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Preparation of chiral key intermediates of morpholine based neurokinin receptor antagonists by asymmetric allylic alkylation

Jérôme Keldenich [a,c], Audrey Denicourt-Nowicki [a,c], Christophe Michon [a,b,c], Francine Agbossou-Niedercorn [a,b,c,*]

[a] Université Lille Nord de France, F-59000 Lille, France
[b] CNRS, UCCS UMR 8181, F-59655 Villeneuve d'Ascq Cedex, France
[c] ENSCL, CCM-CCCF, Av. Mendeleïev, CS90108, F-59652 Villeneuve d'Ascq, France

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ABSTRACT

The preparation of optically active morpholine-2-aryl-2-allyl derivative from morpholine-2-aryl-3-ones is reported. The optically active tetrasubstituted stereocenter is introduced during a palladium promoted asymmetric allylic alkylation. The resulting compounds are useful intermediates in the synthesis and development of potent NK antagonists.

1. Introduction

The neurokinins (also known as tachykinins) constitute a neurotransmettor peptide family covering substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), which share the common carboxy-terminal sequence Phe-X-Gly-Leu-Met-NH_2. They are widely spread in the central and peripheral nervous systems.[1] Relying on the affinity of natural neurokinins, three distinct 7-transmembrane G protein-coupled receptor types have been identified: NK1 (SP-preferring), NK2 (NKA-preferring), NK3 (NKB-preferring).[2] The numerous forms of mammalian neurokinin assume a large number of biological activities, including muscle contraction and relaxation, vasodilatation, secretion, activation of the immune system, pain transmission, and neurogenic inflammation. Thus, antagonists of these NK receptors have attracted a great deal of interest as potent therapeutic agents.[3] Some specific morpholine based derivatives exhibit such properties and optically active SSR240600, SSR144190, and SSR241586 have been described to be active against depression, emesis, irritable bowel syndrome, schizophrenia, and urinary trouble (Fig. 1).[4] To implement the tetrasubstituted stereogenic centre of optically active 2,2′-disubstituted morpholines, which are valuable intermediates in the multistep sequences to access such potent antagonists,[5] a few elegant approaches have been developed. Nishi et al. have applied the Sharpless asymmetric dihydroxylation reaction (AD) to prepare homochiral diols (Scheme 1A).[6] A subsequent recrystallization in the presence of D-(−)-tartaric acid afforded an optically pure 2-aryl-

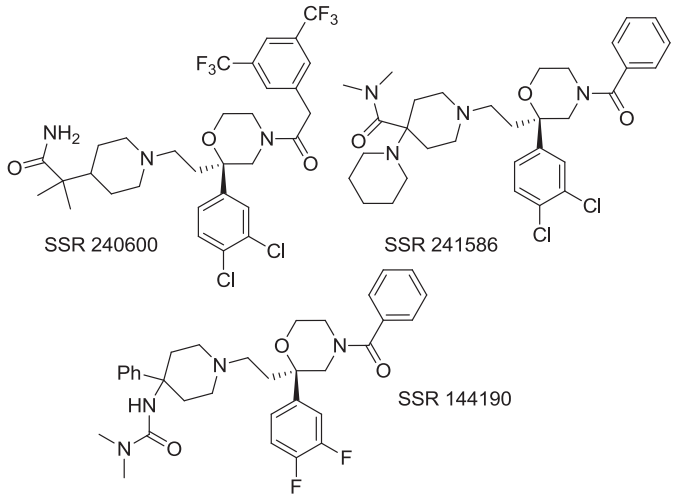

Fig. 1. Examples of morpholine based NK antagonists.

* Corresponding author. Fax: +33 (0)3 20 43 65 85; e-mail address: francine.agbossou@ensc-lille.fr (F. Agbossou-Niedercorn).

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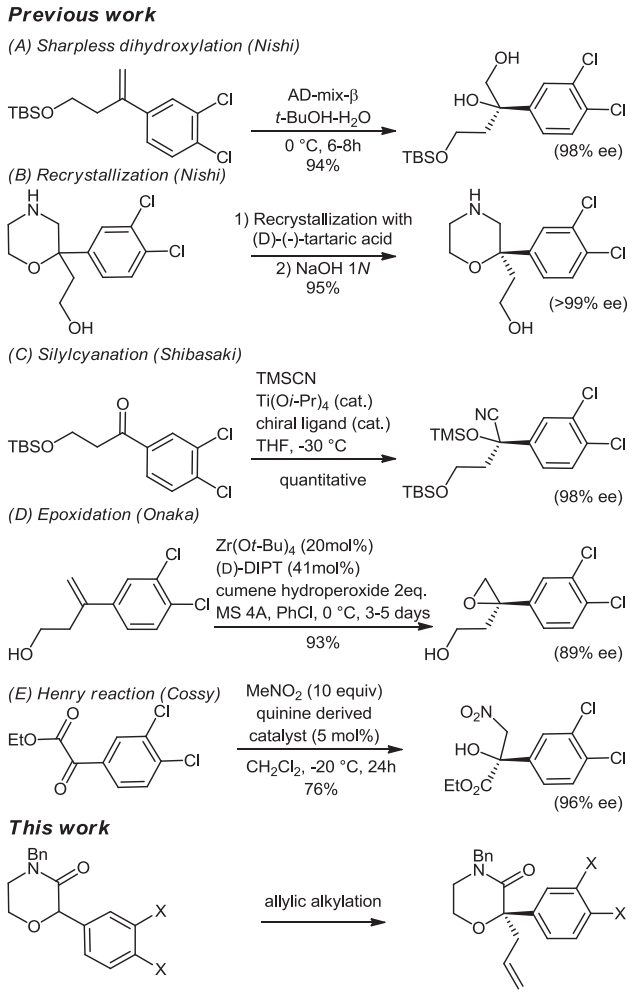
2-ethanol-morpholine intermediate (Scheme 1B).[7] Later on, Shibasaki disclosed an efficient trimethylsilylcyanation reaction to convert a keto silylether into the corresponding cyano disilylether (Scheme 1C).[8]



Scheme 1. Different routes to access the benzylic stereocenter of arylmorpholine precursors.

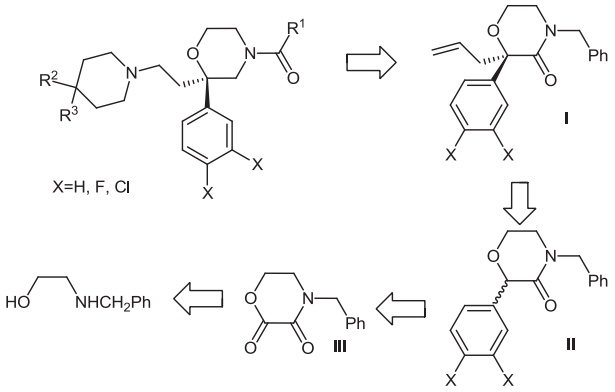
In the mean time, Onaka described an enantioselective epoxidation reaction of a homoallylic alcohol (Scheme 1D).[9] Finally, Cossy recently reported a powerful approach to convert an α-ketoester into a β-nitro alcohol through an organo-catalysed Henry reaction (Scheme 1E).[10]

For several years, our laboratory has been interested in the application of asymmetric allylic alkylation to prepare quaternary stereocenters.[11,12] We applied this methodology to the preparation of morpholines and piperidines exhibiting tetrasubstituted stereocenters.[13] Herein, we report our development of the asymmetric allylic alkylation to access chiral key 2,2′-substituted morpholinone intermediates (Scheme 1).

2. Results and discussion

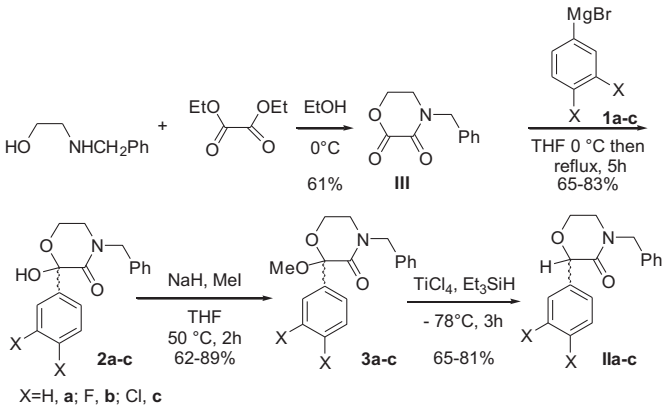
The synthesis of chiral intermediates **I** (R=H, F, Cl) was meant from asymmetric allylation of **II**. This morpholinone could be obtained easily from morpholinedione **III** prepared from 2-(benzylamino)ethanol (Scheme 2). We focused thus on the preparation of optically active **I**.

The three substrates **IIa**–**c** needed for the asymmetric allylic alkylation reactions were prepared easily in a few steps (Scheme 3).



Scheme 2. Retrosynthetic analysis for 2,2′ disubstituted morpholines.

Morpholinedione **III** was readily prepared from 2-(benzylamino) ethanol.[14] Thus, the reaction of commercially available 2-(benzylamino)ethanol (1 equiv) and diethyloxalate (1 equiv) led to dione compound **III** in 61% yield after purification. The subsequent reaction of **III** with the corresponding freshly prepared arylmagnesium bromides **1a**–**c** (1.1 equiv) afforded the cyclic hemiketals **2a**–**c** in 65–83% yield. Then, compounds **2a**–**c** were allowed to react with methyl iodide (1.5 equiv) in the presence of NaH (1.5 equiv).[15] After workup, the cyclic ketals **3a**–**c** were isolated in 62–89% yield.

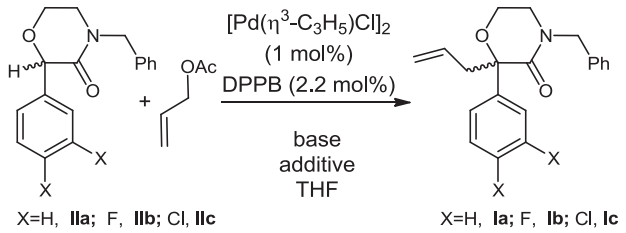


Scheme 3. Synthesis of morpholinones.

Next, a Lewis acid promoted silane reduction of ketals **3a**–**c** furnished morpholinones **IIa**–**c**. Thus, ketals **3a**–**c** were reacted with Et_3SiH (3 equiv) in the presence of $TiCl_4$ (6 equiv) in dichloromethane providing compounds **IIa**–**c** in 65–81% yield (Scheme 3).[15] The preparation of **IIa**–**c** could also be achieved in a one step procedure from **2a**–**c** under similar conditions (3 h, −78 °C, 69–73%).

In order to find the most appropriate conditions for the palladium catalysed allylic alkylation of **II**, we first carried out experiments to screen different bases in the presence of the diphosphine ligand DPPB (1,4-bis(diphenylphosphino)butane) and allylpalladium chloride dimer as the precatalyst (Scheme 4 and Table 1). Among the various bases tried, the best catalytic conditions were found by using a combination of *n*-BuLi and TMEDA (entry 7, 9, 16) in conjunction with the palladium complex.

Hence, the combined use of THF and a bidentate ligand like TMEDA proved to be crucial breaking down *n*-BuLi aggregates to form monomers and dimers and thereby increasing significantly their basicity.[16] Afterwards, asymmetric allylic alkylation reactions of **IIa**–**c** were then studied in the presence of BINAP or one of the Trost ligands and allylpalladium chloride dimer (Fig. 2 and Table 2).



Scheme 4. Palladium catalysed allylation of morpholinones.

Table 1
Variation of the base and additives in the alkylation of **IIa–c**[a]

Entry	Substrate	Base (equiv)	Additive (equiv)	Yield (%)[b]
1	**IIa**	LDA (1.5)		71
2		LiHMDS (1.5)		45
3		(−)sparteine		0
4		NaH		2
5		*sec*-BuLi (2)		0
6		*sec*-BuLi (2)	$ZnCl_2$ (1.3)	25
7		*n*-BuLi (1.5)	TMEDA (1)	95
8	**IIb**	*n*-BuLi (1.5)		11
9		*n*-BuLi (1.5)	TMEDA (1)	95
10	**IIc**	LDA (1.5)	—	68
11		LiHMDS (1.5)	—	49
12		(−)-sparteine	—	0
13		NaH	—	6
14		*sec*-BuLi (2)	—	0
15		*sec*-BuLi (2)	$ZnCl_2$ (1.3)	27
16[c]		*n*-BuLi (1.5)	TMEDA (1)	95

[a] Reactions were carried out in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol %), DPPB (2.2 mol %) in THF at room temperature during 4 h.
[b] Isolated yield.
[c] Addition of the base at −78 °C and reaction carried out at room temperature for 12 h.

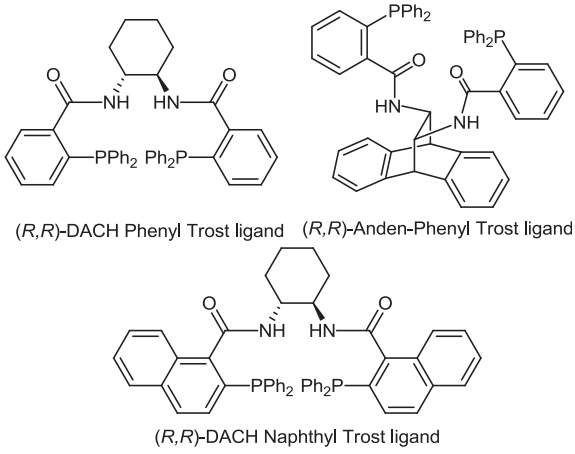


Fig. 2. Chiral Trost ligands used.

Whether yields were average to good for all substrates, enantioselectivities were rather modest to average in most cases. The highest optical purities were obtained with DACH-Naphthyl Trost ligand (entries 3, 6, 10), the two other Trost ligands as well as BINAP being not well designed for this transformation. With a 83% ee for **Ic** (entry 9), reagent **IIc** afforded the highest enantioselectivity.

The absolute configuration of **Ic**, which was the most promising intermediate of the series, could be determined by X-ray structure determination of a single crystal.[17] The allyl derivative **Ic** obtained from the (*R*,*R*)-DACH-Napthyl ligand has a (*R*)-configuration similar to the C2 stereocenter of the morpholine heterocycle in SSR240600 (Fig. 3).

Table 2
Asymmetric allylation of **IIa–c**[a]

Entry	Substrate	Ligand	Yield (%)[b]	ee (%)[c]
1	**IIa**	(*R*,*R*)-BINAP	45	20
2		(*R*,*R*)-DACH-phenyl Trost	50	40
3		(*R*,*R*)-DACH-naphthyl Trost	65	51
4	**IIb**	(*R*,*R*)-BINAP	88	26
5		(*R*,*R*)-DACH-phenyl Trost	90	54
6		(*R*,*R*)-DACH-naphthyl Trost	89	60
7		(*R*,*R*)-Anden-phenyl Trost	84	10
8	**IIc**	(*R*,*R*)-BINAP	95	46
9		(*R*,*R*)-DACH-phenyl Trost	93	64
10		(*R*,*R*)-DACH-naphthyl Trost	90	83
11		(*R*,*R*)-Anden-phenyl Trost	83	16

[a] Reactions were carried out in the presence of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1 mol %), chiral ligand (2.2 mol %) in THF (0.15 M). The addition of the base and TMEDA was done at −78 °C and the reaction carried out at 20 °C for 12 h.
[b] Isolated yield.
[c] Determined by ^{13}C NMR with $Eu(hfc)_3$ or chiral HPLC.

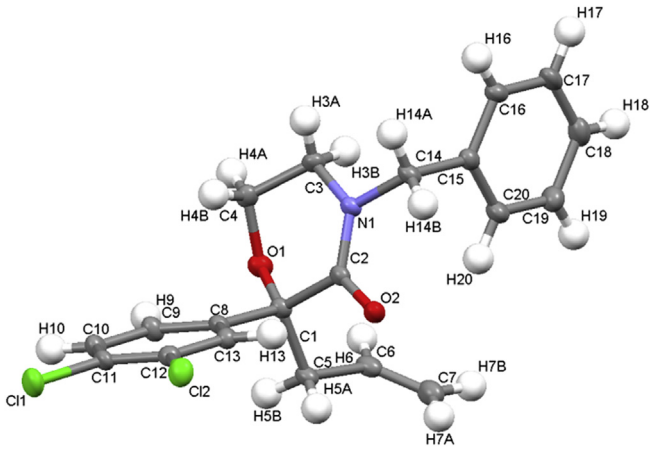
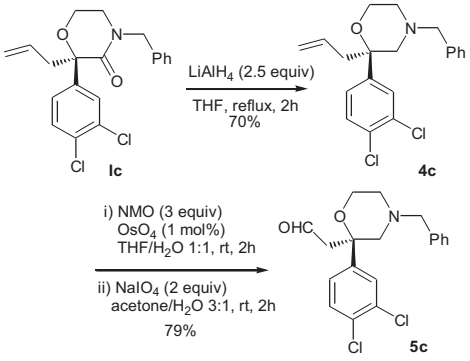


Fig. 3. Ortep view of compound **Ic** with ellipsoids drawn at 50% probability level.[17]

In order to convert the most interesting chiral allyl intermediate **Ic** to aldehyde **5c**, we carried out, first, the reduction of morpholinone **Ic** with lithium aluminium hydride in a 70% yield (Scheme 5). The allyl moiety of the corresponding morpholine **4c** was then oxidized in a two steps procedure using *N*-methylmorpholine-*N*-oxide along with a catalytic amount of osmium tetroxide followed by addition of sodium periodate. After workup, the aldehyde **5c** was isolated in 79% yield and the synthesis of SSR240600 may be performed in a few steps.



Scheme 5. Synthesis of chiral aldehyde **5**.

3. Conclusion

In summary, we have developed a promising route to chiral 2,2′-substituted morpholinones, which are key intermediates of potent neurokinin antagonists, exhibiting a tetrasubstituted stereocenter. To access the desired (*R*)-configuration of such building blocks, the palladium catalysed asymmetric allylic alkylation proved to be an interesting methodology and the highest selectivities were up to 83% ee. Further investigations are under way to apply this methodology to the preparation of lactams bearing also a quaternary stereocenter.[13c]

4. Experimental section

4.1. General remarks

All solvents were dried using standard methods, distilled over CaH_2 and stored over molecular sieves (4 Å). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometer at 300, 75.5, and 282 MHz, respectively. The chemical shifts of the ^1H NMR and ^{13}C are reported relative to the residual signal of $CDCl_3$. ^{19}F NMR chemical shifts are referenced externally relative to $CFCl_3$ (−63 ppm). All coupling constants (*J*) are reported in Hertz (Hz). All commercially chemicals were used as received without further purification. Thin layer chromatography was performed on Merck pre-coated 0.20 mm silica gel Alugram Sil 60 G/UV_{254} plates and visualization effected with short wavelength UV light (254 nm). Flash chromatography was carried out with Macherey silica gel (Kielselgel 60). Melting points were determined using a Barnstead Electrothermal (BI 9300) apparatus and were uncorrected. Infrared spectra were recorded on a ThermoScientific-Nicolet 6700 spectrometer; the samples being prepared with KBr powder. HPLC analysis was performed on a Thermo Finnigan apparatus using Daicel Chiralpak™ IA column and a diode array detector set to 200, 220 and 254 nm. HRMS analyses were performed at CUMA-Pharm. Dept.-University Lille Nord de-France. Elemental analyses were performed by the Service Central d'Analyses, CNRS, Solaize.

4.2. 4-Benzyl-morpholine-2,3-dione (III)

A solution of diethyloxalate (32 g, 0.22 mol) in ethanol (15 mL) was added dropwise at 0 °C to a solution of 2-(benzylamino)ethanol (11.35 g, 75 mmol) in ethanol (50 mL). The mixture was stirred at 0 °C for 1 h, at room temperature for 2 h, and finally at reflux for 1 h. After cooling, the product was precipitated from the crude reaction mixture through addition of petroleum ether providing **III** as a white solid (27.34 g, 61%). Mp 94 °C; ^1H NMR (300 MHz $CDCl_3$) 3.53 (1H, dd, *J* 5.4 and 5.2 Hz, C*H*$_a$H$_b$N), 3.55 (1H, dd, *J* 5.4 and 5.2 Hz, CH$_a$*H*$_b$N), 4.41 (1H, dd, *J* 6.0 and 5.1 Hz, C*H*$_a$H$_b$O), 4.43 (1H, dd, *J* 6.0 and 5.1 Hz, CH$_a$*H*$_b$O), 4.69 (2H, s, C*H*$_2$Ph), 7.26–7.32 (5H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 44.0, 50.6, 65.5, 128.5, 128.6, 129.1, 134.6, 153.8, 156.9. Anal. Calcd for $C_{11}H_{11}NO_3C$, 64.20; H, 5.35; N, 6.90. Found C, 64.38; H, 5.40; N, 6.82%.

4.3. 4-Benzyl-2-phenyl-2-hydroxy-morpholin-3-one (2a)

A solution of 4-benzyl-morpholine-2,3-dione **III** (4.10 g, 20 mmol) in THF (50 mL) was cooled to 0 °C. Commercially available phenylmagnesium bromide (20 mL, 1 M in THF, 1.1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C during 1 h and then 3.5 h at room temperature. Hydrolysis of the medium was carried out through addition of HCl (20 mL, 1 M). The product was then extracted with dichloromethane (2×20 mL). The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, addition of hexane was performed until a precipitation started. After complete crystallization, **2a** was isolated through filtration as a white powder (4.71 g, 83%). Mp 106 °C; R_f (ethyl acetate) 0.85; ^1H NMR (300 MHz $CDCl_3$) 3.17 (1H, m, C*H*$_a$H$_b$N), 3.63 (1H, m, CH$_a$*H*$_b$N), 3.87 (1H, m, C*H*$_a$H$_b$O), 4.28 (1H, ddd, *J* 11.9, 11.0 and 3.2 Hz, CH$_a$*H*$_b$O), 4.49 (1H, d, *J* 14.4 Hz, C*H*$_a$H$_b$Ph), 4.65 (1H, d, *J* 14.4 Hz, CH$_a$*H*$_b$Ph), 7.22–7.64 (10H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.4, 50.4, 58.9, 97.1, 126.3, 127.8, 128.0, 128.1, 128.3, 128.6, 128.9, 135.9, 140.9, 168.0. Anal. Calcd for $C_{17}H_{17}NO_3$ C, 72.07; H, 6.05; N, 4.94. Found C, 71.90; H, 6.00; N, 5.00.

4.4. 4-Benzyl-2-(3,4-difluorophenyl)-2-hydroxy-morpholin-3-one (2b)

A solution of 4-bromo-1,2-difluorobenzene (3.09 g, 1.81 mL, 16 mmol) in THF (15 mL) was added dropwise over magnesium turnings (0.39 g, 16 mmol) at room temperature under vigorous stirring. The mixture was stirred during 3 h at room temperature. The resulting solution was then transferred to a THF (10 mL) solution of morpholinedione **III** (3.01 g, 14.6 mmol). The reaction mixture was heated under reflux during 5 h. After cooling, HCl (30 mL, 1 M) was added. The product was extracted with dichloromethane (2×30 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, hexane was added until precipitation started. After complete crystallization (24 h), the isolated solid was purified through silica gel column chromatography (ethyl acetate) providing **2b** as a white solid (3.11 g, 66%). R_f (ethyl acetate) 0.75; ^1H NMR (300 MHz $CDCl_3$) 3.19 (1H, br d, *J* 11.0 Hz, C*H*$_a$H$_b$N), 3.66 (1H, ddd, *J* 15.0, 11.0, and 4.0 Hz, CH$_a$*H*$_b$N), 3.92 (1H, m, C*H*$_a$H$_b$O), 4.31 (1H, ddd, *J* 15.0, 11.0, and 3.1 Hz, CH$_a$*H*$_b$O), 4.46 (1H, d, *J* 14.4 Hz, C*H*$_a$H$_b$Ph), 4.68 (1H, d, *J* 14.4 Hz, CH$_a$*H*$_b$Ph), 7.13–7.33 (8H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.5, 50.6, 59.0, 65.5, 116.2 (dd, *J* 13.8 and 5.9 Hz), 116.84 (dd, *J* 14.3 and 5.8 Hz), 122.9, 128.1, 128.3, 128.6, 129.0, 129.2, 135.7, 138.0, 148.3 (dd, *J* 11.2 and 3.5 Hz), 153.4 (dd, *J* 12.1 and 5.3 Hz), 167.5; ^{19}F NMR (282 MHz $CDCl_3$) −137.7 (d, *J* 21.0 Hz), −137.8 (d, *J* 21.0 Hz). Anal. Calcd for $C_{17}H_{15}F_2NO_3$ C, 63.95; H, 4.74; N, 4.39. Found C, 63.86; H, 4.78; N, 4.43.

4.5. 4-Benzyl-2-(3,4-dichlorophenyl)-2-hydroxy-morpholin-3-one (2c)

A solution of 1-bromo-3,4-dichlorobenzene (6.14 g, 27 mmol) in THF (25 mL) is added dropwise on magnesium turnings (0.66 g, 27 mmol) at room temperature. The formed Grignard reagent is then added to a solution of morpholinedione **III** (5 g, 24 mmol) in THF (25 mL). The reaction mixture was stirred at reflux for 5 h. After addition of HCl (45 mL, 1 M), the product was extracted with CH_2Cl_2 (2×45 mL). The combined organic phases were washed with brine (45 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the crude product, which was recrystallized in hexane and then purified by flash chromatography (ethyl acetate) providing **2c** as a white solid (6.80 g, 65%). R_f (ethyl acetate) 0.75; ^1H NMR (300 MHz $CDCl_3$) 3.19 (1H, d, *J* 11.2 Hz, C*H*$_a$H$_b$N), 3.66 (1H, td, *J* 11.2 and 4.1 Hz, CH$_a$*H*$_b$N), 3.91 (1H, d, *J* 11.9 Hz, C*H*$_a$H$_b$O), 4.31 (1H, td, *J* 11.9 and 4.1 Hz, CH$_a$*H*$_b$O), 4.46 (1H, d, *J* 14.4 Hz, C*H*$_a$H$_b$Ph), 4.68 (1H, d, *J* 14.4 Hz, CH$_a$*H*$_b$Ph), 7.1–7.42 (8H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.3, 50.5, 59.1, 65.3, 109.7–110.7, 123–121, 129.4, 131.7, 161.0. Anal. Calcd for $C_{17}H_{15}Cl_2NO_3$: C, 57.97; H, 4.29; N, 3.98. Found C, 58.22; H, 4.33; N, 4.04.

4.6. 4-Benzyl-2-phenyl-2-methoxy-morpholin-3-one (3a)

A suspension of NaH (1.2 g, 70% w/w dispersion in oil, 29.7 mmol, washed twice with dry *n*-pentane) in THF (50 mL) was added dropwise to a solution of **2a** (5.6 g, 19.9 mmol) and methyl

iodide (4.22 g, 29.7 mmol) in THF (50 mL) over a period of 10 min. After stirring of the mixture at 50 °C for 2 h, water (35 mL) was added slowly. The solvent was removed under reduced pressure. The product was extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. After evaporation of the solvent and silica gel flash column chromatography (ethyl acetate/petroleum ether 1:1) **3a** was obtained (3.63 g, 62%). R_f (ethyl acetate/petroleum ether 1:1) 0.41. ^{1}H NMR (300 MHz $CDCl_3$) 3.2 (4H, m, CH_aH$_b$N and OCH_3), 3.65 (1H, ddd, *J* 12.1, 6.0, and 2.4 Hz, CH$_a$$H_b$N), 3.92 (1H, dd, *J* 11.7 and 4.3 Hz, CH_aH$_b$O), 4.24 (1H, m, CH$_a$$H_b$O), 4.23 (1H, d, *J* 14.3 Hz, CH_aH$_b$Ph), 4.83 (1H, d, *J* 14.3 Hz, CH$_a$$H_b$Ph), 7.21–7.39 (8H, m, H$_{aryl}$), 7.73 (2H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.1, 49.7, 50.2, 58.1, 127.8, 128.1, 128.3, 128.8, 136.3, 136.8, 166.0. Anal. Calcd for $C_{18}H_{19}NO_3$ C, 72.71; H, 6.44; N, 4.71. Found C, 72.92; H, 6.50; N, 4.66.

4.7. 4-Benzyl-2-(3,4-difluorophenyl)-2-methoxy-morpholin-3-one (3b)

Compound **3b** was prepared following an identical procedure as for the synthesis of **3a** (1.45 g, 88%). R_f (ethyl acetate) 0.75. ^{1}H NMR (300 MHz $CDCl_3$) 3.14 (3H, s, OCH_3), 3.17 (1H, m, CH_aH$_b$N), 3.65 (1H, ddd, *J* 11.9, 11.9 and 4.4 Hz, CH$_a$$H_b$N), 3.92 (1H, br dd, *J* 11.4 and 4.4 Hz, CH_aH$_b$O), 4.20 (1H, dd, *J* 11.9 and 3.0 Hz, CH$_a$$H_b$O), 4.24 (1H, d, *J* 14.6 Hz, CH_aH$_b$Ph), 4.83 (1H, d, *J* 14.6 Hz, CH$_a$$H_b$Ph), 7.15–7.25 (6H, m, H$_{aryl}$), 7.29–7.31 (2H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 43.1, 45.9, 50.2, 51.6, 116.6 (dd, *J* 23.5 and 3.8 Hz), 117.6 (dd, *J* 26.4 and 2.0 Hz), 124.6 (dd, *J* 9.5 and 5.9 Hz), 127.8, 128.2, 128.7, 128.8, 133.9 (dd, *J* 8.1 and 5.0 Hz), 136.0, 148.0 (dd, *J* 11.6 and 4.3 Hz), 150.9 (dd, *J* 11.3 and 3.9 Hz), 171.1; d_F (282 MHz $CDCl_3$) −138.2 (d, *J* 21.0 Hz), −138.0 (d, *J* 21.0 Hz). Anal. Calcd for $C_{18}H_{17}F_2NO_3$ C, 64.86; H, 5.14; N, 4.20. Found C, 64.98; H, 5.22; N, 4.28.

4.8. 4-Benzyl-2-(3,4-dichlorophenyl)-2-methoxy-morpholin-3-one (3c)

Compound **3c** was prepared following an identical procedure as for the synthesis of **3a** (1.47 g, 89%). R_f (ethyl acetate) 0.75; ^{1}H NMR (300 MHz $CDCl_3$) 3.13 (3H, s, OCH_3), 3.19 (1H, d, *J* 11.0 Hz, CH_aH$_b$N), 3.66 (1H, dd, *J* 11.2 and 4.07 Hz, CH$_a$$H_b$N), 3.91 (1H, d, *J* 11.9 Hz, CH_aH$_b$O), 4.31 (1H, dd, *J* 11.0 and 3.1 Hz, CH$_a$$H_b$O), 4.46 (1H, d, *J* 14.6 Hz, CH_aH$_b$Ph), 4.80 (1H, d, *J* 14.6 Hz, CH$_a$$H_b$Ph), 7.15–7.42 (8H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.1, 49.3, 55.8, 58.1, 109.7–110.7, 121.0–129.4, 131.7, 133.5, 133.9, 136.8, 167.8. Anal. Calcd for $C_{18}H_{17}Cl_2NO_3$ C, 59.03; H, 4.68; N, 3.82. Found C, 59.20; H, 4.63; N, 3.89.

4.9. 4-Benzyl-2-phenyl-morpholin-3-one (IIa)

At −78 °C and under nitrogen, $TiCl_4$ (14.7 g, 8.53 mL, 69 mmol, 6 equiv) was added, via cannula and dropwise, to a solution of dichloromethane (20 mL) containing compound **3a** (4.07 g, 13.7 mmol). Then, a solution of triethylsilane (4.01 g, 6.2 mL, 34.5 mmol, 3 equiv) in dichloromethane (10 mL) was added at—78 °C under nitrogen. The reaction mixture was stirred during 3 h at −78 °C and then 30 min at room temperature after removal of the cold bath. The reaction was quenched by slow addition of water (18 mL). The desired product was extracted with dichloromethane (2×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, **IIa** was obtained as a colourless oil. After purification though silica gel column chromatography (ethyl acetale/petroleum ether 1:2), **IIa** was isolated as a white solid (2.96 g, 81%). Mp 65 °C; R_f (ethyl acetate/petroleum ether 1:1) 0.85; ^{1}H NMR (300 MHz $CDCl_3$) 3.28 (1H, ddd, *J* 12.1, 4.3, and 4.4 Hz, CH_aH$_b$N), 3.48 (1H, ddd, *J* 12.2, 7.7, and 4.4 Hz, CH$_a$$H_b$N), 3.83 (1H, ddd, *J* 12.2, 7.7, and 4.3 Hz, CH_aH$_b$O), 3.97 (1H, ddd, *J* 12.1, 7.7, and 4.4 Hz, CH$_a$$H_b$O), 4.67 (2H, s, C$H_2$Ph), 5.26 (1H, s, C*H*O), 7.32–7.50 (10H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CHCl_3$) 45.9, 49.8, 61.6, 79.4, 128.1, 127.7, 127.6, 128.2, 136.2, 138.3, 167.3. Anal. Calcd for $C_{17}H_{17}NO_2$ C, 76.38; H, 6.41; N, 5.24. Found C, 76.52; H, 6.35; N, 5.29.

4.10. 4-Benzyl-2-(3,4-difluorophenyl)-morpholin-3-one (IIb)

Compound **IIb** was prepared following an identical procedure as for the synthesis of **IIa** described above (1.72 g, 65%). R_f (ethyl acetate/petroleum ether 1:2) 0.65; ^{1}H NMR (300 MHz $CDCl_3$) 3.27 (1H, ddd, *J* 12.5, 4.1, and 3.2 Hz, CH_aH$_b$N), 3.49 (1H, ddd, *J* 12.2, 8.4, and 4.1 Hz, CH$_a$$H_b$N), 3.59 (1H, ddd, *J* 12.5, 8.4, and 4.4 Hz, CH_aH$_b$O), 3.99 (1H, ddd, *J* 12.2, 4.4, and 3.2 Hz, CH$_a$$H_b$O), 4.58 (1H, d, *J* 14.4 Hz, CH_aH$_b$Ph), 4.68 (1H, d, *J* 14.4 Hz, CH$_a$$H_b$Ph), 5.18 (1H, s, C*H*O), 7.10–7.41 (8H, m, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$) 46.3, 50.3, 62.4, 78.4, 117.2 (dd, *J* 12.8 and 18.2 Hz), 124.2 (dd, *J* 6.4 and 3.9 Hz), 128.2, 128.6, 129.1, 134.4 (dd, *J* 5.7 and 3.6 Hz), 136.3, 148.0 (dd, *J* 11.3 and 3.1 Hz), 152.9 (dd, *J* 11.3 and 4.6 Hz), 167.1; ^{19}F NMR (282 MHz, $CDCl_3$) −137.8 (d, *J* 21.0 Hz), −138.8 (d, *J* 21.0 Hz). Anal. Calcd for $C_{17}H_{15}F_2NO_2$ C, 67.32; H, 4.98; N, 4.62. Found C, 67.50; H, 5.06; N, 4.66.

4.11. 4-Benzyl-2-(3,4-dichlorophenyl)-morpholin-3-one (IIc)

Compound **IIc** was prepared following the procedure reported above for the synthesis of **IIa** (colourless oil, 3.43 g, 73%). R_f (ethyl acetate/petroleum ether 1:2) 0.85; ^{1}H NMR (300 MHz $CDCl_3$) 3.24 (1H, ddd, *J* 12.4, 4.0, and 3.9 Hz, CH_aH$_b$N), 3.46 (1H, ddd, *J* 12.3, 8.1, and 4.4 Hz, 1H, CH$_a$$H_b$N), 3.82 (1H, ddd, *J* 12.1, 8.3, and 3.7 Hz, CH_aH$_b$O), 3.95 (1H, ddd, *J* 12.1, 4.4, and 4.1 Hz, CH$_a$$H_b$O), 4.53 (1H, d, *J* 14.5 Hz, CH_aH$_b$Ph), 4.65 (1H, d, *J* 14.5 Hz, CH$_a$$H_b$Ph), 5.15 (1H, s, C*H*O), 7.23 (2H, m, H$_{aryl}$), 7.31 (4H, m, H$_{aryl}$), 7.40 (1H, d, *J* 8.4 Hz, H$_{aryl}$), 7.57 (1H, d, *J* 2.2 Hz, H$_{aryl}$); ^{13}C NMR (75 MHz $CDCl_3$): 46.0, 50.2, 62.3, 78.3, 127.3, 128.0, 128.4, 132.5, 132.6, 136.1, 137.6, 166.8. IR (KBr): 3094, 3025, 2988, 2960, 2921, 1684, 1653, 1484, 1472, 1448, 1199, 1030, 802, 749, 728 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}O_2NCl_2$ [MH$^+$]: 336.05526; found: 336.05510. Anal. Calcd for $C_{17}H_{15}Cl_2NO_2$ C, 60.73; H, 4.50; N, 4.17. Found C, 60.85; H, 4.55; N, 4.23.

4.12. General procedure for asymmetric allylic alkylation

In a Schlenk tube, the morpholine substrate (1 mmol) was dissolved in THF (4 mL). The solution was cooled to −78 °C and *n*-BuLi (0.45 mL, 1.5 mmol) and TMEDA (0.15 mL, 1.5 mmol) were added. The solution was stirred at −78 °C for 1 h and then charged with a solution containing $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol), the selected chiral ligand (0.022 mmol) and allyl acetate (0.16 mL, 1.5 mmol) in THF (2 mL). The reaction mixture was stirred under nitrogen at −78 °C for 2 h. The cooling bath was removed and the reaction was allowed proceeding at room temperature for 12 more hours. The reaction was followed by GPC (column BPX-5, 230 °C). The reaction mixture was quenched with a NH_4Cl saturated solution (5 mL) and water (10 mL). The organic phase was extracted with ethyl acetate (3×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified through silica gel column chromatography (ethyl acetate/petroleum ether 1:1) affording the allyl derivative. The enantiomeric excess was determined by ^{13}C NMR with Eu(hfc)$_3$ or by HPLC methods.

4.13. 2-Allyl-4-benzyl-2-phenyl-morpholin-3-one (Ia)

65% yield. ^{1}H NMR (300 MHz $CDCl_3$) 2.64 (1H, m, CH_aH$_b$CH=CH$_2$), 2.99 (2H, m, CH_aH$_b$N and CH$_a$$H_b$CH=CH$_2$), 3.53 (1H, m,

CH_aH_bN), 3.77 (2H, m, CH_2O), 4.67 (2H, s, CH_2Ph), 5.11 (2H, m, CH=CH_2), 5.84 (1H, m, CH=CH_2), 7.25–7.37 (8H, m, H_{aryl}), 7.67–7.70 (2H, m, H_{aryl}); ^{13}C NMR (75 MHz $CDCl_3$) 46.5, 46.7, 50.2, 59.4, 84.0, 126.3, 127.7, 127.8, 128.3, 128.5, 128.8, 133.4, 136.6, 140.9, 168.8. Anal. Calcd for $C_{20}H_{21}NO_2$ C, 78.15; H, 6.89; N, 4.56. Found C, 78.30; H, 6.97; N, 4.50.

4.14. 2-Allyl-4-benzyl-2-(3,4-difluoro-phenyl)-morpholin-3-one (Ib)

89% yield. ^1H NMR (300 MHz $CDCl_3$) 2.59 (1H, dd, *J* 14.1 and 7.0 Hz, CH_aH_bCH=CH_2), 2.93 (1H, dd, *J* 14.1 and 7.0 Hz, CH_aCH_bCH=CH_2), 3.02 (1H, m, CH_aH_bN), 3.53 (1H, ddd, *J* 11.7, 11.2, and 4.5 Hz, CH_aH_bN), 3.7 (1H, ddd, *J* 11.5, 11.2, and 3.2 Hz CH_aH_bO), 3.84 (1H, m, CH_aCH_bO), 4.61 (1H, d, *J* 14.4 Hz, CH_aH_bPh), 4.67 (1H, d, *J* 14.4 Hz, CH_aH_bPh), 5.1 (2H, m, CH=CH_2), 5.8 (1H, m, CH=CH_2), 7.1–7.6 (8H, m, H_{aryl}); ^{13}C NMR (75 MHz $CDCl_3$) 46.5, 46.8, 50.4, 59.7, 83.1, 115.5 (d, *J* 19.1 Hz), 117.0 (d *J* 17.1 Hz), 119.1, 122.5 (dd, *J* 3.5 and 1.5 Hz), 127.9, 128.3, 128.9, 132.7, 136.4, 138.0, 148.4 (dd, *J* 29.2 and 12.2 Hz), 151.7 (dd, *J* 27.0 and 12.7 Hz), 168.4; ^{19}F NMR (282 MHz $CDCl_3$) −137.5 (d, *J* 21.3 Hz), −139.7 (d, *J* 21.3 Hz). Anal. Calcd for $C_{20}H_{19}F_2NO_2$ C 69.96; H 5.58; N 4.08. Found C, 69.45; H, 5.67; N, 3.99.

4.15. 2-Allyl-4-benzyl-2-(3,4-dichloro-phenyl)-morpholin-3-one (Ic)

90% yield. $[\alpha]_D^{20}$ −32 (*c* 2.8 mM, CH_2Cl_2, for 83% ee). ^1H NMR (300 MHz $CDCl_3$) 2.59 (1H, dd, *J* 14.3 and 6.7 Hz, CH_aH_bCH=CH_2), 2.94 (1H, dd, *J* 14.3 and 7.1 Hz, CH_aH_bCH=CH_2), 3.03 (1H, ddd, *J* 11.8, 3.3, and 1.8, CH_aH_bN), 3.54 (1H, dd, *J* 11.3, 11.7, and 3.5 Hz, CH_aH_bO), 3.70 (1H, ddd, *J* 11.4, 11.1, and 3.3 Hz, CH_aH_bO), 3.85 (1H, m, CH_aH_bN), 4.62 (1H, d, *J* 14.3 Hz, CH_aH_bPh), 4.68 (1H, d, *J* 14.6 Hz, CH_aH_bPh), 5.10 (2H, m, CH=CH_2), 5.78 (1H, m, CH=CH_2), 7.29 (5H, m, H_{aryl}), 7.43 (1H, d, *J* 8.1 Hz, H_{aryl}), 7.58 (1H, dd, *J* 8.5 and 2.3 Hz, H_{aryl}), 7.81 (1H, d, *J* 2.0 Hz, H_{aryl}); ^{13}C NMR (75 MHz $CHCl_3$) 46.4, 46.6, 50.4, 59.7, 83.1, 119.3, 126.0, 127.9, 128.3, 128.5, 128.9, 130.4, 132.0, 132.6, 132.7, 136.3, 141.3, 168.1. IR (KBr): 3075, 3029, 2924, 1653, 1484, 1465, 1190, 1030, 995, 920, 825, 786, 727 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}Cl_2NO_2$ $[MH^+]$: 376.0870; found: 376.0870. Anal. Calcd for $C_{20}H_{19}Cl_2NO_2$ C, 63.84; H, 5.09; N, 3.72. Found C, 63.92; H, 5.14; N, 3.68. HPLC (DAICEL CHIRALPAK OJ-H, hexane/*i*-PrOH=9/1, 0.3 mL/min, 200 nm) t_R (major, *R* enantiomer)=41.4 min, t_R (minor, *S* enantiomer)=49.4 min.

4.16. 4-Benzyl-2-(3,4-dichloro-phenyl)-morpholin-2-yl]-acetaldehyde (5c)

Compound **Ic** (500 mg, 1.33 mmol) was introduced in a Schlenk tube with THF (10 mL) and degassed by three freeze-thaw cycles and then cooled to 0 °C. This solution was transferred slowly via cannula to a Schlenk tube containing a THF (10 mL) suspension of $LiAlH_4$ (88 mg, 3.32 mmol). At the end of the addition and after removal of the cold bath, the reaction medium was heated at reflux for 2 h. After cooling, water was added (0.6 mL) and the medium was stirred for 2 h. After filtration, the product was extracted with ethyl acetate (3×10 mL) from the filtrate. The combined organic phase was washed with brine and dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The reduced intermediate **4c** was obtained as yellow oil (70%) and used in the next step without further purification.

R_f (ethyl acetate 1:9) 0.80. ^1H NMR (300 MHz $CDCl_3$) 2.30 (1H, d *J* 12.1 Hz, NCH_aH_bC), 2.50 (4H, m, CH_2N, CH_2CHCH_2), 2.93 (1H, d, *J* 12.1 Hz, NCH_aH_bC), 3.35 (1H, d, *J* 13.0 Hz, CH_aH_bPh), 3.58 (1H, d, *J* 13.0 Hz, CH_aH_bPh), 3.75 (2H, m, CH_2O), 4.90 (2H, m, CH=CH_2), 5.55 (1H, m, CH=CH_2), 7.0–7.3 (8H, m, H_{aryl}); ^{13}C NMR (75 MHz $CDCl_3$) 53.9, 58.9, 62.1, 63.3, 77.0, 118.6, 126.5, 127.5, 128.5, 120.3, 129.4, 130.1, 130.5, 137.8, 143.6.

To a solution of intermediate **4c** (0.750 g, 2.2 mmol) in THF/H_2O (v/v: 1:1) (30 mL) was added dropwise OsO_4 (0.20 mL of a solution of 4% OsO_4 in H_2O, 0.02 mmol). The resulting black solution was then stirred for 5 min before addition of $NaIO_4$ (1.87 g, 8.7 mmol) in little portions over a period of 2 h. After an additional stirring period of 2 h, addition of a saturated solution of $Na_2S_2O_3$ (26 mL), stirring of 30 min, dilution with Et_2O (40 mL) and washing with brine (26 mL), extraction by Et_2O, drying ($MgSO_4$) and evaporation gave a yellow oil, which was purified by silica gel flash chromatography (ethyl acetate/petroleum ether 1:1), to give a colourless oil (0.66 g, 79%). $[\alpha]_D^{20}$ +102 (*c* 11.0 mM, CH_2Cl_2, for 83% ee). ^1H NMR (300 MHz $CDCl_3$) 2.48 (1H, d, *J* 11.7 Hz, NCH_aH_bC), 2.54 (2H, t, *J* 4.9 Hz, CH_2NCH_2), 2.63 (1H, dd, *J* 15.7 and 2.3 Hz, CH_aH_bCHO), 2.83 (1H, br d, *J* 12.6 Hz, NCH_aH_bC), 3.04 (1H, br dd, *J* 15.7 and 3.1 Hz, CH_aH_bCHO), 3.42 (1H, d, *J* 13.1 Hz, CH_aH_bPh), 3.59 (1H, d, *J* 13.1 Hz, CH_aH_bPh), 3.75 (1H, m, CH_aH_bO), 3.85 (1H, m, CH_aH_bO), 7.17 (1H, dd, *J* 8.4 and 2.4 Hz), 7.33 (5H, m, H_{aryl}), 7.43 (2H, 2d, *J* 5.7, *J* 5.3, H_{aryl}), 9.62 (1H, t, *J* 3.0 Hz, *HC*=O); ^{13}C NMR (75 MHz $CDCl_3$) 53.5, 59.7, 59.8, 62.2, 63.1, 75.9, 125.7, 127.7, 128.6, 128.7, 129.2, 130.6, 131.7, 132.9, 137.4, 142.8, 200.7.

IR (KBr): 3028, 2965, 2873, 2766, 1722, 1469, 1461, 1138, 818, 791, 747 cm^{-1}. MS (ESI): *m*/*z* 320.0597 $[MH^+-CH_2CHO]$, 364.0859 $[MH^+]$, 396.1117 $[MH^++CH_3OH]$. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}Cl_2NO_2$ $[MH^+]$: 364.08656; found: 364.08585.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.097. These data include MOL files and InChiKeys of the most important compounds described in this article.

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17. X-ray crystal data of compound **Ic** were deposited under reference CCDC 836129. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre:www.ccdc.cam.ac.uk/data_request/cif.