 3, 5 and 7).

The *Z* : *E* ratios of compounds **3** and **5** were determined for the crude reaction products by ^{1}H NMR spectroscopy (300 MHz) and/or GC-MS, showing the presence of single stereoisomers. The *Z*-stereochemistry of the C–C double bond of both α-haloacrylates **3** and α-haloacrylamides **5** was established by NOESY experiments in the case of compounds **3b**, **3c**, **3e**, **3i–k**, **3l**, **5d**, **5f**, **5k**, **5l** and by comparison with the NMR data previously described in the literature for compound **3c**.[11] In the case of the fluoro derivatives **3l** and **3m**, the configuration was established based on the value of ^{1}H NMR coupling constants between the olefinic proton and the fluorine atom ($^3J_{HF}$ = 34 and 33 Hz, for **3l** and **3m** respectively).[20] The *Z*-configuration of the other compounds **3** or **5**, different from those mentioned above, was established by analogy.

Mechanism

To rationalize the synthesis of compounds **3** or **5**, we propose a similar mechanism to that previously used to explain the preparation of α,β-unsaturated esters[13] or amides[14] through a sequential reaction promoted by Mn* (Scheme 1). Thus, a sequential reaction is proposed to explain the formation of

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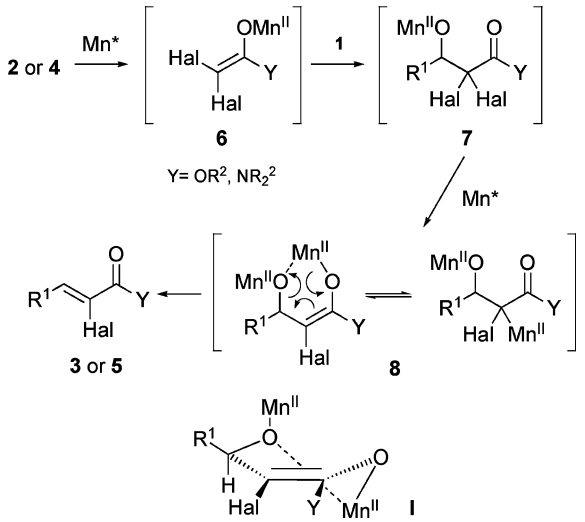


Scheme 1 Proposed mechanism.

products **3** or **5**. In the first stage an aldolic reaction between the enolate obtained by the metalation of trihaloesters **2** or amides **4** took place. The Reformatsky adduct **7** was metalated by Mn* to give the organomanganese intermediate **8** which undergoes a spontaneous β-elimination affording the unsaturated ester **3** or amide **5**. The complete *Z*-stereoselectivity of this process can be explained by assuming the transition state **I**, which is generated as a consequence of the coordination between the manganese(II) and the oxygen atom of the alcoholate group in the enolate **8**.[21] In this chair-like transition state the R^1 group occupies a pseudoequatorial position to reduce the 1,3-steric hindrance. Elimination through this transition state **I**, such as that depicted in **8**, would afford the *Z*-stereoisomer. Indirect support for this mechanism was given by the isolation of the corresponding 2,2-dichloro-3-hydroxyester or amide, (obtained by hydrolysis of the intermediates **7**) from the crude reaction during the synthesis of compounds **3d** and **5c**.[22] When these isolated intermediates **7** were treated with 2.5 equiv. of Mn*, compounds **3d** and **5c** were also stereoselectively obtained.

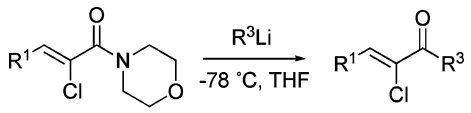
Synthetic applications of (*Z*)-α-haloacrylates 3 and α-chloroacrylamides 5

To demonstrate the synthetic applications of the α-haloacrylates and α-chloroacrylamides obtained, selected examples were readily transformed into various unsaturated compounds, such as (*Z*)-α-chloro-α,β-unsaturated ketones **9** and carboxylic acids **10**, and (*Z*)-haloallylic alcohols **11**.

As has been reported,[23] amides derived from morpholine (Table 2, entries 3, 5, and 7) are especially useful. Thus, the reaction of different (*Z*)-α,β-unsaturated α-haloamides derived from morpholine **5** with various organolithium compounds at −78 °C for 30 min afforded the corresponding unsaturated ketones **9** in high yields (>77%) (Table 3).

The transformation seems to be general and a range of morpholine-based unsaturated amides and organolithium compounds can be used. It is noteworthy that the integrity of the C–C double bond was unaffected under the reaction conditions used to perform this transformation, with the ketone being obtained as a single *Z*-stereoisomer (^{1}H NMR of the crude reaction products).

Table 3 Synthesis of (*Z*)-α,β-unsaturated α-chloroketones **9**



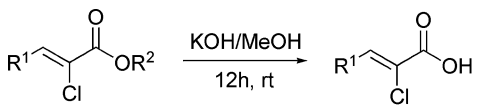
Entry	5	9	R^1	R^3	*Z* : *E*	Yield (%)[a]
1	**5c**	**9a**	*n*-C_7H_{15}	Me	98 : 2	97
2	**5c**	**9b**	*n*-C_7H_{15}	*n*-Bu	98 : 2	90
3	**5e**	**9c**	Cy	CH_2Cl	98 : 2	79
4	**5g**	**9d**	*i*-Bu	$CH_2CH{=}CH_2$	98 : 2	77

[a] Yield of the isolated product after column chromatography based on the corresponding compound **5**.

The *Z*-configuration of the alkene function was established by a NOESY experiment, with a nuclear Overhauser effect being observed between the olefinic proton and *n*-PrCH_2 on ketone **9b**. This assignment allowed indirect determination of the *Z*-configuration of the starting unsaturated amide **5c**, which could not be established directly by a NOESY experiment.

The synthesis of alkyl alk-1-enyl ketones, **9** (R^3 = aliphatic) by other alternative methods is difficult to achieve,[24] and it is worth mentioning the synthesis of the chlorinated ketone **9c**, by reaction with chloromethyllithium generated *in situ*.[25] Remarkably, the use of morpholine amides as starting materials, to transform amides derived from morpholine into ketones, is more advantageous than using the corresponding Weinreb derivatives since the morpholine derivatives are cheaper.

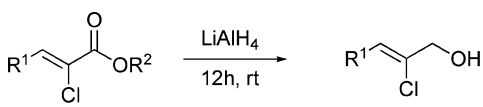
(*Z*)-α-Chloro-α,β-unsaturated carboxylic acids **10a** and **10b** can be obtained by basic hydrolysis of the α-chloroacrylates **3d** and **3f** respectively, with potassium hydroxide in methanol at room temperature for 12 h. Compounds **10** were obtained in high yield (>89%) and as single *Z*-stereoisomers (^{1}H NMR of the crude reaction products). No important differences in the yields of the acids obtained were observed when different (ethyl or isopropyl) esters **3** were employed as starting compounds (Scheme 2).



3d **10a** R^1 = Cy, 89%, *Z*/*E* >98/2
3f **10b** R^1 = *s*-Bu, 91%, *Z*/*E* >98/2

Scheme 2 Synthesis of (*Z*)-α,β-unsaturated-α-chlorocarboxylic acids **10**.

Finally the treatment of α-chloroacrylates **3b** and **3c** with lithium aluminium hydride at room temperature for 12 h afforded the corresponding (*Z*)-haloallylic alcohols **11a** and **11b** (Scheme 3) in high yield and without loss of the diastereoisomeric purity (^{1}H NMR of the crude reaction products). Again, no differences



3b **11a** R^1 = *n*-C_7H_{15}, 80%, *Z*/*E* >98/2
3c **11b** R^1 = Cy, 83%, *Z*/*E* >98/2

Scheme 3 Synthesis of (*Z*)-chloroallylic alcohols **11**.

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were observed when this transformation was performed using the different ethyl or isopropyl α-chloroacrylates.

Conclusion

In conclusion, a simple, straightforward and general sequential method has been developed to synthesize α,β-unsaturated α-haloesters (bromo, chloro, and fluoro) **3** and α-chloroamides **5** with total *Z*-stereoselectivity, through a sequential process promoted by the non-toxic and cheap Mn*. This reported synthesis of (*Z*)-α-halo-α,β-unsaturated esters or amides, combined with their transformation into different halounsaturated compounds, constitutes easy and efficient access to (*Z*)-α-chloro-α,β-unsaturated ketones and carboxylic acids, and (*Z*)-haloallylic alcohols.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum-line techniques and glassware that was flame dried and cooled under nitrogen before use. THF was distilled from sodium–benzophenone ketyl immediately prior to use. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. All reagents were purchased in the highest quality available and were used without further purification. Organic layers were dried over Na_2SO4. Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica. Plates were visualized using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica. NMR spectra were recorded in the deuterated solvent stated and the field was locked by external referencing to the relevant deuteron resonance. ^{1}H NMR spectra were recorded on spectrometers at 300 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 75 or 100 MHz. Unless otherwise noted NMR spectra were recorded at room temperature. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which was used as an internal standard. GC-MS and HRMS were measured at 70 eV. Only the most important IR absorptions (in cm^{-1}) and the molecular ions and/or base peaks in the MS are given.

General procedure for the preparation of Rieke-manganese. A mixture of lithium (26 mmol) and 2-phenylpyridine (4 mmol) in THF (20 mL) under a nitrogen atmosphere was stirred for 1h. 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-halo-α,β-unsaturated esters 3 or amides 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 successively 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**. In the particular case of the synthesis of α-bromo or α-fluoro derivatives, instead of refluxing for 5 h the reaction was carried out at room temperature for 12 h.

Ethyl (*Z*)-2-chlorodec-2-enoate (3a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (t, J = 6.8 Hz, 1 H), 4.29 (q, J = 7.0 Hz, 2 H), 2.42–2.32 (m, 2 H), 1.69–1.48 (m, 2 H), 1.37–1.24 (m, 11 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (C), 142.8 (CH), 125.9 (C), 63.0 (CH_2), 32.6 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 23.5 (CH_2), 15.3 (CH_3), 14.9 (CH_3); MS (70 eV, EI) *m*/*z* (%) 232 [M^+, 5], 137 (32), 135 (100), 122 (58), 107 (73); HRMS (70 eV) calc. for $C_{12}H_{21}ClO_2$ 232.1230, found 232.1227; IR (neat): ν 2928, 1750, 1267 cm^{-1}; R_f = 0.5 (hexane : EtOAc 10:1).

Isopropyl (*Z*)-2-chloro-3-cyclohexylacrylate (3d). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (d, J = 9.3 Hz, 1 H), 5.18–5.02 (m, 1 H), 2.69–2.52 (m, 1 H), 1.81–1.72 (m, 2 H), 1.39–1.18 (m, 8 H), 1.31 (d, J = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C), 146.3 (CH), 123.2 (C), 69.8 (CH), 38.5 (CH), 30.9 (2 × CH_2), 25.7 (CH_2), 25.3 (2 × CH_2), 21.7 (2 × CH_3); MS (70 eV, EI) *m*/*z* (%) 230 [M^+, 2], 188 (64), 82 (100), 67 (66), 55 (16); HRMS (70 eV) calc. for $C_{12}H_{19}ClO_2$ 230.1074, found 230.1084; IR (neat): ν 2982, 1729, 1628, 1145 cm^{-1}; R_f = 0.39 (hexane : EtOAc 20 : 1).

Ethyl (*Z*)-2-chloro-4-methylhex-2-enoate (3f). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, J = 9.6 Hz, 1 H), 4.29 (q, J = 7.1 Hz, 2 H), 2.87–2.59 (m, 1 H), 1.49–1.33 (m, 2 H), 1.23 (t, J = 7.0 Hz, 3 H), 1.07 (d, J = 6.8 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (C), 147.4 (CH), 130.6 (C), 62.1 (CH_2), 35.9 (CH), 28.9 (CH_2), 18.6 (CH_3), 14.1 (CH_3), 11.6 (CH_3); MS (70 eV, EI) *m*/*z* (%) 190 [M^+, 8], 225 (36), 179 (28), 69 (100); HRMS (70 eV) calc. for $C_9H_{15}ClO_2$ 190.0761, found 190.0769; IR (neat): ν 3415, 1645, 1263 cm^{-1}; R_f = 0.37 (hexane : EtOAc 10 : 1).

Ethyl (*Z*)-2-chlorotrideca-2,12-dienoate (3g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (t, J = 7.5 Hz, 1 H), 5.97–5.74 (m, 1 H), 5.04–4.93 (m, 2 H), 4.14 (q, J = 6.9 Hz, 2 H), 2.43–2.24 (m, 2 H), 2.10–2.00 (m, 2 H), 1.70–1.55 (m, 2 H), 1.44–1.25 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7 (C), 142.4 (C), 139.1 (CH), 126.7 (CH), 114.1 (CH_2), 60.1 (CH_2), 33.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 24.9 (CH_2), 14.2 (CH_3); MS (70 eV, EI) *m*/*z* (%) 272 [M^+, 8], 135 (100), 107 (66), 69 (86); HRMS (70 eV) calc. for $C_{15}H_{25}ClO_2$ 272.1543, found 272.1524; IR (neat): ν 2928, 2853, 1737, 1641 cm^{-1}; R_f = 0.42 (hexane : EtOAc 10 : 1).

Ethyl (*Z*)-2-chloro-3-(4-methoxyphenyl)acrylate (3h). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.6 Hz, 2 H), 7.89 (s, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 3.90 (s, 3 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7 (C), 161.6 (C), 136.4 (CH), 132.6 (2 × CH), 130.2 (C), 126.9 (C), 113.9 (2 × CH), 62.3 (CH_2), 55.3 (CH_3), 14.2 (CH_3);

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MS (70 eV, EI) *m/z* (%) 240 [M^+, 100], 177 (20), 132 (70), 89 (10); HRMS (70 eV) calc. for $C_{12}H_{13}ClO_3$ 240.0553, found 240.0505; IR (neat): *ν* 3055, 1717, 1603, 738 cm^{-1}; R_f = 0.32 (hexane : EtOAc 10 : 1).

Isopropyl (*Z*)-2-bromo-3-cyclohexylacrylate (3j). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.04 (d, *J* = 7.8 Hz, 1 H), 5.17–5.09 (m, 1 H), 2.60–2.51 (m, 1 H), 1.75–1.66 (m, 2 H), 1.37 (d, *J* = 6.0 Hz, 6 H), 1.35–1.14 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.0 (C), 149.7 (CH), 114.6 (C), 70.0 (CH), 40.9 (CH), 30.5 (2 × CH_2), 25.6 (CH_2), 25.1 (2 × CH_2), 21.5 (CH_3), 21.3 (CH_3); MS (70 eV, EI) *m/z* (%) 274 [M^+, <1], 225 (42), 183 (100), 165 (68), 101 (27); HRMS (70 eV) calc. for $C_{12}H_{19}BrO_2$ 274.0568, found 274.0659; IR (neat): *ν* 2929, 1726, 1450, 1264 cm^{-1}; R_f = 0.62 (cyclohexane : EtOAc 30 : 1).

Ethyl (*Z*)-2-bromo-5-methylhex-2-enoate (3k). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 6.77 (t, *J* = 7.5 Hz, 1 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 2.22–2.02 (m, 1 H), 1.87–1.72 (m, 2 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 0.97 (d, *J* = 5.7 Hz, 3 H), 0.95 (d, *J* = 5.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 167.6 (C), 142.2 (CH), 134.0 (C), 60.5 (CH_2), 42.5 (CH_2), 28.3 (CH), 22.6 (CH_3), 22.4 (CH_3), 14.1 (CH_3); MS (70 eV, EI) *m/z* (%) 205 [M^+ − Et, 10], 139 (77), 118 (72), 69 (100), 55 (32); HRMS (70 eV) calc. for [$C_9H_{15}BrO_2$ – Et] 204.9864, found 204.9888; IR (neat): *ν* 2995, 1745, 1472 cm^{-1}; R_f = 0.55 (cyclohexane : EtOAc 30 : 1).

Ethyl (*Z*)-2-fluorocyclohexyl-2-enoate (3l). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.01 (dd, *J* = 34.2, 9.6 Hz, 1 H), 4.43 (q, *J* = 6.8 Hz, 2 H), 2.61–2.53 (m, 1 H), 1.94–1.84 (m, 2 H), 1.74–1.63 (m, 4 H), 1.41 (t, *J* = 6.8 Hz, 3 H), 1.34–1.11 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.9 (C), 146.5 (d, *J* = 253.5 Hz, C), 125.5 (d, *J* = 11.7 Hz, CH), 64.7 (CH_2), 33.9 (CH), 31.9 (2 × CH_2), 25.7 (CH_2), 25.3 (2 × CH_2), 13.6 (CH_3); MS (70 eV, EI) *m/z* (%) 200 [M^+, 28], 81 (100), 67 (83), 55 (59); HRMS (70 eV) calc. for $C_{11}H_{17}FO_2$ 200.1213, found 200.1223; IR (neat): *ν* 1729, 1265, 740 cm^{-1}; R_f = 0.20 (hexane : EtOAc 20 : 1).

(*Z*)-2-Chloro-*N*,*N*-diethyldec-2-enamide (5a). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.96 (t, *J* = 7.1 Hz, 1 H), 3.41–3.33 (m, 4 H), 2.24 (apparent q, *J* = 7.2 Hz, 2 H), 1.41–1.39 (m, 2 H), 1.25–1.15 (m, 8 H), 1.19 (t, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H), 0.85 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 165.8 (C), 131.0 (CH), 124.3 (C), 42.8 (CH_2), 38.8 (CH_2), 31.7 (2 × CH_2), 29.1 (CH_2), 27.8 (CH_2), 22.6 (2 × CH_2), 14.2 (CH_3), 13.9 (CH_3), 12.3 (CH_3); MS (70 eV, EI) *m/z* (%) 259 [M^+, 15], 224 (100), 187 (32), 160 (79); HRMS (70 eV) calc. for $C_{14}H_{26}ClNO$ 259.1703, found 259.1727; IR (neat): *ν* 3451, 2974, 1642, 1460 cm^{-1}; R_f = 0.52 (hexane : EtOAc 3 : 1).

(*Z*)-2-Chloro-*N*,*N*-diisopropyldec-2-enamide (5b). ^{1}H NMR (400 MHz, $CDCl_3$, 233 K): *δ* 5.81 (t, *J* = 7.2 Hz, 1 H), 4.02–3.95 (m, 1 H), 3.80–3.40 (m, 1 H), 2.11 (apparent q, *J* = 6.8 Hz, 2 H), 1.40–1.09 (m, 10 H), 1.30 (d, *J* = 5.8 Hz, 6 H), 1.17 (d, *J* = 6.0 Hz, 6 H), 0.81 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 165.4 (C), 129.3 (CH), 126.7 (C), 48.0 (CH), 44.2 (CH), 31.6 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 22.5 (CH_2), 20.5 (2 × CH_3), 20.2 (CH_2), 20.0 (2 × CH_3), 13.9 (CH_3); MS (70 eV, EI) *m/z* (%) 287 [M^+, 8], 252 (100), 201 (41); HRMS (70 eV) calc. for $C_{16}H_{30}ClNO$ 287.2016, found 287.2025; IR (neat): *ν* 3444, 2927, 1643, 1431 cm^{-1}; R_f = 0.55 (hexane : EtOAc 10 : 1).

4-[(*Z*)-(1-Chlorocyclohex-1-en-1-yl)carbonyl]morpholine (5e). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.86 (d, *J* = 9.0 Hz, 1 H), 3.72–3.60 (m, 4 H), 3.54–3.44 (m, 4 H), 1.91–1.81 (m, 1 H), 1.71–1.60 (m, 2 H), 1.33–1.11 (m, 4 H), 1.03–0.91 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.1 (C), 137.8 (CH), 122.4 (C), 66.6 (CH_2), 66.4 (CH_2), 47.4 (CH_2), 45.9 (CH_2), 41.6 (CH), 32.9 (4 × CH_2), 25.7 (CH_2); MS (70 eV, EI) *m/z* (%) 257 [M^+, 14], 135 (26), 86 (50), 56 (88), 41 (100); HRMS (70 eV) calc. for $C_{13}H_{20}ClNO_2$ 257.1183, found 257.1139; IR (neat): *ν* 2926, 1712, 1642, 1448 cm^{-1}; R_f = 0.57 (hexane : EtOAc 10 : 1).

4-[(*Z*)-(1-Chloro-4-methylpent-1-en-1-yl)carbonyl]morpholine (5g). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.07 (t, *J* = 7.4 Hz, 1 H), 3.72–3.53 (m, 8 H), 2.14 (apparent t, *J* = 7.2 Hz, 2 H), 1.78–1.68 (m, 1 H), 0.89 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 165.0 (C), 132.5 (CH), 124.3 (C), 66.5 (CH_2), 66.3 (CH_2), 47.2 (CH), 42.1 (CH_2), 36.7 (CH_2), 27.6 (CH_2), 22.3 (2 × CH_3); MS (70 eV, EI) *m/z* (%) 231 [M^+, 20], 216 (32), 196 (36), 174 (86), 86 (100); HRMS (70 eV) calc. for $C_{11}H_{18}ClNO_2$ 231.1020, found 231.1021; IR (neat): *ν* 2959, 1641, 1439, 1116 cm^{-1}; R_f = 0.25 (hexane : EtOAc 3 : 1).

(*Z*)-2-Chloro-*N*,*N*-diethyl-4-methylhex-2-enamide (5h). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 5.73 (d, *J* = 9.4 Hz, 1 H), 3.41 (q, *J* = 7.1 Hz, 4 H), 2.71–2.61 (m, 1 H), 1.48–1.39 (m, 2 H), 1.19 (t, *J* = 7.1 Hz, 6 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 164.1 (C), 136.0 (CH), 123.8 (C), 42.9 (CH_2), 39.1 (CH_2), 34.6 (CH), 29.1 (CH_2), 19.2 (CH_3), 14.0 (CH_3), 12.4 (CH_3), 11.9 (CH_3); MS (70 eV, EI) *m/z* (%) 217 [M^+, 50], 182 (99), 160 (100), 145 (68); HRMS (70 eV) calc. for $C_{11}H_{20}ClNO$ 217.1233, found 217.1222; IR (neat): *ν* 3511, 2949, 1643, 1458 cm^{-1}; R_f = 0.41 (hexane : EtOAc 3 : 1).

(*Z*)-2-Chloro-*N*,*N*-diethyltrideca-2,12-dienamide (5i). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.94 (t, *J* = 7.1 Hz, 1 H), 5.84–5.75 (m, 1 H), 5.01–4.89 (m, 2 H), 3.42–3.30 (m, 4 H), 2.25–2.20 (m, 2 H), 2.04–1.96 (m, 2 H), 1.42–1.10 (m, 12 H), 1.17 (t, *J* = 6.9 Hz, 3 H), 1.13 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 166.2 (C), 139.8 (CH), 131.3 (CH), 124.7 (C), 114.4 (CH_2), 43.2 (CH_2), 39.2 (CH_2), 34.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 28.3 (2 × CH_2), 14.3 (CH_3), 12.7 (CH_3); MS (70 eV, EI) *m/z* (%) 299 [M^+, 6], 264 (100), 160 (94), 41 (72); HRMS (70 eV) calc. for $C_{17}H_{30}ClNO$ 299.2016, found 299.2022; IR (neat): *ν* 3440, 2927, 1659, 1462 cm^{-1}; R_f = 0.42 (hexane : EtOAc 3 : 1).

(*Z*)-2-Chloro-*N*,*N*-diethyl-4-phenylpent-2-enamide (5j). ^{1}H NMR (400 MHz, $CDCl_3$, 233 K): *δ* 7.42–7.10 (m, 5 H), 5.94 (d, *J* = 9.2 Hz, 1 H), 3.93–3.84 (m, 1 H), 3.28–3.19 (m, 2 H), 3.15–3.06 (m, 2 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 0.98 (t, *J* = 6.8 Hz, 3 H), 0.96 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 233 K): *δ* 165.2 (C), 143.1 (C), 134.4 (CH), 128.4 (2 × CH), 127.2 (C), 126.5 (2 × CH), 123.0 (CH), 42.7 (CH), 38.9 (CH_2), 38.0 (CH_2), 20.2 (CH_3), 13.6 (CH_3), 12.1 (CH_3); MS (70 eV, EI) *m/z* (%) 265 [M^+, 47], 230 (100), 158 (98), 129 (89), 72 (71); HRMS (70 eV) calc. for $C_{15}H_{20}ClNO$ 265.1233, found 265.1191; IR (neat): *ν* 3425, 1615, 1451, 701cm^{-1}; R_f = 0.35 (hexane : EtOAc 3 : 1).

General procedure for the synthesis of α-halo-α,β-unsaturated ketones 9. The requisite organolithium compound (3.0 mmol) was added dropwise to the corresponding morpholine amide **3**

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(1.0 mmol) in THF (4 mL) at −78°C. After stirring for 30 min the reaction was quenched with an aqueous saturated solution of NH_4Cl (10 mL), followed by extraction with diethyl ether (3 × 10 mL). The usual workup provided crude products **9**, which were purified by flash column chromatography on silica gel (hexane : EtOAc 10 : 1).

(*Z*)-1,3-Dichloro-4-cyclohexylbut-3-en-2-one (9c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, J = 9.3 Hz, 1 H), 4.56 (s, 2 H), 2.71–2.59 (m, 1 H), 1.79–1.59 (m, 4 H), 1.43–1.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4 (C), 147.5 (CH), 128.2 (C), 46.4 (CH_2), 38.6 (CH), 30.7 (2 × CH_2), 25.6 (CH_2), 25.1 (2 × CH_2); MS (70 eV, EI) m/z (%) 220 [M^+, 18], 151 (10), 89 (15), 81 (100); HRMS (70 eV) calc. for $C_{10}H_{14}Cl_2O$ 220.0422, found 220.0413; IR (neat): ν 2932, 1711, 1266, 739 cm^{-1}; R_f = 0.22 (hexane : EtOAc 20 : 1).

(*Z*)-5-Chloro-8-methylnona-1,5-dien-4-one (9d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (t, J = 7.2 Hz, 1 H), 6.05–5.91 (m, 1 H), 5.25–5.15 (m, 2 H), 3.56 (d, J = 7.2 Hz, 2 H), 2.31 (apparent t, J = 7.2 Hz, 2 H), 1.92–1.82 (m, 1 H), 0.98 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3 (C), 140.6 (CH), 133.3 (C), 130.4 (CH), 118.9 (CH_2), 43.4 (CH), 38.4 (CH_2), 27.9 (CH_2), 22.4 (2 × CH_3); IR (neat): ν 3055, 1726, 1266, 739 cm^{-1}; R_f = 0.42 (hexane : EtOAc 10 : 1).

General procedure for the synthesis of α-halo-α,β-unsaturated acids 10. To a solution of the corresponding compound **3** (1.0 mmol) in MeOH (2 mL) under a nitrogen atmosphere was added KOH (3.0 mmol). After stirring the mixture for 12 h at room temperature the reaction was quenched by the addition of HCl 1M (5 mL). The organic material was then extracted with diethyl ether (3 × 10 mL) and dried over Na_2SO_4. Solvents were removed *in vacuo*. Purification by flash column chromatography on silica gel (hexane : EtOAc 1 : 1) afforded pure compounds **10**.

(*Z*)-2-Chloro-3-cyclohexylacrylic acid (10a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (br s, 1 H), 7.07 (d, J = 9.3 Hz, 1 H), 2.66 (m, 1 H), 1.79–1.66 (m, 4 H), 1.43–1.15 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (C), 149.8 (CH), 122.0 (C), 38.8 (CH), 30.7 (2 × CH_2), 25.7 (CH_2), 25.2 (2 × CH_2); MS (70 eV, EI) m/z (%) 188 [M^+, 11], 107 (17), 82 (100), 67 (74), 41 (22); HRMS (70 eV) calc. for $C_9H_{13}ClO_2$ 188.0604, found 188.0608; IR (neat): ν 3430, 2925, 1692, 1624 cm^{-1}; R_f = 0.17 (hexane : EtOAc 1 : 1).

(*Z*)-2-Chloro-4-methylhex-2-enoic acid (10b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.37 (br s, 1 H), 7.27 (t, J = 7.4 Hz, 1 H), 2.31 (t, J = 7.2 Hz, 2 H), 1.94–1.81 (m, 1 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (C), 144.6 (CH), 124.3 (C), 38.5 (CH), 27.7 (CH_2), 22.3 (2 × CH_3); MS (70 eV, EI) m/z (%) 162 [M^+, 8], 120 (100), 69 (15), 56 (25); HRMS (70 eV) calc. for $C_7H_{11}ClO_2$ 162.0448, found 162.0450; IR (neat): ν 3426, 1630, 1466, 1266 cm^{-1}; $_Rf$ = 0.17 (hexane : EtOAc 3 : 1).

General procedure for the synthesis of α-haloallylic alcohols 11. To a suspension of $LiAlH_4$ (1.0 mmol) in THF was added dropwise the corresponding compound **3** (1.0 mmol) in THF (1 mL) at 0 °C. After stirring the mixture for 12 h at room temperature the reaction was quenched by the addition of a mixture of water–ice and extracted with ether. The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude products **11** were purified by flash column chromatography on silica gel (hexane : EtOAc 3 : 1).

Compound **11a** has been previously described.[26]

(*Z*)-2-Chloro-3-cyclohexylprop-2-en-1-ol (11b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64 (d, J = 9.0 Hz, 1 H), 4.17 (s, 2 H), 2.54–2.44 (m, 1 H), 2.08 (br s, 1 H), 1.82–1.52 (m, 6 H), 1.35–1.16 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.5 (CH), 131.1 (C), 67.4 (CH_2), 34.3 (CH), 33.6 (2 × CH_2), 32.1 (2 × CH_2), 31.8 (CH_2); MS (70 eV, EI) m/z (%) 174 [M^+, 4], 159 (59), 123 (100), 81 (85), 55 (55); HRMS (70 eV) calc. for $C_9H_{15}ClO$ 174.0811, found 174.0817; IR (neat): ν 3357, 2924, 1449 cm^{-1}; R_f = 0.46 (hexane : EtOAc 5 : 1).

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