Chapter 2

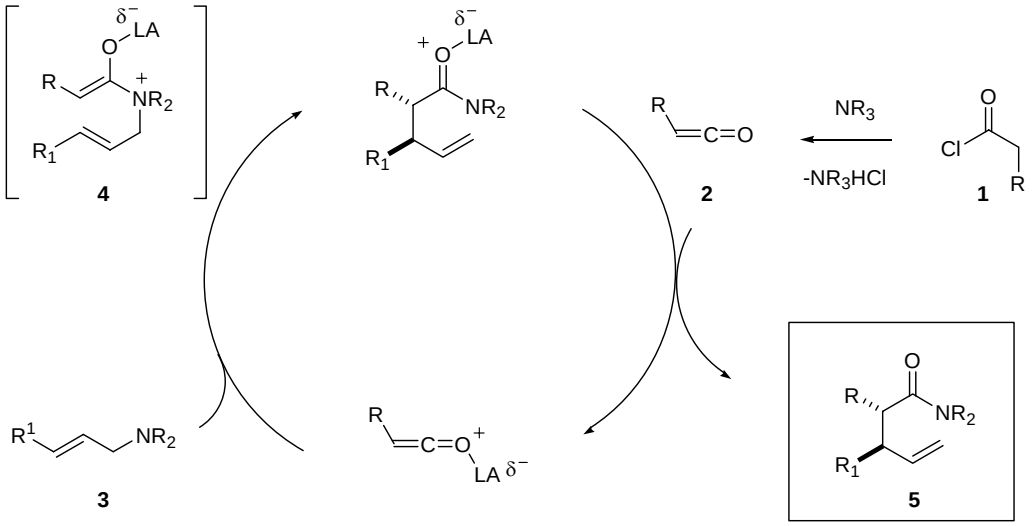
The Lewis acid–Catalyzed Acyl-Claisen Rearrangement[1]

Reaction Design

In the previous chapter, we developed a ketene-Claisen rearrangement that was susceptible to Lewis acid catalysis, and effective with a range of allylic pyrrolidines. The synthetic utility of this method, however, was hampered by difficulties associated with preparing, storing and isolating the inherently unstable ketene. Therefore, we decided to investigate an alternative strategy by generating the ketenes *in situ*. In 1911, Staudinger demonstrated the amine-promoted dehydrohalogenation of acid chlorides to form ketenes.[2,3] We reasoned that acid chlorides could be advantageous as ketene surrogates as they are more readily available and bench-stable precursors.[4] Furthermore, the Ward procedure (Chapter 1) resulted in ethereal ketene solutions, while the Staudinger method would permit the use of non-coordinating solvents less likely to buffer the Lewis acidity of catalytic metal salts.

As illustrated in Scheme 1, we envisioned that a range of acid chlorides (**1**) would undergo amine-promoted dehydrohalogenation to form ketenes (**2**) *in situ*. In the presence of Lewis acids, ketenes (**2**) would undergo addition by tertiary allyl amines (**3**), forming the metal-bound zwitterionic intermediates (**4**). Complex **4** would subsequently undergo [3,3]-sigmatropic rearrangement to afford Claisen products (**5**).

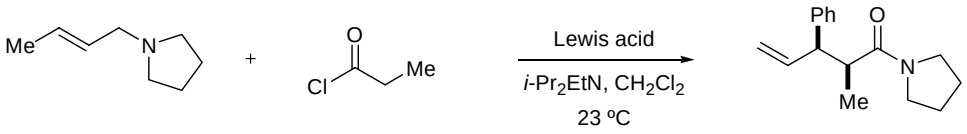
Scheme 1. Proposed Lewis–acid catalyzed acyl-Claisen rearrangement



Results and Discussion

Initial investigations of our proposed Lewis acid–catalyzed acyl-Claisen rearrangement was conducted using crotyl pyrrolidine **6** and propionyl chloride **7** in the presence of Hünig's base and a variety of metal salts (Table 1). This process produces rearrangement product **8** efficiently using one equivalent of Me_2AlCl. Unfortunately, poor efficiency was observed using catalytic amounts of various Lewis acids, with $Yb(OTf)_3$ being the only exception (87% yield, entry 7).[5]

Table 1. Effect of Lewis acid on the acyl–Claisen rearrangement of cinnamyl pyrrolidine



6 **7** **8**

entry	Lewis acid	equivalents	% conversion[a]	*syn:anti*[b]
1	--	--	--	--
2	$AlMe_2Cl$	1.0	94	>991:
3	$AlMe_2Cl$	0.1	34	>99:1
4	$MgBr_2$	0.1	20	>99:1
5	$Zn(OTf)_2$	0.1	<5	>90:1
6	$TiCl_4(THF)_2$	0.1	13	>99:1
7	$Yb(OTf)_3$	0.1	84	>99:1

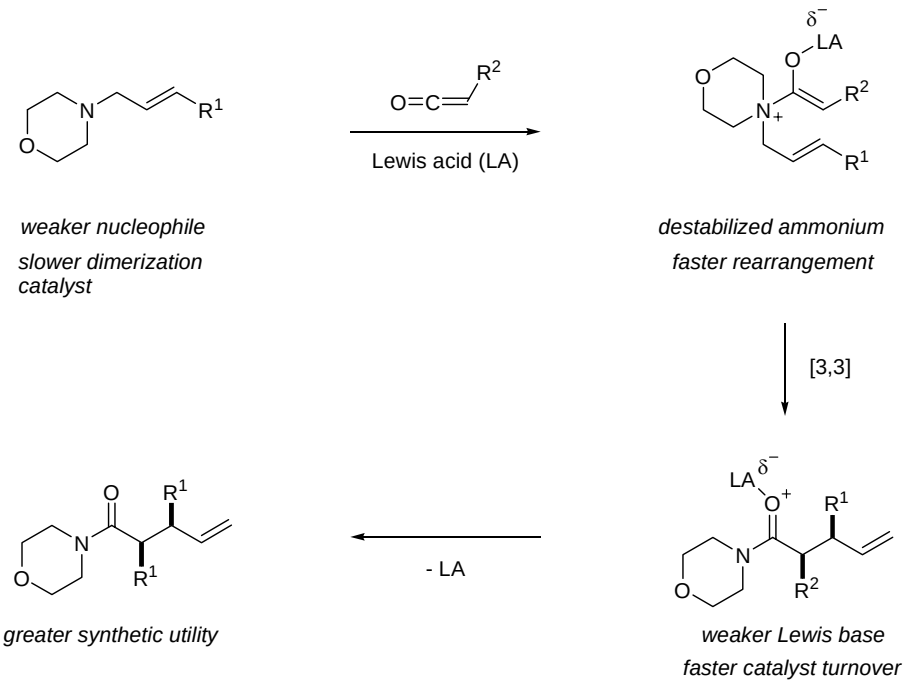
[a] Conversion based on ^1H NMR analysis of the unpurified reaction mixture. [b] Product ratios determined by GLC using a Bodman CC1701 column.

With these initial reaction parameters, competitive consumption of ketene occurs by the pyrrolidine-catalyzed dimerization pathway, resulting in poor conversion to the desired products (see Chapter 1). In the Lewis acid–catalyzed ketene-Claisen rearrangement, the ketene component was used in large excess. As such, ketene dimerization was not detrimental to the efficiency of the reaction with respect to the limiting pyrrolidine reagent. Concerns over the ability of pyrrolidines to dimerize ketenes prompted us to investigate allyl morpholines which might better participate in the acyl-Claisen rearrangement without significantly promoting the nonproductive ketene dimerization process.

N-allyl morpholines appeared to be attractive substrates for further investigation based on many reasons (Scheme 2). First, in comparison to pyrrolidine, the morpholine nitrogen has reduced basicity and nucleophilicity.[6] Consequently, allyl morpholines should be less efficient nucleophilic catalysts for ketene dimerization. Second, the electron-withdrawing effect of the oxygen in the morpholine ring should destabilize the

cationic charge on the nitrogen in the zwitterionic intermediate, and thereby increase the rate of sigmatropic rearrangement. Third, because the resulting morpholine amide products are less Lewis basic than pyrrolidine amides, dissociation of the product from the metal center should be more facile, thus improving catalyst turnover. Finally, morpholine amides own greater synthetic utility than their pyrrolidine counterparts. Similar to Weinreb amides,[7] morpholine-derived amides can be converted to ketones by treatment with alkylmetal nucleophiles,[8] and to aldehydes by reduction with LAH.[9]

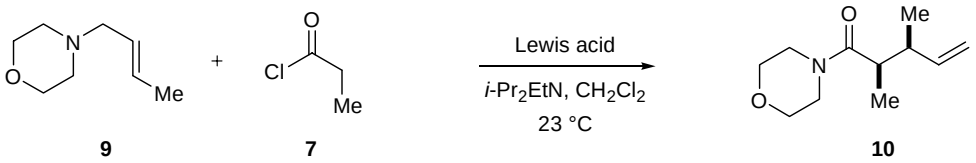
Scheme 2. *N*-allyl morpholines for the acyl-Claisen rearrangement



In contrast to our results with allyl pyrrolidines, the acyl-Claisen strategy was successful using propionyl chloride (**7**) and (*E*)-crotyl morpholine (**9**) in the presence of *i*-Pr_2EtN and *catalytic* amounts of Lewis acids, including $Yb(OTf)_3$, $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ and $TiCl_4(THF)_2$ (cf. Table 1 and Table 2). In all cases the 1,2-disubstituted Claisen

adduct **10** was formed in high yield (>75%, entries 2–5) and with excellent levels of stereocontrol (>99:1 *syn*:*anti*). The excellent levels of diastereoselectivity and catalyst efficiency displayed by $TiCl_4(THF)_2$ defined this metal salt as the optimal catalyst for exploration of this new acyl-Claisen rearrangement.

Table 2. Catalyzed acyl-Claisen rearrangement between crotyl morpholine and propionyl chloride



9 **7** **10**

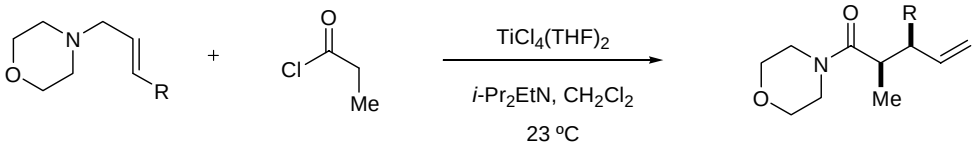
entry	Lewis acid	mol% cat	% yield	*syn*:*anti*[a]
1	--	10	NR	--
2	$Yb(OTf)_3$	10	80	>99:1
3	$AlCl_3$	10	90	>99:1
4	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	10	76	>99:1
5	$TiCl_4(THF)_2$	5	92	>99:1

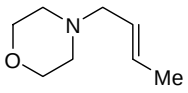
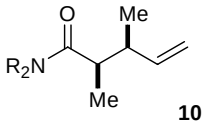
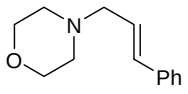
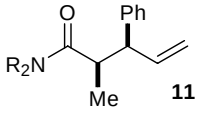
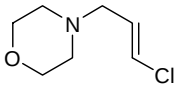
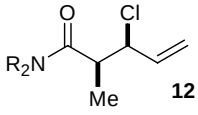
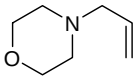
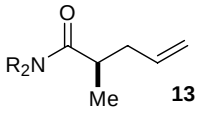
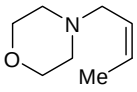
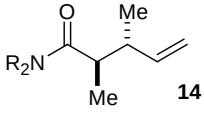
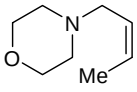
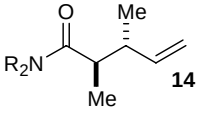
[a] Conversion based on ^{1}H NMR analysis of the unpurified reaction mixture.

Scope of the Acyl-Claisen Rearrangement

Allyl morpholine components. Experiments that probe the scope of the allyl morpholine reaction component are summarized in Table 3. Significant structural variation in the allyl substituent (R_1 = H, alkyl, aryl or halogen, entries 1–4) is possible without loss in yield or diastereoselectivity (>76% yield, >99:1 *syn*:*anti*).

Table 3. Catalyzed acyl–Claisen rearrangement between representative allyl morpholines and propionyl chloride



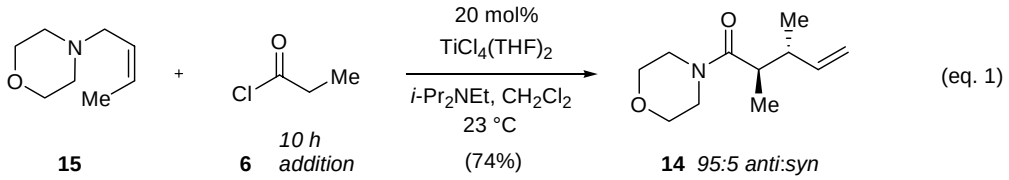
entry	amine	mol% cat	product[a]	yield	*syn:anti* [b,c]
1		5	 **10**	92	>99:1
2		10	 **11**	76	>99:1
3		10	 **12**	95	>99:1
4		10	 **13**	95	>99:1
5	 **15**	10	 **14**	NR	--
6	 **15**	100	 **14**	>95[d]	<5:95[d]

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single crystal X-ray analysis or chemical correlation to a known compound (See Experimental Methods). [d] Conversion and diastereoselectivity determined by 1H NMR analysis of unpurified reaction mixture.

While *trans*-disubstituted allylic morpholines reacted efficiently with propionyl chloride under catalysis of $TiCl_4(THF)_2$, our initial experiment with the corresponding *cis* isomer was unsuccessful (cf. entry 1 and entry 5). However, the desired *anti*-1,2-

dimethyl- substituted Claisen product **14** could be formed when stoichiometric amounts of $TiCl_4(THF)_2$ was used to promote the reaction (entry 6).

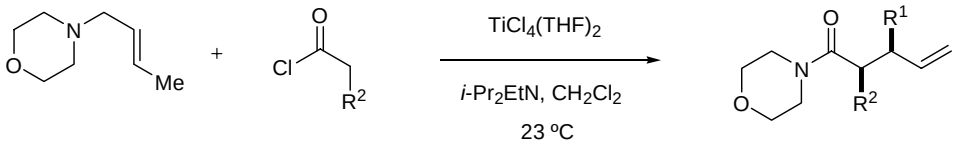
The underlying reason for the failure of the Lewis acid–catalyzed rearrangement of *cis*-crotyl morpholine substrates is non-productive ketene dimerization. We speculated that the ketene-Claisen rearrangement for *cis*-crotyl morpholine could be rendered catalytic in $TiCl_4(THF)_2$, if the rate of ketene dimerization was significantly decelerated. Because ketene dimerization is presumably second-order with respect to ketene, we expected that maintaining a lower concentration of ketene in the reaction solution would inhibit dimerization. Furthermore, we reasoned this could be achieved by slower addition of the acid chloride (i.e., ketene precursor) to the reaction mixture. Indeed, when propionyl chloride is added by syringe pump over the course of 10 h, the reaction of **15** proceeds to give the desired **14** in 74% yield (95:5 *anti:syn*) using 20 mol% $TiCl_4(THF)_2$ (equation 1).

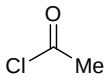
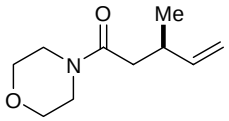
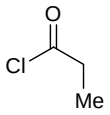
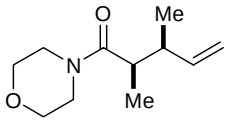
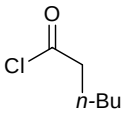
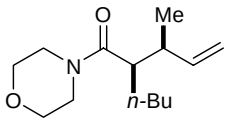
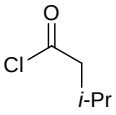
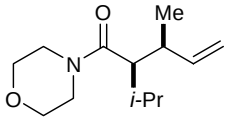
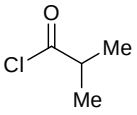
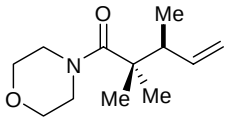


(eq. 1)

Acid chloride components. As shown in Table 4, a variety of sterically unhindered alkyl substituted acid chlorides, such as acetyl chloride, propionyl chloride, and hexenoyl chloride, reacted successfully (entries 1–3). Acid chlorides which are sterically more encumbered were not well tolerated by this process. Isovaleroyl chloride reacts more sluggishly (entry 4), and the α-disubstituted isobutyroyl chloride produced no observable Claisen products (entry 5).

Table 4. Acyl-Claisen rearrangement of allyl morpholines and representative acid chlorides



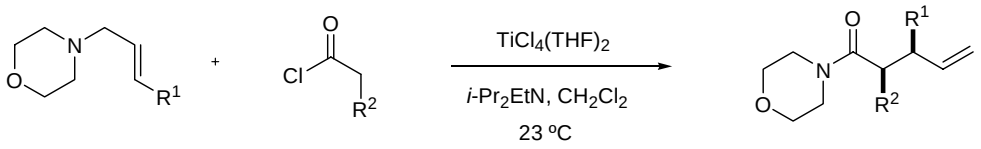
entry	acid-Cl	product	yield	*syn*:*anti*[a,b]
1			81	--
2[c]			92	>99:1
3			93	>99:1
4			28[d]	>99:1
5			NR	--

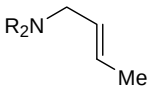
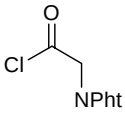
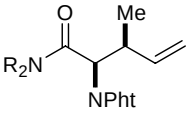
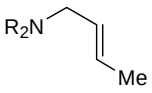
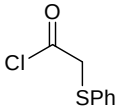
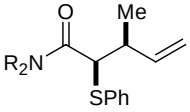
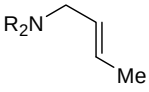
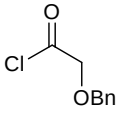
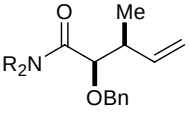
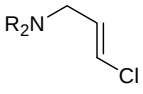
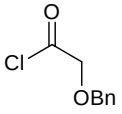
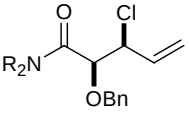
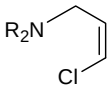
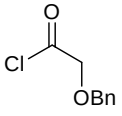
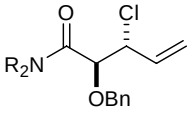
[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Relative configurations assigned by analogy to results summarized in Table 4. [c] Reaction conducted with 5 mol% $TiCl_4(THF)_2$. [d] Conversion determined by ^1H NMR analysis of unpurified reaction mixture.

Heteroatom-substituted acid chlorides were also examined and were found to participate in the acyl-Claisen rearrangement (Table 5). This process provides a new Lewis acid–catalyzed strategy for the production of unnatural β-substituted α-amino acids using α-phthalylglycyl chloride (77% yield, 99:1 *syn*:*anti*, entry 1). This reaction is also tolerant of oxygen[10] and sulfur substituents on the acyl chloride component (>81% yield, >86:14 *syn*:*anti*, entries 2–3). A powerful feature of this new Claisen

rearrangement is the capacity to build diverse functional and stereochemical arrays that are not readily available using conventional catalytic methods. For example, both the *syn* and *anti*-α-oxy-β-chloro Claisen isomers and can be accessed in high yield and stereoselectivity from chloro-substituted allyl morpholines and α-benzyloxyacetyl chloride (entries 4–5).[11]

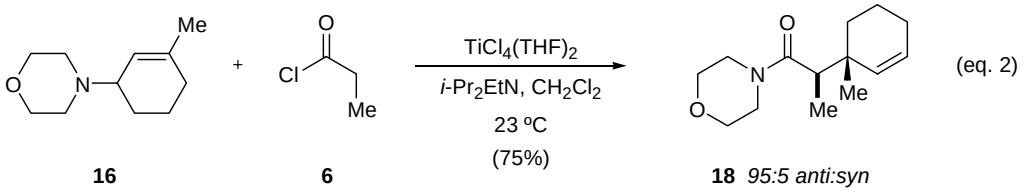
Table 5. Catalyzed Acyl–Claisen rearrangement between allyl morpholines and representative acid chlorides



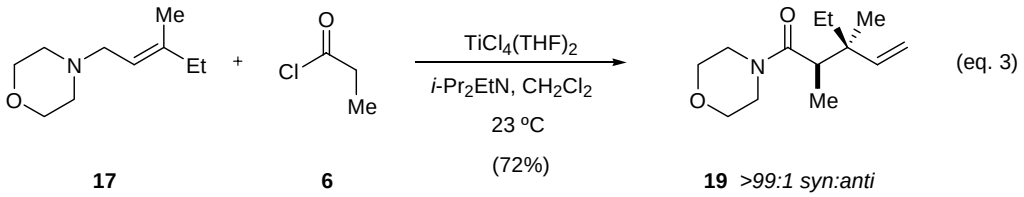
entry	amine[a]	acid-Cl	product[a]	yield	*syn:anti*[b,c]
1				77	>99:1
2				81	92:8
3				91	86:14
4				83	90:10
5				70	10:90

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single crystal X-ray analysis or chemical correlation to a known compound (see Experimental Methods).

A further illustration of the ability of this methodology to access elusive structural motifs is presented in the rearrangement of 3,3-disubstituted allyl morpholines **16** and **17** (equations 2 and 3). The key issue in these reactions is π-facial discrimination in the transition state to selectively build quaternary carbon stereocenters on both cyclic and acyclic architecture. The reaction of propionyl chloride with 1-methyl-3-*N*-morpholino-cyclohexene **16** provides excellent levels of diastereocontrol in the formation of the quaternary carbon bearing cyclic adduct **18** (equation 2). As illustrated in equation 3, the methyl versus ethyl substitution pattern on morpholine **17** can be distinguished in the reaction to furnish the acyclic product **19** with complete diastereselectivity (>99:1 *syn*:*anti*).



16 **6** **18** *95:5 anti:syn* (eq. 2)



17 **6** **19** *>99:1 syn:anti* (eq. 3)

Concluding Remarks

A new Lewis acid–catalyzed acyl-Claisen rearrangement that tolerates a range of alky, aryl and heteroatom-substituted acid chloride and allylic morpholine reaction partners has been achieved. Based on these studies, we have subsequently accomplished

two novel enantioselective variants of the zwitterionic-Claisen rearrangement: (1) a chiral magnesium (II)-bis(oxazoline) Lewis acid promoted enantioselective acyl-Claisen rearrangement with chelating acid chlorides, and (2) a chiral boron Lewis acid promoted enantioselective acyl-Claisen rearrangement (for details, see Tehshik Yoon's Ph.D. thesis).[12] Furthermore, these fundamental studies established a foundation for the design of a novel tandem acyl-Claisen rearrangement presented in the following chapter.

Experimental Method

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[13] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N*,*N*-diisopropylethylamine and dichloromethane were distilled from calcium hydride prior to use. Air sensitive solids were dispensed in an inert atmosphere glovebox. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63 according to the method of Still.[14] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C are reported in terms of chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Berkeley Mass Spectral facility. Gas chromatography was performed on Hewlett-Packard 5890A and

6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm).

General Procedure A: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added dropwise over 1 min. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

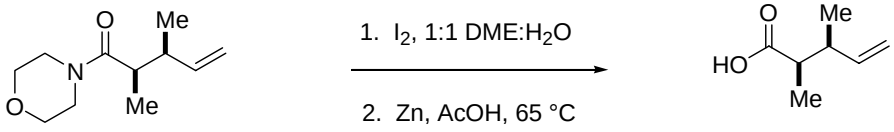
General Procedure B: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added slowly by syringe pump over 4–10 h. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and

concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

(2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (10).** Prepared according to general procedure A from (*E*)-*N*-but-2-enyl morpholine (**9**) (115 mg, 0.81 mmol), $TiCl_4(THF)_2$ (27 mg, 81 µmol), *i*-Pr_2NEt (213 µL, 1.22 mmol), and propionyl chloride (980 µL, 1 M solution in CH_2Cl_2, 0.98 mmol) in CH_2Cl_2 (8.1 mL) to provide the purified product as a colorless oil in 92% yield (148 mg, 0.75 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 2926, 2860, 1633, 1459, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 7.3, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 4.87–4.96 (m, 2H, CH=C**H**$_2$), 3.34–3.60 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.52 (dq, *J* = 7.1, 7.1 Hz, 1H, C**H**CH_3), 2.37 (q, *J* = 7.1 Hz, 1H, C**H**CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 142.3, 114.3, 67.3, 67.0, 46.5, 42.3, 40.5, 40.3, 16.3, 14.8; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{11}H_{19}NO_2)^+$ requires *m/z* 197.1416, found *m/z* 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.

Determination of the Relative Configuration of (2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (5) by Correlation with (2*R**,3*S**)-2,3-Dimethyl-4-pentenoic acid.** A solution of (2*R**,3*S**)-*N*-(2,3-dimethyl-4-pentenoyl)-morpholine (**10**) (22 mg, 0.11 mmol) in 1,2-DME (0.25 mL) and H_2O (0.25 mL) was placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine

(61 mg, 0.24 mmol) and was stirred in the absence of light. After 30 min, the reaction was diluted with Et_2O (1 mL) and washed sequentially with 10% aqueous $Na_2S_2O_3$ (1 mL) and brine (1 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated to give (2*S**,3*S**,4*R**)-4-iodomethyl-2,3-dimethyl-γ-butyrolactone as a yellow oil. This crude residue was dissolved in glacial AcOH (1 mL) and placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with zinc dust (65 mg, 1.0 mmol) and stirred at 65 °C for 3 h. After allowing the reaction to cool to rt, 1 *N* HCl (aq) (1 mL) was added, and the mixture was extracted with ether (3 x 1 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to give a light pink oil that exhibited spectral data identical in all respects to those reported for (2*R**,3*S**)-2,3-dimethyl-4-pentenoic acid.[15]



(2*S,3*S**)-*N*-(2-Methyl-3-phenyl-4-pentenoyl)-morpholine (11).** Prepared according to general procedure A from (*E*)-*N*-(3-phenyl-2-propenyl)-morpholine (201 mg, 0.99 mmol), $TiCl_4(THF)_2$ (33 mg, 99 μmol), *i*-Pr_2NEt (258 μL, 1.43 mmol), and propionyl chloride (1.48 mL, 1 M solution in CH_2Cl_2, 1.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C to provide the pure product as white needles in 74% yield (194 mg, 0.75 mmol); >99:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3057, 2988, 2968, 2930, 1637, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H, Ph), 5.99 (ddd, *J* = 7.8, 10.4, 17.9 Hz, 1H, C**H**=CH_2), 4.95–5.02 (m, 2H, CH=C**H**$_2$), 3.48–3.66 (m, 9H, N(C**H**$_2$C**H**$_2$)$_2$, C**H**Ph), 3.04 (dq, *J* = 6.8, 9.9 Hz, 1H, C**H**CH_3), 0.90 (d, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ

174.0, 141.7, 139.8, 128.6, 128.3, 126.7, 115.7, 67.0, 66.7, 53.4, 46.2, 42.1, 39.7, 16.7; LRMS (FAB) m/z 259; HRMS (FAB) exact mass calcd for ($C_{16}H_{21}NO_2$) requires *m/z* 259.1572, found *m/z* 259.1569. Diastereomer ratio was determined by GLC with a CC-1701 column (70 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 31.3 min, *anti* adduct t_r = 30.2 min.

(2*R,3*S**)-*N*-(3-Chloro-2-methyl-4-pentenoyl)-morpholine (12).** Prepared according to general procedure A from (*E*)-*N*-(3-chloro-2-propenyl) morpholine (112 mg, 0.69 mmol), $TiCl_4(THF)_2$ (23 mg, 69 µmol), *i*-Pr_2NEt (181 µL, 1.04 mmol), and propionyl chloride (1.04 mL, 1 M solution in CH_2Cl_2, 1.04 mmol) in CH_2Cl_2 (7 mL) to provide the pure product as a pale yellow oil in 95% yield (143 mg, 0.66 mmol); >99:1 *syn*:*anti* . *Syn* isomer: IR (CH_2Cl_2) 3057, 2976, 2864, 1640, 1463, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.12–5.31 (m, 2H, CH=C**H**$_2$), 4.51 (t, *J* = 8.4 Hz, 1H, C**H**Cl), 3.50–3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.98 (dq, *J* = 6.8, 8.8 Hz, 1H, C**H**CH_3), 1.27 (d, *J* = 6.8, 3H, CH_3); ^{13}C NMR (75 MHz) δ 172.0, 136.6, 118.4, 67.2, 67.0, 65.4, 46.7, 42.7, 42.5, 16.7; LRMS (FAB) *m/z* 217 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{16}ClNO_2$) requires *m/z* 217.0870, found *m/z* 217.0868. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 7 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 18.7 min and 19.2 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 19.6 min and 19.8 min. Relative configuration assigned by analogy.

***N*-(2-Methyl-4-pentenoyl)-morpholine (13).** Prepared according to general procedure A from *N*-allyl morpholine (161 mg, 1.3 mmol), $TiCl_4(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (336 μL, 0.94 mmol), and propionyl chloride (1.5 mL, 1 M solution in CH_2Cl_2, 1.5 mmol) in CH_2Cl_2 (13 mL) to provide the pure product as a clear oil in 95% yield (221 mg, 1.2 mmol); IR (CH_2Cl_2) 2976, 2864, 1640, 1467, 1436 cm^{-1}; ^1H NMR (400 MHz) δ 5.66–5.77 (m, 1H, C**H**=CH_2), 4.96–5.05 (m, 2H, CH=C**H**$_2$), 3.47–3.64 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.64–2.72 (m, 1H, C**H**CH_3), 2.35–2.42 (m, 1H, C**H**$_2$CH=CH_2), 2.06–2.13 (m, 1H, C**H**$_2$CH=CH_2), 1.08 (d, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.5, 136.0, 116.7, 67.0, 66.8, 46.0, 42.1, 38.1, 35.1, 17.3; LRMS (FAB) *m/z* 183 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{17}NO_2$) requires *m/z* 183.1259, found *m/z* 183.1253.

(2*R,3*R**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (14)**. Prepared according to general procedure B from (*Z*)-*N*-but-2-enyl morpholine (**15**) (88 mg, 0.62 mmol), $TiCl_4(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (163 μL, 0.94 mmol), and propionyl chloride (750 μL, 1 M solution in CH_2Cl_2, 0.75 mmol), added over 8h, in CH_2Cl_2 (4.2 mL) to provide the pure product as a clear oil in 74% yield (91 mg, 0.46 mmol); 95:5 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 2976, 2864, 1637, 1463, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, *J* = 8.2, 10.2, 18.3 Hz, 1H, C**H**=CH_2), 4.96–5.12 (m, 2H, CH=C**H**$_2$), 3.44–3.66 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.36–2.49 (m, 2H, C**H**CH3), 1.02 (d, *J* = 6.5 Hz, 3H, CH_3), 0.94 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 141.6. 115.4, 67.4, 67.1, 46.5, 42.4, 41.8, 40.4, 19.3; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass for ($C_{11}H_{19}NO_2$) requires *m/z* 197.1416, found 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn*

adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.

(2*R,3*S**)-*N*-(Methyl-2-phthalimido-4-pentenoyl)-morpholine (Table 5, entry 1).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (75 mg, 0.53 mmol), $TiCl_4(THF)_2$ (17.7 mg, 53 μmol), *i*-Pr_2NEt (139 μL, 0.80 mmol), and phthalylglycyl chloride (1.3 mL, 0.5 M solution in CH_2Cl_2, 0.64 mmol), added over 3h, in CH_2Cl_2 (10.6 mL) to provide the pure product as white crystals in 77% yield (134 mg, 0.41 mmol); 98:2 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3065, 2976, 2864, 1776, 1718, 1660, 1459, 1436, 1382, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.81 (m, 4H, Ph**H**), 5.79 (ddd, *J* = 7.6, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 5.04–5.18 (m, 2H, CH=C**H**$_2$), 4.76 (d, *J* = 10.2 Hz, 1H, C**H**NR_2), 3.63–3.71 (m, 1H, C**H**CH_3), 3.39–3.56 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.5, 139.6, 134.4, 131.3, 123.6, 116.6, 66.8, 66.5, 54.5, 46.3, 42.5, 36.5, 16.5; LRMS (FAB) *m/z* 329 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{18}H_{21}N_2O_4)^+$ requires *m/z* 329.1501, found *m/z* 329.1504. Diastereomer ratio was determined by GLC with a CC-1701 column (50 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 51.8 min, *anti* adduct t_r = 49.2 min.

(2*R,3*S**)-*N*-(3-Methyl-2-phenylthio-4-pentenoyl)-morpholine (Table 5, entry 2).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (67 mg, 0.48 mmol), $TiCl_4(THF)_2$ (15.9 mg, 47.5 μmol), *i*-Pr_2NEt (124 μL, 0.71 mmol), and phenylthioacetyl chloride (569 μL, 1 M solution in CH_2Cl_2, 0.57 mmol), added over 4 h,

in CH_2Cl_2 (9.5 mL) to provide the pure product as a light orange oil in 81% yield (107 mg, 0.39 mmol); *syn*:*anti* 92:8. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2864, 1640, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.49 (m, 2H, Ph), 7.28–7.30 (m, 3H, Ph), 5.75 (ddd, *J* = 7.5, 8.8, 16.3 Hz, 1H, C**H**=CH_2), 4.99–5.10 (m, 2H, CH=C**H**$_2$), 3.73 (d, *J* = 9.7 Hz, 1H, C**H**SPh), 3.11–3.58 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.76–2.82 (m, 1H, C**H**CH_3), 1.28 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 140.3, 134.0, 129.1, 128.4, 115.6, 78.3, 66.9, 66.4, 53.9, 46.4, 42.3, 39.7, 17.9; LRMS (FAB) *m/z* 292 $(MH)^+$; HRMS (FAB) exact mass calcd for ($C_{16}H_{22}NO_2S$) requires *m/z* 292.1371, found *m/z* 292.1373. Diastereomer ratios were determined by ^1H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-methyl-4-pentenoyl)-morpholine (Table 5, entry 3).** Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (**9**) (60 mg, 0.43 mmol), $TiCl_4(THF)_2$ (14 mg, 43 μmol), *i*-Pr_2NEt (111 μL, 0.64 mmol), and benzyloxyacetyl chloride (0.51 mL, 1 M solution in CH_2Cl_2, 0.51 mmol), added over 2h, in CH_2Cl_2 (8.5 mL) to provide the pure product as a pale yellow oil in 91% yield (112 mg, 0.39 mmol); 86:15 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3068, 2746, 2864, 1640, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.36 (m, 5H, Ph), 5.68 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.00–5.08 (m, 2H, CH=C**H**$_2$), 4.62 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 4.43 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 3.92 (d, *J* = 8.9, 1H, C**H**OCH_2Ph), 3.55–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.55–2.62 (m, 1H, C**H**CH_3), 1.15 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.9, 137.3, 128.5, 128.0, 115.8, 84.2, 72.2, 67.1, 66.8, 45.7, 42.5, 41.5, 17.0; LRMS (FAB) *m/z* 290 $(MH)^+$; HRMS (FAB) exact mass calcd for

($C_{17}H_{24}NO_3$) requires *m/z* 289.1756, found *m/z* 290.1755. Diastereomer ratios were determined by ^{1}H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 4).** Prepared according to the general procedure A from (*E*)-*N*-(3-chloro-2-propenyl)-morpholine (100 mg, 0.62 mmol), $TiCl_4(THF)_2$, (21 mg, 62 μmol), *i*-Pr_2NEt (151 μL, 86.7 mmol), and propionyl chloride (0.74 mL, 1 M solution in CH_2Cl_2, 0.74 mmol) in CH_2Cl_2 (12 mL) to provide the pure product as a yellow oil in 84% yield (160 mg, 0.52 mmol); 90:10 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2907, 2864, 1648, 1444, 1274, 1247, 1116 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.30–7.40 (m, 5H, Ph), 5.92 (ddd, *J* = 8.5 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2) 5.39 (d, *J* = 16.9 Hz, 1 H, CH=C**H**$_2$), 5.26 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.72–4.73 (m, 1H, C**H**Cl), 4.71 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 7.4 Hz, 1H, C**H**OCH_2Ph), 3.50–3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.0, 136.5, 134.4, 128.5, 128.3, 128.1, 119.5, 82.4, 72.5, 66.9, 66.7, 62.4, 45.8, 42.8; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10 °C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

(2*R,3*R**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 5).** Prepared according to the general procedure A from (*Z*)-*N*-(3-chloro-2-propenyl)-morpholine (82 mg, 0.51 mmol), $TiCl_4(THF)_2$, (17 mg, 51 μmol), *i*-Pr_2NEt (290 μL, 1.66

mmol), and propionyl chloride (1.52 mL, 1 M solution in CH_2Cl_2, 1.52 mmol) in CH_2Cl_2 (10 mL) to provide the pure product as a yellow oil in 71% yield (110 mg, 0.36 mmol); 90:10 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 3057, 2976, 2907, 1652, 1444, 1239, cm^{-1}; ^1H NMR (400 MHz) δ 7.29–7.38 (m, 5H, Ph), 6.00 (ddd, *J* = 8.4 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2), 5.48 (dd *J* = 0.9 Hz, *J* = 16.0 Hz, 1 H, CH=C**H**$_2$), 5.35 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.75 (t, *J* = 8.3 Hz, 1H, C**H**Cl), 4.63 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.51 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 8.3 Hz, 1H, C**H**OCH_2Ph), 3.50–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.3, 136.7, 134.5, 128.6, 128.3, 128.1, 119.8, 78.5, 71.9, 66.9, 66.6, 60.5, 46.0, 42.7; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10`°C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

(*E*)-*N*-(3-Ethyl-3-methyl-2-propenyl)-morpholine (17). 2-Methyl-3-penten-1-ol was prepared using a modification of the procedure outlined by Corey and coworkers:[16] To a solution of 2-pentyn-1-ol (2.5 mL, 27 mmol) in THF (100 mL) was added Red-Al (8.1 mL of a 3.5 M solution in toluene, 28 mmol). The resulting solution was warmed to reflux for 3.5 h and then cooled to –78 ^oC, before a solution of iodine (20.5 g, 81.0 mmol) in THF (50 mL) was added dropwise by syringe. The resulting solution was then allowed to warm to rt before Et_2O (200 mL) was added, and the reaction mixture washed with 5% Na_2SO_4 (3 x 200 mL), dried (Na_2SO_4), and

concentrated to afford 3-iodo-2-penten-1-ol as a crude product that was used without further purification.

To a solution of copper (I) iodide (20.1 g, 0.11 mol) and methyl lithium (162 mL of a 1.3 M solution in Et_2O, 0.21 mol) in Et_2O (60 mL) at 0 °C was added a solution of the crude 3-iodo-2-penten-1-ol. The reaction mixture was stirred at 0 ^oC for 62 h and then washed with sat. aq. NH_4Cl (3 x 200 mL), dried (Na_2SO_4), and concentrated to provide 2-methyl-3-penten-1-ol in 91% yield (2.1 g, 21 mmol) as a pure oil by ^1H NMR analysis. Spectroscopic data of this material were in complete agreement with reported literature values.[17]

Morpholine **17** was prepared using a modification of the procedure outlined by Froyen and coworkers:[18] To a solution of 2-methyl-3-peten-1-ol (1.3 g, 13 mmol) and triphenylphosphine (3.6 g, 14 mmol) in THF (10 mL) was added *N*-bromosuccinimide (2.5 g, 14 mmol). After 15 min, morpholine (2.7 mL, 31 mmol) was added dropwise and the resulting brown solution was heated to 70 °C for 2.5 h. Upon cooling to rt, the reaction mixture was diluted with Et_2O (25 mL) and filtered through a pad of Celite©. The filtrate was then extracted with aqueous 1*N* HCl (100 mL). The product containing aqueous layer was then washed with Et_2O (3 x 100 mL), and then made alkaline by the addition of NaOH (4 g). The aqueous solution was then extracted with Et_2O (3 x 100 mL), the combined organic layers dried (Na_2SO_4), and then concentrated by rotary evaporation at 0 ^oC under reduced pressure. The resulting residue was then distilled (110 °C, 20 mm) to afford (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (**17**) as a colorless oil in 49% yield (1.0 g, 6.0 mmol); IR 2968, 1455, 1293, 1116, 1004, 907 cm^{-1}; ^1H NMR (400 MHz) δ 5.21–5.25 (m, 1H, C**H**=CCH_3), 3.65–3.77 (m, 4H, O(C**H**$_2$)$_2$), 2.96 (d, *J* =

7.0 Hz, 2H, C**H**$_2$C=CH), 2.44 (m, 4H, N(C**H**$_2$)$_2$), 2.01 (q, *J* = 7.3 Hz, 2H, CH$_3$C**H**$_2$), 1.63 (s, 3H, C**H**$_3$C=CH), 0.97–1.04 (m, 3H, CH$_3$C**H**$_2$); ^{13}C NMR (100 MHz) δ 141.1, 118.7, 67.0, 56.0, 53.5, 32.4, 16.4, 12.5; LRMS (FAB) *m/z* 169 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{19}NO)^+$ requires *m/z* 169.1467, found *m/z* 169.1464.

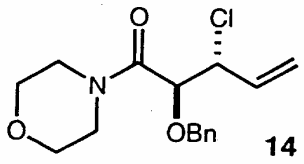
(1´*S,2*R*)-*N*-(2-(1´-Methylcyclohex-2´-enyl)-propanoyl)-morpholine (18).** Prepared according to general procedure A from 1-methyl-3-*N*-morpholino-cycohexene[19] (**16**) (50 mg, 0.28), $TiCl_4(THF)_2$, (9 mg, 27 μmol), *i*-Pr$_2$NEt (71 μL, 0.41 mmol), and propionyl chloride (0.41 mL, 1M solution in CH_2Cl_2, 0.41 mmol) in CH_2Cl_2 (3 mL) to provide the product as a yellow oil in 72% yield (45 mg, 0.36 mmol); 95:5 dr. Major isomer: IR (CH_2Cl_2) 2968, 2934, 2864, 1633, 1459, 1432, 1239, 1116 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.72 (d, *J* = 10.2 Hz, 1H, CH$_2$CH=C**H**), 5.64 (m, 1H, CH$_2$C**H**=CH), 3.54–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.62 (q, *J* = 6.9 Hz, 1H CHC=O), 1.92 (m, 2H, C**H**$_2$CH=CH), 1.68–1.73 (m, 1H, CH$_2$), 1.53–1.67 (m, 2H, CH$_2$), 1.34–1.39 (m, 1H, CH$_2$), 1.09 (d, *J* = 6.9Hz, 3H, C**H**$_3$CHC=O), 1.06 (s, 3H, C**H**$_3$CCH=CH); ^{13}C NMR (100 MHz) δ 174.5, 134.1, 126.4, 67.1, 66.8, 50.1, 46.9, 42.1, 37.4, 33.2, 25.0, 24.7, 19.2, 13.3; LRMS (FAB) *m/z* 237 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{14}H_{23}NO_2)$ requires *m/z* 237.1729, found *m/z* 237.1731. Diastereomer ratios were determined by ^{1}H NMR analysis.

(2*R,3*R**)-*N*-(2,3-Dimethyl-3-ethyl-4-pentenoyl)-morpholine (19).** Prepared according to general procedure B from (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (135 mg, 0.80 mmol), $TiCl_4(THF)_2$, (27 mg, 81 μmol), *i*-Pr$_2$NEt (0.56 mL, 3.2 mmol),

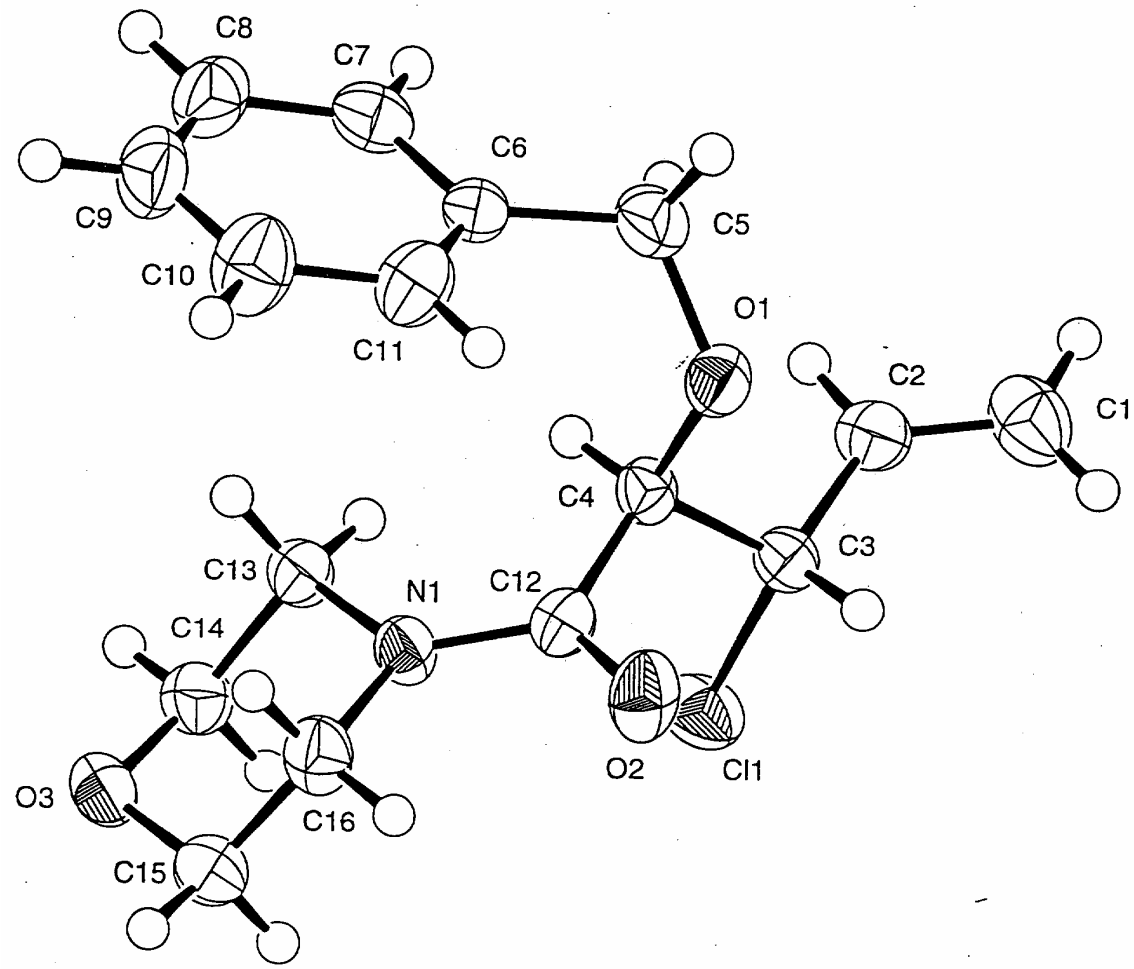
and propionyl chloride (2.4 mL, 1 M solution in CH_2Cl_2, 2.4 mmol) in CH_2Cl_2 (2.7 mL) to provide the pure product as a yellow oil in 72% yield (130 mg, 0.58 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 1633, 1459, 1432, 1235 cm^{-1}; ^1H NMR (400 MHz) δ 5.88 (dd, *J* = 10.9 Hz, 17.6 Hz, 1H, CH=C**H**$_2$), 5.03 (dd, *J* = 1.5, 10.9 Hz, 1H, CH=C**H**$_2$), 4.88 (dd, *J* = 1.4, 17.6 Hz, 1H, CH=C**H**$_2$), 3.49–3.64 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.63 (q, *J* = 6.9 Hz, 1H, C**H**C=O), 1.32–1.49 (m, 2H, C**H**$_2$CH$_3$), 1.02 (d, *J* = 6.9 Hz, 3H, C**H**$_3$CHC=O), 0.99 (s, 3H, C**H**$_3$C), 0.73 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz) δ 174.1, 143.8, 67.0, 66.7, 66.6, 46.8, 42.7, 42.2, 41.8, 30.9, 18.7, 13.3, 8.3; LRMS (FAB) *m/z* 225 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{13}H_{23}NO_2)^+$ requires *m/z* 225.1710, found *m/z* 225.1727.

X-ray Crystal Data

(2*R,3*R**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 5, entry 5)**



14



EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}ClNO_3H_{20}$
Formula Weight	309.79
Crystal Color, Habit	colorless, blades
Crystal Dimensions	0.45 X 0.21 X 0.15 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 19.9407(11)Å b = 15.6857(9) Å c = 10.1045(5) Å V = 3160.5(3) Å^3
Space Group	Pbcn (#60)
Z value	8
D_{calc}	1.302 g/cm^3
F_{000}	1312.00
μ(MoKα)	19.12 cm^{-1}

B. Intensity Measurements

Diffractometer	SMART CCD
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{max}$	52.1°

No. of Reflections Measured	Total: 15231 Unique: 3290 (R_{int} = 0.041)
Corrections	Lorentz-polarization Absorption (Tmax = 0.96 Tmin = 0.56)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1777
No. Variables	190
Reflection/Parameter Ratio	9.35
Residuals: R; Rw; Rall	0.031 ; 0.035; 0.065
Goodness of Fit Indicator	1.38
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.25 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.17 $e^-/Å^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Cl(1)	0.83240(3)	0.11510(3)	0.02084(6)	3.579(14)
O(1)	0.75978(7)	0.33195(9)	0.16424(13)	2.90(3)
O(2)	0.71559(7)	0.18075(9)	0.27638(14)	3.59(4)
O(3)	0.57402(7)	0.04944(10)	-0.05896(14)	3.40(4)
N(1)	0.65927(8)	0.16133(10)	0.08421(15)	2.56(4)
C(1)	0.93863(11)	0.29648(16)	0.0967(2)	4.11(6)
C(2)	0.88327(11)	0.27408(13)	0.0392(2)	2.97(5)
C(3)	0.83158(10)	0.21842(12)	0.10154(18)	2.47(5)
C(4)	0.76076(10)	0.25370(12)	0.09084(18)	2.36(5)
C(5)	0.73829(11)	0.40391(13)	0.0879(2)	3.56(6)
C(6)	0.66668(11)	0.39854(12)	0.0404(2)	2.68(5)
C(7)	0.65122(12)	0.41985(14)	-0.0891(2)	3.24(6)
C(8)	0.58538(13)	0.42017(15)	-0.1329(2)	3.81(6)
C(9)	0.53508(13)	0.39724(16)	-0.0480(3)	4.26(7)
C(10)	0.54949(13)	0.37448(18)	0.0792(3)	4.62(7)
C(11)	0.61497(12)	0.37572(15)	0.1243(2)	3.74(6)
C(12)	0.70977(10)	0.19433(13)	0.1567(2)	2.46(5)
C(13)	0.64871(11)	0.17191(13)	-0.0577(2)	2.73(5)
C(14)	0.63127(11)	0.08704(14)	-0.1191(2)	3.15(5)
C(15)	0.58707(11)	0.03529(15)	0.0781(2)	3.33(6)
C(16)	0.60405(11)	0.11653(14)	0.1495(2)	3.12(5)
H(1)	0.9482	0.2772	0.1838	4.9264
H(2)	0.9697	0.3322	0.0517	4.9264
H(3)	0.8751	0.2943	-0.0480	3.5670
H(4)	0.8424	0.2110	0.1924	2.9675
H(5)	0.7492	0.2635	0.0009	2.8288
H(6)	0.7667	0.4086	0.0128	4.2751
H(7)	0.7427	0.4535	0.1411	4.2751
H(8)	0.6862	0.4345	-0.1486	3.8833
H(9)	0.5752	0.4362	-0.2213	4.5746
H(10)	0.4899	0.3972	-0.0777	5.1143
H(11)	0.5144	0.3577	0.1371	5.5463
H(12)	0.6245	0.3608	0.2135	4.4851
H(13)	0.6885	0.1934	-0.0972	3.2782
H(14)	0.6130	0.2109	-0.0722	3.2782
H(15)	0.6224	0.0953	-0.2106	3.7837

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(16)	0.6683	0.0496	-0.1090	3.7837
H(17)	0.5483	0.0109	0.1176	3.9984
H(18)	0.6237	-0.0031	0.0862	3.9984
H(19)	0.5657	0.1524	0.1507	3.7446
H(20)	0.6168	0.1034	0.2378	3.7446

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	0.0470(4)	0.0319(3)	0.0571(4)	0.0003(3)	0.0037(3)	-0.0104(3)
O(1)	0.0386(9)	0.0325(9)	0.0392(8)	0.0064(7)	-0.0102(7)	-0.0091(7)
O(2)	0.0427(10)	0.0692(12)	0.0244(8)	-0.0075(9)	-0.0030(8)	0.0041(7)
O(3)	0.0420(10)	0.0422(10)	0.0448(9)	-0.0137(8)	-0.0089(8)	0.0040(7)
N(1)	0.0343(11)	0.0381(11)	0.0247(10)	-0.0083(9)	-0.0022(8)	0.0023(8)
C(1)	0.0364(15)	0.0516(17)	0.0680(17)	-0.0040(12)	0.0069(13)	-0.0093(13)
C(2)	0.0327(13)	0.0347(13)	0.0455(13)	0.0018(11)	0.0038(11)	0.0008(11)
C(3)	0.0348(12)	0.0277(12)	0.0314(12)	-0.0004(10)	-0.0026(11)	-0.0050(9)
C(4)	0.0324(12)	0.0312(12)	0.0260(11)	-0.0007(10)	-0.0039(10)	-0.0047(9)
C(5)	0.0410(14)	0.0320(14)	0.0624(16)	-0.0002(11)	-0.0080(13)	-0.0062(11)
C(6)	0.0360(13)	0.0243(12)	0.0415(14)	0.0036(10)	-0.0064(12)	-0.0061(9)
C(7)	0.0504(15)	0.0291(13)	0.0434(15)	-0.0010(11)	0.0036(12)	-0.0073(10)
C(8)	0.0587(18)	0.0443(15)	0.0418(14)	0.0059(13)	-0.0165(13)	-0.0043(12)
C(9)	0.0385(15)	0.0575(18)	0.0660(18)	0.0077(13)	-0.0143(14)	-0.0075(14)
C(10)	0.0393(16)	0.080(2)	0.0566(17)	0.0045(14)	0.0042(14)	0.0025(14)
C(11)	0.0478(16)	0.0558(17)	0.0385(13)	0.0060(13)	-0.0021(13)	0.0000(12)
C(12)	0.0298(13)	0.0349(13)	0.0288(13)	0.0035(11)	0.0003(11)	-0.0006(10)
C(13)	0.0394(13)	0.0355(13)	0.0289(12)	-0.0059(10)	-0.0044(10)	0.0029(9)
C(14)	0.0465(15)	0.0382(14)	0.0351(13)	-0.0047(11)	-0.0064(11)	-0.0007(11)
C(15)	0.0372(13)	0.0427(15)	0.0467(14)	-0.0073(11)	-0.0008(11)	0.0096(11)
C(16)	0.0338(13)	0.0507(15)	0.0340(12)	-0.0061(11)	0.0010(11)	0.0039(11)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

References

(1) The research described in this chapter was conducted in collaboration with Tehshik Yoon and has been previously reported, see Yoon, T. P.; Dong, V. M.; MacMillan, D.W.C. *J. Am. Chem.* **1999**, *121*, 9726 and Yoon, T.P., Ph.D. Thesis, California Institute of Technology, 2002, chapter 3.

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(4) As the ketene was prepared as a solution in THF, the exact amounts of ketene added to the reaction were not determined.

(5) Use of triethyl amine, pyridine, DMAP, and DBU all resulted in diminished yields of the desired product in comparison to the use of Hünig's base.

(6) The p*K*a of protonated *N*-methylpyrrolidine is 10.3, while the protonated *N*-methylmorpholine has a p*K*a of 7.4. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution;* Butterworths: London, 1965.

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(11) An enantioselective proline-catalyzed α-chlorination of aldehydes has recently been discovered in our research group (Brochu, M. P.; Brown, P. S; MacMillan, D.W.C.M., unpublished results). For a review of chiral auxiliary–based methods for construction of halogenated stereocenters, see: Duhamael, P. *Ind. Chem. Libr.* **1996**, 8, 176.

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