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Sequential Reactions Promoted by Manganese: Completely Stereoselective Synthesis of (*E*)-α,*β*-Unsaturated Amides, Ketones, Aldehydes, and Carboxylic Acids‡

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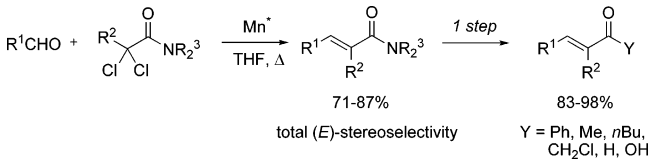

A complete *E*-selective synthesis of α,*β*-unsaturated amides through a sequential reaction of a range of dichloroamides with a variety of aldehydes promoted by Rieke manganese (Mn*) is reported. A mechanism based on a sequential aldol-type reaction and a completely stereoselective *β*-elimination is proposed to explain these results. The unsaturated amides obtained are readily and efficiently transformed into α,*β*-unsaturated ketones, aldehydes, or carboxylic acids without loss of the diastereoisomeric purity of the C−C double bond.

Introduction

In an ideal organic synthesis, the starting materials should be cheap and readily available, the number of steps should be minimized, and the desired target compounds should be prepared in both high yields and with complete selectivity. In general, the two first requirements are achievable by sequential processes and consequently, in recent years, these methodologies have shown a great deal of development. In this context, we recently reported the SmI_2-mediated synthesis of a range of unsaturated compounds such as α,*β*-unsaturated esters,[1] carboxylic acids,[2] or ketones[3] through a sequential process (an aldolic/elimination reaction). However, these methods present a drawback in the relatively high cost of the SmI_2. For this reason an alternative method to form the fore-mentioned unsaturated compounds by using a reagent cheaper than samarium diiodide would be desirable. To this end, we have published very recently a sequential synthesis of α,*β*-unsaturated esters by reaction of dihaloesters with aldehydes, promoted by cheap[4] active manganese[5] (Mn*). This synthesis is the first example of a sequential reaction mediated by manganese,[6] which afforded α,*β*-unsaturated esters in high yields, with complete *E*-selectivity. The experimental procedure was very straightforward and easy, demonstrating that this sequential reaction mediated by Mn* is an improvement to our previously described sequential synthesis of α,*β*-unsaturated esters mediated by SmI_2,[1] and constitutes a valuable alternative to obtain α,*β*-unsaturated esters.

These previous results prompted us to test the application of a Mn*-promoted sequential reaction toward the synthesis of other unsaturated compounds such as α,*β*-unsaturated amides, since these compounds belong to an important class of natural products which show both biological and insecticide properties.[7] In addition, from a synthetic point of view, α,*β*-unsaturated amides are useful building blocks in organic synthesis[8] and have

‡ Dedicated to the memory of Prof. Lorenzo Pueyo Casaus.

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(4) Aldrich Catalogue (2007−2008): manganese (325 mesh): 250 g, 37.00 euros; samarium (40 mesh): 50 g, 357.50 euros; 1 mmol SmI_2 (prepared by the method described in: Concellón, J. M.; Rodríguez-Solla, H.; Bardales, E.; Huerta, M. *Eur. J. Org. Chem.* **2003**, 1775−1778),1.2 euros; 1 mmol Mn* (prepared by the method herein described), 0.30 euros.

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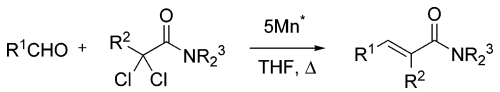
been used as starting materials to obtain many natural products.[9] However, compared to the synthesis of other α,β-unsaturated acid derivatives such as esters, the preparation of α,β-unsaturated amides has been scarcely reported and the development of effective general methods for their stereoselective synthesis is of significant value. The previously reported preparations of α,β-unsaturated amides are generally achieved by C=C bond formation by Horner−Wadsworth−Emmons[10] or by Peterson[11] reactions, from acetylenic compounds,[9,12] by carbonylation processes[13] or by using 2,2-difluorovinyllithium.[14] Previously, our group reported the synthesis of α,β-unsaturated amides with complete or high *E*-selectivity and in good yields, from 2-chloro-3-hydroxyamides[15] or α,β-epoxyamides,[16] the process being promoted, in both cases, by SmI_2.

Herein, we describe a new and easy route to (*E*)-α,β-unsaturated amides with total stereoselectivity and in high yield, via a sequential reaction using readily available dichloroamides and a variety of aldehydes. Moreover, the interesting transformation of amides into various unsaturated compounds without loss of the diastereoisomeric purity of the C−C double bond previously generated is reported. A mechanism to explain the *E*-stereoselectivity is also proposed.

SCHEME 1. Synthesis of (*E*)-α,β-Unsaturated Amides 3



1 **2** **3**

TABLE 1. Synthesis of α,β-Unsaturated Amides 3

entry	**3**	R^1	R^2	$NR_2{}^3$	yield (%)[a]
1	**3a**	*n*-C_7H_{15}	H	NEt_2	87
2	**3b**	*n*-C_7H_{15}	H	*b*	84
3	**3c**	*s*-Bu	H	NEt_2	78
4	**3d**	*i*-Bu	H	NEt_2	84
5	**3e**	*i*-Bu	H	*b*	83
6	**3f**	CH_2=$CH(CH_2)_8$	H	NEt_2	81
7	**3g**	CH_2=$CH(CH_2)_8$	H	*b*	80
8	**3h**	Cy	H	NEt_2	85
9	**3i**	Cy	H	N*i*-Pr_2	85
10	**3j**	PhCH(Me)	H	NEt_2	77
11	**3k**	$PhCH_2CH_2$	H	NEt_2	82
12	**3*l***	Ph	H	NEt_2	71
13	**3m**	Ph	H	*b*	79
14	**3n**	*p*-$MeOC_6H_4$	H	NEt_2	82
15	**3o**	*p*-$MeOC_6H_4$	H	N*i*-Pr_2	83
16	**3p**	*p*-ClC_6H_4	H	NEt_2	80
17	**3q**	*n*-C_7H_{15}	Me	NEt_2	75
18	**3r**	*s*-Bu	Me	*b*	73
19	**3s**	*i*-Bu	Me	NEt_2	77
20	**3t**	$PhCH_2CH_2$	Me	NEt_2	78
21	**3u**	Ph	Me	*b*	76
22	**3v**	*n*-C_7H_{15}	$PhCH_2$	NEt_2	71
23	**3w**	CH_2=$CH(CH_2)_8$	$PhCH_2$	NEt_2	73

[a] Yields of the isolated products after column chromatography based on aldehydes **1**; in all cases a single diastereoisomer was observed the diastereoisomeric ratio (>98%/2) being determined from the crude reaction product by GC-MS and/or ^{1}H NMR (300 MHz). [b] From morpholine.

Results and Discussion

Synthesis of α,β-Unsaturated Amides 3. The active manganese was readily prepared by using the method described by Cahiez.[5d] Thus, treatment of Li_2MnCl_4 (or $MnCl_2$.2LiCl) (13 mmol) 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.

Our first attempts were performed with *n*-octanal **1a** and *N*,*N*-diethyldichloroacetamide, as starting materials, at room temperature and under a variety of reaction conditions. The reaction did not proceeded to completion and long reaction times were required. The reaction was hence carried out at reflux in THF, and the best results were obtained by treating a solution of a range of aldehydes **1** (1 equiv.) and the corresponding dichloroacetamide **2** (1.2 equiv) in THF at reflux with active manganese (5 equiv) for 5 h (Scheme 1).

The corresponding disubstituted (*E*)-α,β-unsaturated amides **3a**−**p** were obtained with total *E*-stereoselectivity and high yields after hydrolysis (Scheme 1, Table 1). Taking into account that the highly stereoselective preparation of trisubstituted alkenes is one of the most challenging problems in organic chemistry,[17] we have also applied this methodology for synthesizing α,β-unsaturated amides in which the C=C bond is trisubstituted (Table 1, entries 17−23). To this end, 2,2-dichloropropanamide (R^2 = Me) or 2,2-dichloro-3-phenylpropanamide (R^2 = $PhCH_2$) was employed, using the above-mentioned reaction conditions.

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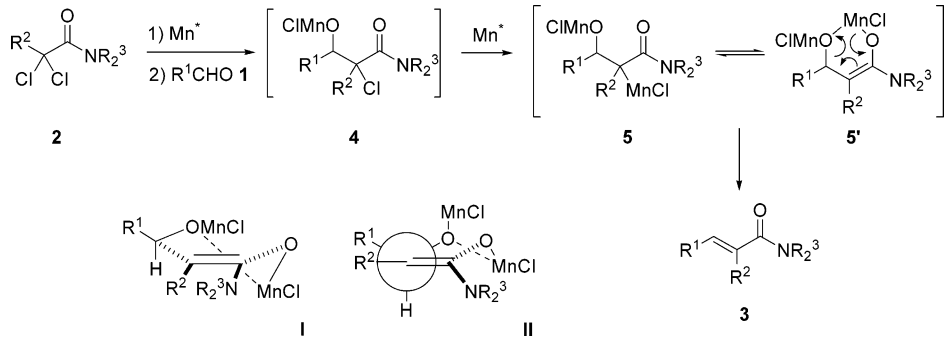
SCHEME 2. Proposed Mechanism



Attempts to synthesize tetrasubstituted amides from ketones and 2,2-dichloroamides failed, however. After studying several sets of conditions, a mixture of products without synthetic value was obtained.

This synthesis of α,*β*-unsaturated amides via a sequential reaction of aldehydes **1** with the corresponding dichloroamide **2** is general. Thus, unsaturated amides are obtained from aliphatic (linear, branched, or cyclic) aldehydes in high yields and as a single diastereoisomer. The synthesis of aromatic (*E*)-α,*β*-unsaturated amides has been performed with aldehydes having donor and withdrawing substituents. Interestingly, the selectivity and yield of these reactions were unaffected when the reaction was carried out from dichloroamides derived from different amines (Table 1, entries 1/2, 4/5, 6/7, 8/9, 12/13, and 14/15). Therefore, it was possible to synthesize amides such as those derived from morpholine (Table 1, entries 2, 5, 7, 13, 18, and 21), which can be easily transformed into other synthetically valuable compounds (see below). In addition, unsaturated amides **3** were also obtained by using an aldehyde with high proclivity to enolize (Table 1, entry 10) and from some functionalized aldehydes, the reported transformation being compatible with the presence of a C−C double bond (Table 1, entries 6, 7, and 23), an alkoxy (Table 1, entries 14 and 15), or a chlorine atom (Table 1, entry 16) in the molecule.

The diastereoisomeric ratio of the α,*β*-unsaturated amides **3** was determined based on the crude reaction products by ^{1}H NMR spectroscopy (300 MHz) and GC-MS. In all cases, the (*E*)-stereoisomer was isolated as the only isomer and other isomers were not detected in the crude reaction.[18]

The *E* stereochemistry in the C=C bond was assigned on the basis of the value of ^{1}H NMR coupling constant between the olefinic protons of compounds **3**[19] in the case of compounds **3a**−**p**, and by comparison of the NMR spectra for compounds **3a**,[15,20] **3d**,[20] **3e**,[21] **3i**,[16b] **3j**,[15] **3*l***,[15,16a] and **3n**[16a] with those described in the literature for the same unsaturated amides. In the case of trisubstituted amides **3q**−**w**, the total stereoselectivity was again observed and ascertained as above. The relative configuration of compounds **3r**, **3t**, and **3v** was assigned by NOESY experiments, or in the case of compounds **3u**[22] and **3q**[16b] by comparison of its NMR spectra with those previously described in the literature for the same unsaturated amide. The *E*-stereochemistry of compounds **3s** and **3w** was assigned by analogy.

The synthesis described herein of α,*β*-unsaturated amides constitutes an improvement of our previous syntheses of α,*β*-unsaturated amides promoted by SmI_2[15,16] since the starting materials are readily available, the experimental procedure is very simple, and the unsaturated amides are obtained in higher overall yields, based on the starting aldehyde and with complete stereoselectivity (unsaturated amides were obtained by using SmI_2 with a *E*/*Z* ratio ranging between 81/19 and >98/2).[15,16]

To rationalize the synthesis of amides **3**, we proposed a similar mechanism to that previously used to explain the preparation of α,*β*-unsaturated esters through a sequential reaction promoted by Mn*.[6] Thus, an aldolic reaction initially takes place between the enolate generated by metalation of the dichloroamide and the aldehyde affording the Reformatsky adducts **4**. A second metalation of **4** by Mn* affords the intermediate **5**, which undergoes a spontaneous *β*-elimination reaction to give amides **3**. The complete *E*-selectivity of the elimination reaction can be explained by assuming a cyclic six-membered transition state **I**, as a consequence of the coordination between the manganese and the oxygen. The R^1 group occupies an equatorial position in this transition state to reduce the 1,3-steric hindrance. The elimination through this transition state **I** generates a C−C double bond with an *E*-relative configuration as that shown by products **3** (Scheme 2).

Synthesis of α,*β*-Unsaturated Ketones 6, Aldehydes 7, and Carboxylic Acids 8. To demonstrate the synthetic applications of the obtained amides **3**, selected examples were readily transformed into various unsaturated compounds, such as ketones **6**, aldehydes **7**, or carboxylic acids **8** (Scheme 3).

The preparation of α,*β*-unsaturated ketones **6** was carried out starting from various α,*β*-unsaturated amides derived from morpholine. Thus, the reaction of different α,*β*-unsaturated amides with the corresponding organolithium compound at −78 °C for 30 min afforded the corresponding unsaturated ketone in very high yields (>83%) (Scheme 3, Table 2).[23]

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 by this transformation, with the ketone being obtained as a single *E*-stereoisomer. The

(18) When the minor diastereoisomer was not observed the *E*/*Z* ratio was assigned >98/2.

(19) The coupling constant between the olefinic protons of compounds **3** ranging between J = 14.9 and 15.4 Hz were in accordance with the average literature values: Silverstein, R. M.; Bassler, G. C.; Morrill T. C. In *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1991; Chapter 4, Appendix F, p 221.

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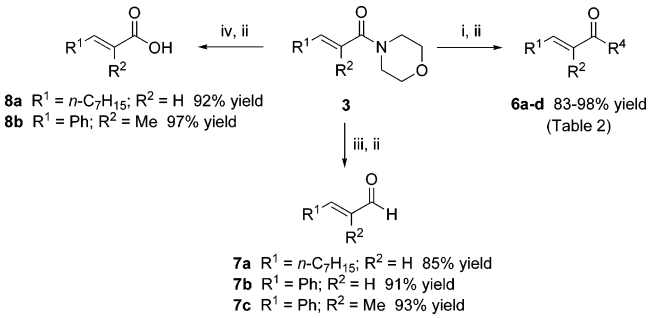
SCHEME 3. Synthesis of α,β-Unsaturated Ketones 6, Aldehydes 7, and Carboxylic Acids 8[a]



[a] Reagents and conditions: (i) R^4Li, −78 °C, THF, 30 min; (ii) H_3O^+; (iii) $LiAlH_4$, −78 °C, THF, 12 h; (iv) *t*-BuOK, H_2O, THF, reflux, 12 h.

TABLE 2. Synthesis of α,β-Unsaturated Ketones 6

entry	6	R^1	R^2	R^4	yield (%)[a]
1	**6a**	*i*-Bu	H	Ph	94
2	**6b**	*n*-C_7H_{15}	H	Me	98
3	**6c**	*s*-Bu	Me	*n*-Bu	89
4	**6d**	*s*-Bu	Me	CH_2Cl	83

[a] Yields of the isolated products after column chromatography based on the unsaturated amides **3**.

synthesis of alkyl alk-1-enyl ketones, such as **6b**,**c**, by other alternative methods would present special difficulty.[24] In addition it is worthy to mention that in the synthesis of the chlorinated ketone **6d**, chloromethyllithium was generated in situ.[25] Remarkably, the use of morpholine amides as starting materials, to transform α,β-unsaturated amides into ketones, is more advantageous than the corresponding Weinreb derivatives since the morpholine derivatives are cheaper.

The α,β-unsaturated aldehydes **7a**−**c** can be obtained by reduction of unsaturated morpholine-based amides **3**, with lithium aluminum hydride at low temperature (−78 °C).[26] Compounds **7** were obtained in high yield (>85%) and as a single *E*-diastereoisomer (Scheme 3). No important differences in the yields of the obtained aldehydes were observed when different morpholine amides **3** were employed as starting compounds.

Finally, unsaturated carboxylic acids **8** were also obtained from amides **3**, as is shown in Scheme 3. Thus, the treatment of the morpholine amide **3b** or **3u** with *t*-BuOK/H_2O/THF[27] at reflux afforded the corresponding (*E*)-α,β-unsaturated carboxylic acid **8a** and **8b** in very high yield (92% and 97% yield, respectively) and without loss of stereochemistry. This transformation also could be carried out with the *N*,*N*-diethyl amides instead of the *N*-morpholine amide. So, the treatment of *N*,*N*-diethylcinnamamide **3*l*** under the same reaction conditions afforded the cinnamic acid **8c** in very high yields (95%).

Therefore the reported synthesis of α,β-unsaturated amides combined with their transformation into different unsaturated carbonyl compounds constitutes an easy and efficient access to α,β-unsaturated ketones, aldehydes, or carboxylic acids **6**, **7**, or **8**, respectively. Thus, unsaturated ketones **6** were obtained from the corresponding aldehydes in an overall yield ranging between 61% and 82%, aldehydes **7** in an overall yield of 71% or 72%, and finally, in the case of carboxylic acids **8**, the yields ranged between 74% and 77%.

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Conclusions

We have described a complete *E*-selective synthesis of α,β-unsaturated amides through a sequential reaction of a range of dichloroamides with a variety of aldehydes promoted by Rieke manganese (Mn*). This synthetic method is an advantageous alternative to other methods of synthesis of (*E*)-*a*,β-unsaturated amides, because (a) the reaction takes place with complete *E*-selectivity, (b) high yields are obtained, (c) an easy experimental procedure is utilized, and (d) the requisite starting materials are very cheap. Moreover, it has been shown that the obtained unsaturated amides could be readily transformed into α,β-unsaturated ketones, aldehydes, or carboxylic acids with very high yields and without losing diastereoisomeric purity of the C−C double bond. A mechanism based on a successive aldol-type reaction and a β-elimination is proposed to explain these results. Further studies directed toward the development of the synthetic applications of this method are currently under investigation in our laboratory.

Experimental Section

General Procedure. Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF was distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased in the highest quality available and were used without further purification. ^1H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were recorded at 75 or 100 MHz. GC-MS spectra were measured at 70 eV.

Preparation of Starting Dichloroamides 2. A mixture of diethylamine, diisopropylamine, or morpholine (40 mmol) and dichloroacetyl chloride (1.9 mL, 20 mmol) in dry CH_2Cl_2 (54 mL) was refluxed for 5 h. After that time, the mixture was quenched with aqueous HCl (1.0 M) and extracted with dichloromethane. The combined extracts were dried over Na_2SO_4 and the solvent was removed in vacuuo to afford *N*,*N*-diethyldichloroacetamide, *N*,*N*-diisopropyldichloroacetamide, or *N*-dichloroacetylmorpholine.

2,2-Dichloropropionamides were prepared by alkylation of the corresponding dichloroacetamides as is described in the following procedure: A solution of lithium diisopropylamide [prepared from MeLi (36 mmol, 14.4 mL, 2.5 M solution in hexane) and diisopropylamine (40 mmol, 5.8 mL) in THF (20 mL) at −78 °C] was added dropwise to a stirred solution of the dichloroacetamide (28 mmol) in dry THF (2 mL) at −78 °C and the mixture was stirred for 15 min. After that time a solution of MeI or BnBr (28 mmol) in THF (5 mL) was added dropwise and stirring was continued for 15 min. The mixture was warmed to room temperature and then quenched with an aqueous saturated solution of NH_4Cl (20 mL) followed by extraction with diethyl ether (3 × 20 mL). The usual workup provided crude products, which were purified by flash column chromatography on silica gel (hexane: EtOAc 10:1).

***N*,*N*-Diethyldichloroacetamide:** yellow oil (95% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1 H), 3.45 (q, J = 7.1 Hz, 2 H), 3.38 (q, J = 7.1 Hz, 2 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.13 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (C), 64.9 (CH), 42.3 (CH_2), 41.2 (CH_2), 14.1 (CH_3), 12.1 (CH_3).

***N*,*N*-Diisopropyldichloroacetamide:** yellow oil (90% yield); ^1H NMR (200 MHz, $CDCl_3$) δ 5.97 (s, 1 H), 4.05 (m, 1 H), 3.26 (m, 1 H), 1.14 (d, J = 6.5 Hz, 6 H), 1.02 (d, J = 6.5 Hz, 1 H); ^{13}C

NMR (50 MHz, $CDCl_3$) δ 161.5 (C), 66.8 (CH), 49.1 (CH), 46.5 (CH), 19.9 (2 × CH_3), 19.3 (2 × CH_3).

***N*-Dichloroacetylmorpholine:** white solid (92% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1 H), 3.71−3.68 (m, 4 H), 3.61−3.59 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (C), 66.3 (CH_2), 65.9 (CH_2), 65.3 (CH), 46.8 (CH_2), 43.2 (CH_2).

2,2-Dichloro-*N*,*N*-Diethylpropionamide: yellow oil (80% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (q, J = 7.0 Hz, 2 H), 3.18 (q, J = 7.0 Hz, 2 H), 2.40 (s, 3 H), 1.14 (t, J = 7.0 Hz, 3 H), 1.01 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C), 80.3 (C), 43.1 (CH_2), 42.3 (CH_2), 14.8 (CH_3), 12.9 (CH_3).

***N*-(2,2-Dichloropropionyl)morpholine:** yellow oil (72% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78−3.76 (m, 4 H), 3.51−3.49 (m, 4 H), 2.08 (S, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (C), 79.7 (C), 66.1 (2 × CH_2), 48.3 (CH_2), 43.8 (CH_2), 35.9 (CH_3).

2,2-Dichloro-*N*,*N*-diethyl-3-phenylpropionamide: yellow oil (71% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.33 (m, 5 H), 3.84 (q, J = 6.9 Hz, 2 H), 3.77 (s, 2 H), 3.41 (q, J = 6.9 Hz, 2 H), 1.27 (t, J = 6.9 Hz, 3 H), 1.20 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (C), 134.4 (C), 132.3 (2 × CH), 127.5 (2 × CH), 127.3 (CH), 83.4 (C), 50.5 (CH_2), 43.1 (CH_2), 41.9(CH_2), 13.1 (CH_3), 11.9 (CH_3).

Preparation of Highly Active 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 Amides 3. The slurry of Mn* (2.5 mmol, 8.5 mL) in THF was added to a stirred solution of 1,1-dichloroacetamide (0.6 mmol) and the corresponding aldehyde (0.5 mmol) in THF (2 mL) under 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), and the combined organic extracts were washed sequentially with HCl (3 M; 2 × 10 mL), saturated $NaHCO_3$ (2 × 20 mL), saturated $Na_2S_2O_3$ (2 × 20 mL), and brine (2 × 20 mL) and dried over Na_2SO_4. Solvents were removed in vacuuo. Purification by flash column chromatography on silica gel (hexane:EtOAc 3:1) provided pure compounds **3**.

Compounds **3a**, **3d**,**e**, **3i**,**j**, **3*l***, **3n**, **3q**, and **3u** displayed analytical data in accordance with the published values.[15,16,20−22]

***N*-[(*E*)-Dec-2-enoyl]morpholine (3b):** yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.0, 7.1 Hz, 1 H), 6.07 (dt, J = 15.0, 1.4 Hz, 1 H), 3.56−3.41 (m, 8 H), 2.07 (apparent q, J = 7.05 Hz, 2 H), 1.35−1.30 (m, 2 H), 1.19−1.14 (m, 8 H), 0.75 (t, J = 8.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 148.0 (CH), 118.2 (CH), 66.4 (CH_2), 66.3 (CH_2), 45.4 (CH_2), 41.5 (CH_2), 32.5 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 22.5 (CH_2), 14.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 239 [M^+, <1], 168 (100), 140 (17), 81 (35); HRMS (70 eV) calcd for $C_{14}H_{25}NO_2$ 239.1885, found 239.1853; IR (neat) 3440, 2924, 1654, 1653, 1116 cm^{-1}; R_f 0.44 (hexane:EtOAc 1:1).

(*E*)-*N*,*N*-Diethyl-4-methylhex-2-enamide (3c): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, J = 14.9, 7.9 Hz, 1 H), 6.14 (d, J = 14.9 Hz, 1 H), 3.46−3.34 (m, 4 H), 2.21 (apparent q, J = 6.7 Hz, 3 H), 1.27−1.10 (m, 6 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.95−0.86 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (C), 151.1 (CH), 118.7 (CH), 42.0 (CH_2), 40.7 (CH_2), 38.3 (CH), 28.9 (CH_2), 19.2 (CH_3), 14.7 (CH_3), 13.0 (CH_3), 11.5 (CH_3); MS (70 eV, EI) *m*/*z* (%) 183 [M^+, 12], 126 (100), 111 (79), 55 (43); HRMS (70 eV) calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1624; IR (neat) 2965, 1657, 1608, 983 cm^{-1}; R_f 0.27 (hexane:EtOAc 3:1).

(*E*)-*N*,*N*-Diethyltrideca-2,12-dienamide (3f): pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.1, 7.1 Hz, 1 H), 6.19 (dt, J = 15.0, 1.5 Hz, 1 H), 5.87−5.77 (m, 1 H), 5.02−4.91 (m, 2 H), 3.43 (q, J = 7.1 Hz, 2 H), 3.38 (q, J = 7.1 Hz, 2 H), 2.21 (q, J = 7.1 Hz, 2 H), 2.08−2.02 (m, 2 H), 1.47−1.25 (m, 12 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.15 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (C), 146.2 (CH), 139.1 (CH), 120.2 (CH), 114.0 (CH_2), 42.0 (CH_2), 40.7 (CH_2), 33.7 (CH_2), 32.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (2 × CH_2), 28.8 (CH_2), 28.3 (CH_2), 14.7 (CH_3), 13.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 265 [M^+, 9], 154 (19), 126 (100), 55 (25); HRMS (70 eV) calcd for $C_{17}H_{31}NO$ 265.2406, found 265.2412; IR (neat) 3412, 2927, 1660, 1619, 1431 cm^{-1}; R_f 0.28 (hexane:EtOAc 3:1).

***N*-[(*E*)-Tridec-2,12-dienoyl]morpholine (3g):** colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, J = 15.0, 6.9 Hz, 1 H), 6.19 (dt, J = 15.0, 1.5 Hz, 1 H), 5.88−5.74 (m, 1 H), 5.03−4.91 (m, 2 H), 3.69−3.49 (m, 8 H), 2.34−2.27 (m, 1 H), 2.20 (dq, J = 6.9, 1.3 Hz, 1 H), 2.03 (apparent q, J = 6.9 Hz, 2 H), 1.48−1.26 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C), 147.4 (CH), 139.1 (CH), 119.2 (CH), 114.1 (CH_2), 66.7 (2 × CH_2), 45.6 (CH_2), 41.5 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.2 (CH_2); MS (70 eV, EI) *m*/*z* (%) 279 [M^+, 52], 168 (69), 140 (100), 129 (30), 69 (79); HRMS (70 eV) calcd for $C_{17}H_{29}NO_2$ 279.2198, found 279.2188; IR (neat) 2930, 1665, 1267, 907 cm^{-1}; R_f 0.12 (hexane:EtOAc 3:1).

(*E*)-3-Cyclohexyl-*N*,*N*-diethylacrylamide (3h): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, J = 15.1, 7.0 Hz, 1 H), 6.12 (d, J = 15.1 Hz, 1 H), 3.44−3.32 (m, 4 H), 3.11−2.02 (m, 1 H), 1.76−1.61 (m, 4 H), 1.30−1.10 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 151.0 (CH), 117.8 (CH), 41.9 (CH_2), 40.7 (CH_2), 40.5 (CH), 31.9 (2 × CH_2), 25.8 (CH_2), 25.6 (2 × CH_2), 14.6 (CH_3), 12.9 (CH_3); MS (70 eV, EI) *m*/*z* (%) 209 [M^+, 21], 137 (36), 126 (100), 55 (49); HRMS (70 eV) calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1785; IR (neat) 2926, 1657, 1614, 980 cm^{-1}; R_f 0.22 (hexane:EtOAc 3:1).

(*E*)-*N*,*N*-Diethyl-5-phenylpent-2-enamide (3k): orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5 H), 7.00 (dt, J = 15.1, 6.9 Hz, 1 H), 6.24 (dt, J = 15.1, 1.6 Hz, 1 H), 3.49 (q, J = 7.0 Hz, 2 H), 3.37 (q, J = 7.0 Hz, 2 H), 2.86 (t, J = 8.2 Hz, 2 H), 2.65−2.57 (m, 2 H), 1.21 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 144.5 (CH), 141.1 (C), 128.3 (4 × CH), 125.9 (CH), 121.2 (CH), 42.0 (CH_2), 40.6 (CH_2), 34.6 (CH_2), 34.0 (CH_2), 14.7 (CH_3), 13.0 (CH_3); MS (70 eV, EI) *m*/*z* (%) 231 [M^+, 18], 159 (46), 126 (69), 91 (100), 72 (17); HRMS (70 eV) calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1600; IR (neat) 2932, 1659, 1616, 670 cm^{-1}; R_f 0.15 (hexane:EtOAc 3:1).

***N*-Cinnamoylmorpholine (3m):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 15.5 Hz, 1 H), 7.56−7.37 (m, 5 H), 6.86 (d, J = 15.5 1 H), 3.75 (apparent s, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C), 143.1 (CH), 134.2 (C), 129.7 (CH), 128.6 (2 × CH), 127.6 (2 × CH), 115.3 (CH), 66.6 (CH_2), 66.5 (CH_2), 45.6 (CH_2), 41.9 (CH_2); HRMS (70 eV) calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1093; IR (neat) 3426, 1649, 1265, 909, 739 cm^{-1}; R_f 0.52 (EtOAc).

(*E*)-*N*,*N*-Diisopropyl-3-(4-methoxyphenyl)acrylamide (3o): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 15.2 Hz, 1 H), 7.49 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.77 (d, J = 15.2 Hz, 1 H), 4.30−4.27 (m, 1 H), 3.83 (s, 3 H), 3.47−3.42 (m, 1 H), 1.45 (d, J = 6.6 Hz, 6 H), 1.23 (d, J = 6.3 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C), 159.9 (C), 140.6 (CH), 128.9 (2 × CH), 127.5 (C), 116.9 (CH), 113.6 (2 × CH), 55.1 (CH_3), 45.7 (2 × CH), 20.2 (4 × CH_3); MS (70 eV, EI) *m*/*z* (%) 261 [M^+, 12], 161 (100), 134 (14), 77 (4); HRMS (70 eV) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1701; IR (neat) 3452, 2966, 1643, 1641, 1511, 825 cm^{-1}; R_f 0.22 (hexane:EtOAc 3:1).

(*E*)-3-(4-Chlorophenyl)-*N*,*N*-diethylpropenamide (3p): pale orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 15.4 Hz, 1 H), 7.43−7.09 (m, 4 H), 6.71 (d, J = 15.4 Hz, 1 H), 3.39−3.36 (m, 4 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.08 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 142.2 (CH), 129.3 (C), 128.6 (2 × CH), 127.7 (2 × CH), 126.9 (C), 117.6 (CH), 42.2 (CH_2),

41.0 (CH_2), 14.9 (CH_3), 13.1 (CH_3); MS (70 eV, EI) *m*/*z* (%) 203 [$M^+ - Cl$, 16], 131 (100), 103 (56), 77 (45); HRMS (70 eV) calcd for $C_{13}H_{16}NO$ 203.1310, found 203.1298; IR (neat) 3387, 1649, 1601, 1454 cm^{-1}; R_f 0.17 (hexane:EtOAc 3:1).

***N*-[(*E*)-2,4-Dimethylhex-2-enoyl]morpholine (3r):** yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (d, $J = 9.7$ Hz, 1 H), 3.61−3.50 (m, 4 H), 3.48−3.44 (m, 4 H), 2.28−2.16 (m, 1 H), 1.71 (s, 3 H), 1.32−1.23 (m, 1 H), 1.21−1.11 (m, 1 H), 0.85 (d, $J = 6.63$ Hz, 3 H), 0.74 (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C), 137.3 (CH), 128.4 (C), 66.6 (CH_2), 66.4 (CH_2), 47.1 (CH_2), 41.2 (CH_2), 33.6 (CH), 29.5 (CH_2), 20.2 (CH_3), 14.5 (CH_3), 12.3 (CH_3); HRMS (70 eV) calcd for $C_{12}H_{21}NO_2$ 211.1572, found 211.1568; IR (neat) 3440, 1619, 1460, 1266, 909, 739 cm^{-1}; R_f 0.22 (hexane:EtOAc 1:1).

(*E*)-*N*,*N*-Diethyl-2,5-dimethylhex-2-enamide (3s): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (t, $J = 7.1$ Hz, 1 H), 3.35 (q, $J = 6.9$ Hz, 2 H), 3.29 (q, $J = 7.1$ Hz, 2 H), 1.94−1.90 (m, 2 H), 1.85 (s, 3 H), 1.66−1.59 (m, 1 H), 1.12−1.10 (m, 6 H), 0.85 (d, $J = 6.4$ Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (C), 132.4 (C), 128.5 (CH), 42.8 (CH_2), 38.5 (CH_2), 36.7 (CH_2), 28.6 (CH), 22.7 (2 × CH_3), 14.9 (CH_3), 14.5 (CH_3), 12.9 (CH_3); MS (70 eV, EI) *m*/*z* (%) 197 [M^+, 12], 140 (100), 125 (69), 55 (51); HRMS (70 eV) calcd for $C_{12}H_{23}NO$ 197.1780, found 197.1782; IR (neat) 2942, 1620, 1615, 1369 cm^{-1}; R_f 0.39 (hexane:EtOAc 3:1).

(*E*)-*N*,*N*-Diethyl-2-methyl-5-phenylpent-2-enamide (3t): yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.21 (m, 5 H), 5.49 (t, $J = 7.4$ Hz, 1 H), 3.35 (q, $J = 7.1$ Hz, 2 H), 3.13 (q, $J = 7.0$ Hz, 2 H), 2.73 (t, $J = 7.6$ Hz, 2 H), 2.43 (apparent q, $J = 7.4$ Hz, 2 H), 1.76 (s, 3 H), 1.11 (t, $J = 7.1$ Hz, 3 H), 1.02 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C), 141.3 (C), 132.2 (C), 128.2 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 125.8 (CH), 42.3 (CH_2), 38.1 (CH_2), 34.7 (CH_2), 29.1 (CH_2), 14.5 (CH_3), 14.1 (CH_3), 12.5 (CH_3); MS (70 eV, EI) *m*/*z* (%) 245 [M^+, 21], 173 (55), 140 (100), 91 (74); HRMS (70 eV) calcd for $C_{16}H_{23}NO$ 245.1780, found 245.1782; IR (neat) 3441, 2933, 1621, 1454, 700 cm^{-1}; R_f 0.15 (hexane:EtOAc 3:1).

(*E*)-2-Benzyl-*N*,*N*-diethyldec-2-enamide (3v): orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−1.67 (m, 5 H), 5.45 (t, $J = 7.2$ Hz, 1 H), 3.67 (s, 2 H), 3.26 (q, $J = 6.9$ Hz, 2 H), 2.81 (apparent q, $J = 6.9$ Hz, 2 H), 2.27 (q, $J = 6.5$ Hz, 2 H), 1.43−1.41 (m, 2 H), 1.31−1.26 (m, 8 H), 0.95 (t, $J = 6.9$ Hz, 3 H), 0.87 (t, $J = 6.5$ Hz, 3 H), 0.80 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C), 138.2 (C), 134.5 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.3 (C), 126.1 (CH), 41.7 (CH_2), 37.9 (CH_2), 38.4 (CH_2), 31.7 (CH_2), 29.2 (3 × CH_2), 27.6 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 13.6 (CH_3), 11.9 (CH_3); MS (70 eV, EI) *m*/*z* (%) 315 [M^+, 13], 232 (100), 204 (97), 91 (57), 72 (45); HRMS (70 eV) calcd for $C_{21}H_{33}NO$ 315.2562, found 315.2593; IR (neat) 3402, 2934, 1610, 909 cm^{-1}; R_f 0.39 (hexane:EtOAc 5:1).

(*E*)-2-Benzyl-*N*,*N*-diethyltrideca-2,12-dienamide (3w): yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.16 (m, 5 H), 5.89−5.76 (m, 1 H), 5.49 (t, $J = 7.2$ Hz, 1 H), 5.03−4.93 (m, 2 H), 3.67 (s, 2 H), 3.14−2.90 (m, 4 H), 2.27 (q, $J = 7.1$ Hz, 1 H), 2.06 (apparent q, $J = 6.9$ Hz, 2 H), 1.51−1.28 (m, 13 H), 0.98 (t, $J = 7.1$ Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C), 139.1 (CH), 135.2 (C), 129.1 (C), 129.0 (CH), 128.9 (2 × CH), 128.3 (2 × CH), 126.1 (CH), 114.1 (CH_2), 41.4 (CH_2), 40.4 (CH_2), 34.9 (CH_2), 33.7 (CH_2), 29.5 (CH_2), 29.3 (2 × CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 14.0 (CH_3), 12.5 (CH_3); MS (70 eV, EI) *m*/*z* (%) 355 [M^+, 36], 216 (100), 130 (28), 91 (16); HRMS (70 eV) calcd for $C_{24}H_{37}NO$ 355.2875, found 355.2881; IR (neat) 3418, 2927, 1621, 1454, 701 cm^{-1}; R_f 0.30 (hexane:EtOAc 3:1).

General Procedure for the Synthesis of Ketones 6. The requisite organolithium compound (3.0 mmol) was added dropwise to the corresponding morpholine amide **3** (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). Usual workup provided crude products **6**, which were purified by flash column chromatography on silica gel (hexane:EtOAc 10:1).

Compounds **6a** and **6b** displayed analytical data in accordance with the published values.[28]

(*E*)-6,8-Dimethyldec-6-en-5-one (6c): colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (d, $J = 9.6$ Hz, 1 H), 2.53 (t, $J = 7.3$ Hz, 2 H), 2.41−2.29 (m, 1 H), 1.66 (s, 3 H), 1.51−1.38 (m, 2 H), 1.29−1.14 (m, 4 H), 0.90 (d, $J = 6.8$ Hz, 3 H), 0.80 (t, $J = 7.2$ Hz, 3 H), 0.75 (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6 (C), 147.9 (CH), 135.8 (C), 36.9 (CH_2), 35.1 (CH), 29.7 (CH_2), 27.2 (CH_2), 22.4 (CH_2), 19.6 (CH_3), 13.9 (CH_3), 11.8 (CH_3), 11.5 (CH_3); HRMS (70 eV) calcd for $C_{12}H_{22}O$ 182.1671, found 182.1676; IR (neat) 2960, 1670, 1459, 1056 cm^{-1}; R_f 0.52 (hexane:EtOAc 10:1).

(*E*)-1-Chloro-3,5-dimethylhept-3-en-2-one (6d): yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 6.39 (dd, $J = 9.7$, 1.1 Hz, 1 H), 4.45 (s, 2 H), 2.58−2.48 (m, 1 H), 1.85 (s, 3 H), 1.53−1.37 (m, 2 H), 1.05 (d, $J = 6.6$ Hz, 3 H), 0.89 (t, $J = 6.5$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8 (C), 150.5 (CH), 133.8 (C), 45.0 (CH_2), 33.4 (CH), 31.5 (CH_2), 19.5 (CH_3), 14.0 (CH_3), 11.8 (CH_3); HRMS (70 eV) calcd for $C_9H_{15}ClO$ 174.0811, found 178.0815; IR (neat) 3406, 1443, 1266, 739 cm^{-1}; R_f 0.30 (hexane:EtOAc 20:1).

General Procedure for the Synthesis of Aldehydes 7. A solution of $LiAlH_4$ (1.0 mmol, 1.5 M in THF) was added dropwise to a mixture of the corresponding morpholine amide **3** (1 mmol) in THF (4 mL) at −78 °C. Then the mixture was stirred for 12 h and quenched with an ice/water mixture (10 mL), followed by extraction with diethyl ether (2 × 10 mL). Usual workup provided crude products, which were purified by flash column chromatography on silica gel (hexane:EtOAc 10:1).

Compounds **7a**,[29] **7b**,[30] and **7c**[30] displayed analytical data in accordance with the published values or with those of the commercial sample.

General Procedure for the Synthesis of Carboxylic Acids 8. A slurry of potassium *tert*-butoxide (3.0 mmol), water (1.0 mmol), and the corresponding amide **3** (0.5 mmol) in THF (4 mL) was stirred vigorously at reflux for 12 h. After that time, the reaction mixture was cooled with an ice bath and a mixture of ice/water (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). Usual workup provided crude products, which were purified by flash column chromatography on silica gel (hexane:EtOAc 1:1).

Compounds **8a**,[2] **8b**,[30] and **8c**[30]displayed analytical data in accordance with the published values or with those of the commercial sample.

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Supporting Information Available: General experimental details and copies of ^1H and ^{13}C NMR spectra for all new compounds **3** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) (a) Compound **6a**: Concellón, J. M.; Rodríguez-Solla, H.; Méjica, C. *Tetrahedron* **2006**, *62*, 3292−3300. (b) Compound **6b**: Trost, B. M.; Parquette, J. R. *J. Org. Chem*. **1993**, *58*, 1579−1581.

(29) Vasil'ev, A.; Engman, L. *J. Org. Chem*. **2000**, *65*, 2151−2162.

(30) ^1H and ^{13}C NMR spectra of the product obtained were identical with those of a commercial sample.