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Tandem Reactions

N,2,3,4-Tetrasubstituted Pyrrolidines through Tandem Lithium Amide Conjugate Addition/Radical Cyclization/Oxygenation Reactions

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Abstract: Enantioselective syntheses of densely functionalized pyrrolidines deriving their chirality from (*R*)-1-(phenyl)ethylamine are reported. Allylic amines and β-substituted-α,β-unsaturated esters are used as the building blocks in this one-pot reaction. Single electron transfer (SET) oxidation served to merge the reactivities of anionic enolate and radical intermediates. Ferrocenium hexafluorophosphate, which is easy to prepare, store and handle, was applied as SET oxidant and persistent free radical TEMPO served as the oxygenating agent introducing a protected hydroxy function, which proved to be beneficial for further derivatization. Exclusive 2,3-*trans* and up to 6:1 3,4-*cis*/*trans* diastereoselectivities were achieved in the targeted tetrasubstituted pyrrolidines.

Introduction

Polysubstituted pyrrolidines are ubiquitous in Nature.[1] Selected examples are the neuroexcitatory compounds kainic and allokainic acids,[2] the DNA polymerase inhibitor plakoridine A,[3] the anti-inflammatory compounds codonopsine[4] and (+)-erysotrine,[5] and the antitussic and anthelminthic compound neostenine, which comes from the *Stemona* family of alkaloids (Figure 1).[6] Moreover, this ring system has many applications in medicinal chemistry,[7] and also in the preparation of unnatural amino acids, which have been used in the synthesis of peptidomimetic foldamers, for example.[8]

This means that efficient enantio- and diastereoselective approaches to polysubstituted pyrrolidines are required. Among the many potential approaches, tandem reactions are an attractive way to assemble polyfunctionalized derivatives in a time- and resource-efficient manner.[9] Tandem processes, in which the oxidation level of intermediates can be switched, are particularly appealing, because their reactivity patterns can be modified without the need to isolate reaction intermediates. Single-electron transfer (SET) is the key to the interconversion of radical and polar intermediates by overall oxidative, reductive, or redox-neutral pathways.[10] It also enables the consecutive generation of multiple types of reactive intermediates, such as carbanions, radicals, or carbocations, at will,[11] thus overcoming potential reactivity pitfalls.[12] Such polar–radical or radical–polar crossover reactions have found a number of applications in natural product synthesis.[13]

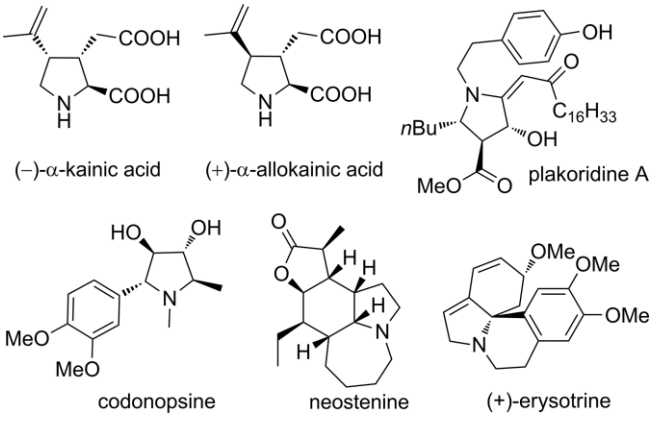

Figure 1. Pyrrolidine-ring-containing natural products.

Oxidative SET reactions can be mediated by iron(III),[14] manganese(III),[14,15] copper(II),[10c] or cerium(IV) ammonium nitrate (CAN).[14] Organic molecules, such as 2-iodoxybenzoic acid (IBX) have also been used as SET oxidants.[16] The use of photoredox catalysis for carrying out SET-induced transformations has gained growing interest.[17] Among the Fe^{III}-based SET oxidants, ferrocenium hexafluorophosphate holds a privileged role[18] because of its easy preparation and handling, and the possibility of tuning its redox properties by the choice of substituents.[19] SET oxidation-mediated tandem anionic conjugate addition/5-*exo* radical cyclization reactions were recently used in the synthesis of polysubstituted tetrahydrofurans[20] and densely func-

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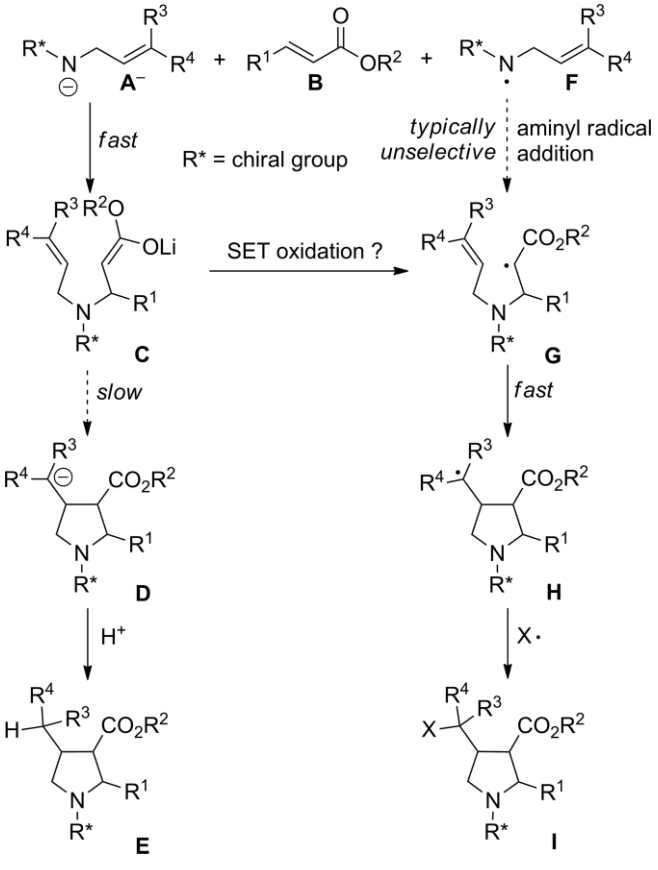
tionalized cyclopentanes.[21] Ferrocenium ion induced oxidative 5-*exo* radical cyclizations of enolates coupled with oxygenation by the persistent free radical TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] have also been used in the synthesis of natural products, such as the oxidative-stress marker 15-F_{2t}-isoprostane,[22] or the (–)-enantiomer of the antimetastatic fusarisetin A.[23]

Based on an early racemic lithium amide conjugate addition/SET oxidation/radical cyclization sequence,[24] we hypothesized that enantiomerically enriched pyrrolidines could be synthesized through tandem organometallic–radical reactions initiated by aza-Michael additions of enantiomerically pure lithium amides **A**$^-$ to (*E*)-β-substituted α,β-unsaturated esters **B** to give β-amino ester enolates **C** (Scheme 1). This is based on pioneering work by Davies,[25] who showed that homochiral lithium *N*-(1-phenyl)ethylamides **A**$^-$ undergo highly diastereoselective aza-Michael additions to α,β-unsaturated esters **B**. So far, however, amides **A**$^-$ have merely played the role of a chiral ammonia surrogate, i.e., the *N*-substituents were removed later in the reaction sequence. Only recently have more "carbon-economic" examples been found, in which the alkyl[26] or aryl[27] substituents of the lithium amides remain as functional groups in the target molecules. A unique carbon-economic combination of amide conjugate additions with [3+2] cycloadditions to give cyclic α,β,γ-triamino-acid derivatives was developed very recently.[28]



Scheme 1. Tandem anionic/radical vs. purely organometallic or radical strategies for the synthesis of tetrasubstituted pyrrolidines.

In contrast, intermolecular additions of *N*-centered radicals **F** to unactivated alkenes do not typically proceed well.[29] Recently, additions of amidyl radicals to activated styrene-type olefins have been reported, but these reactions are limited to this substrate class.[30] Similarly, anionic 5-*exo* cyclizations of enolate **C** to **D** are slow and limited to highly electron-deficient alkenes (R^3 = EWG, electron-withdrawing group). Anionic cyclizations using zinc enolates,[31] or zinc-ene[32] reactions have been reported, but the possible substitution patterns are very limited. Moreover, the functionality of cyclized organometallic intermediate **D** cannot easily be increased; protonated pyrrolidines **E** are normally obtained. Therefore, SET seems to be a very attractive prospect for joining the easier steps from the purely radical and anionic approaches to create a tandem process. Upon SET oxidation, enolate **C** forms an α-carbonyl radical **G**, which cyclizes in a favored 5-*exo* mode to give radical **H**. Coupling of radical **H** with with a radical X$^\cdot$ or its surrogate gives the final pyrrolidine carboxylate **I**, with additional functionality at the exocyclic position.

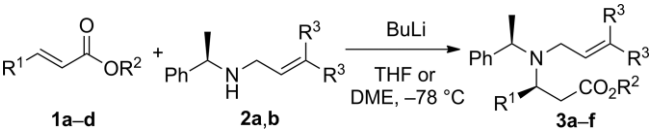
In this paper, we report a modular asymmetric tandem anionic/radical approach to *N*,2,3,4-tetrasubstituted pyrrolidines using homochiral allylic lithium amides and α,β-unsaturated esters. The chirality of (*R*)-1-(phenyl)ethylamine induces the configuration of three contiguous stereocenters in the pyrrolidine ring in this one-pot reaction. Coupling with the persistent radical TEMPO terminates the sequence, introducing a useful masked hydroxy group that can subsequently be released.

Results

Aza-Michael Additions

A series of *N*-allylic β-amino esters **3a**–**3f** was synthesized from α,β-unsaturated ester acceptors **1** and allylic lithium amides **2a**$^-$ and **2b**$^-$, in analogy with Davies' procedure (Table 1).[33] The conjugate additions of **2a**$^-$ to *tert*-butyl esters **1a** and **1b** proceeded in good yields and with good diastereoselectivities (Table 1, entries 1–3). The yields were better in THF than in 1,2-

Table 1. Conjugate addition of allylic lithium amides to unsaturated esters.[a]



1a–d 2a,b 3a–f

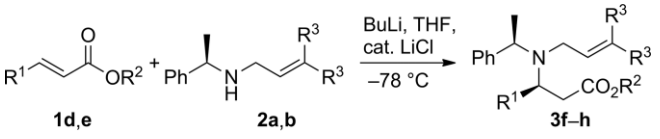
Entry[a]	1	R^1	R^2	2	R^3	Time [min]	3, yield [%]	*dr*
1[b]	**1a**	Me	*t*Bu	**2a**	H	60	**3a**, 96	>99:1
2[b]	**1b**	Ph	*t*Bu	**2a**	H	90	**3b**, 56[c]	>99:1
3	**1b**	Ph	*t*Bu	**2b**	Me	70	**3c**, 95	>15:1
4	**1c**	Me	Me	**2a**	H	60	**3d**, 95	>99:1
5	**1d**	Ph	Me	**2a**	H	60	**3e**, 92	>99:1
6	**1d**	Ph	Me	**2b**	Me	60	**3f**, 39	3.7:1

[a] General conditions: BuLi (1.1–1.3 mmol) was added to **2** (1.1–1.3 mmol) in THF at –78 °C, and after 15 min **1** (1 mmol) was added. [b] Carried out in DME at –78 °C. [c] Better yields were obtained using THF in the tandem sequence, vide infra.

dimethoxyethane (DME) (Table 1, entry 2 vs. 3–5). Methyl esters **1c** and **1d** gave high yields and diastereoselectivities only with amide **2a**$^-$ (Table 1, entries 4 and 5). Both the yield and the diastereoselectivity of the addition dropped when prenylamine-derived **2b**$^-$ was used (Table 1, entry 6). Ethyl (*E*)-4-(benzyloxy)but-2-enoate and ethyl (*E*)-4-{[(*tert*-butyl)dimethylsilyl]oxy}but-2-enoate gave rather complex reaction mixtures with little or none of the desired products (i.e., **3**) isolated (not shown). The likely explanation is a competitive γ-deprotonation by the lithium amides (i.e., **2**), giving rise to side products (vide infra).

Ethyl sorbate **1e** proved to be a difficult acceptor, prone to Michael-type polymerization that negatively affected the yield (Table 2, entry 1); a good diastereoselectivity was nevertheless retained. Therefore, the low yield was attributed to an unfavorable reaction rate. Collum and coworkers have recently described a positive effect of catalytic lithium chloride (1–2 mol-%) on the rate of lithium amide conjugate additions.[34] Therefore, selected conjugate additions to α,β-unsaturated esters **1** were carried out in the presence of lithium chloride (1–8 mol-%; Table 2, entries 2, 3, 5, and 6). Indeed, when catalytic lithium chloride was used and the addition temperature was raised to –40 °C, an increase in the yield of 18–33 % was found (Table 2, entry 3 vs. 1, and entry 5 vs. 4). The diastereoselectivity was not significantly influenced by using the catalyst for the reaction of **1e** with **2a**$^-$, but it decreased slightly in the reaction with **2b**$^-$ (Table 2, entry 5). A significant yield increase was also observed for the addition of **2b**$^-$ to methyl cinnamate **1d** (Table 2, entry 6, compare Table 1, entry 6); the diastereoselectivity, however, remained low at 4.4:1.

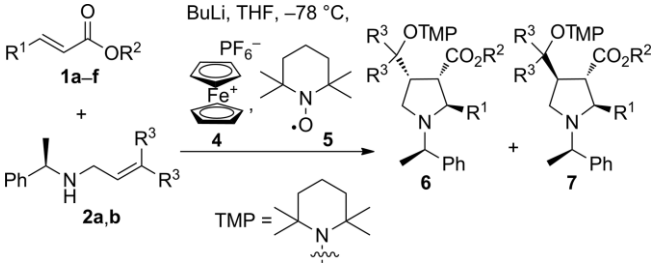
Table 2. Lithium amide conjugate additions catalyzed by lithium chloride.[a]



Entry	**1**	R^1	R^2	**2**	Temp. [°C]	LiCl [mol%]	*t* [min]	**3**, yield [%]	*dr*
1	**1e**	MeCH=CH	Et	**2a**	–78	–	120	**3g**, 39	10:1
2	**1e**	MeCH=CH	Et	**2a**	–40	8	30	**3g**, 65	19:1
3	**1e**	MeCH=CH	Et	**2a**	–40	1	25	**3g**, 72	9:1
4	**1e**	MeCH=CH	Et	**2b**	–78	–	30	**3h**, 49	10:1
5	**1e**	MeCH=CH	Et	**2b**	–40	2	150	**3h**, 67	7.4:1
6	**1d**	Ph	Me	**2b**	–78	1	120	**3f**, 66	4.4:1

[a] General conditions as in Table 1, addition of LiCl as 0.1 M solution after formation of the lithium amide.

Table 3. Tandem conjugate addition/radical cyclization/oxygenation reactions.[a]

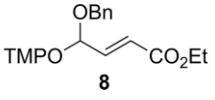


Entry	**1**	R^1	R^2	**2**	R^3	Solvent	**6** + **7**, yield [%]	**6**/**7**	Other products, yield [%]
1	**1a**	Me	*t*Bu	**2a**	H	THF	**a**, 64	3.5:1	**3a**, 16
2	**1a**	Me	*t*Bu	**2a**	H	DME	**a**, 54	4:1	**3a**, 21
3	**1b**	Ph	*t*Bu	**2a**	H	THF	**b**, 76	6:1	**3b**, 7
4	**1b**	Ph	*t*Bu	**2a**	H	DME	**b**, 40	6:1	**3b**, 8
5[b]	**1a**	Me	*t*Bu	**2b**	Me	THF	**c**, 72	2:1	–
6	**1b**	Ph	*t*Bu	**2b**	Me	THF	**d**, 78	1:1	**3c**, 7
7	**1c**	Me	Me	**2a**	H	THF	**e**, 59	3:1	–
8	**1d**	Ph	Me	**2a**	H	THF	**f**, 49	6:1	–
9	**1e**	MeCH=CH	Et	**2a**	H	THF	**g**, 42	2.5:1	–
10[c]	**1e**	MeCH=CH	Et	**2a**	H	THF	**g**, 48	2.5:1	**3g**, 8
11	**1f**	CH_2OBn	Et	**2a**	H	THF	**h**, 42	3:1	**3i**, 21

[a] General conditions: BuLi (1.1 mmol) was added to **2** (1.1 mmol) in THF at –78 °C, and after 30 min **1** (1 mmol) was added. After the formation of **3**$^-$ was complete, **5** (0.2 mmol) was added, followed by a mixture of **4** (1 mmol) and **5** (0.8 mmol) in portions. Further **4** was added, until the reaction mixture remained green-blue. [b] Experiment was run in duplicate with an identical outcome. [c] With catalytic LiCl (1 mol-%).

Tandem Aza-Michael Addition/Radical Cyclization/ Oxygenation Reactions

The ester enolates formed after the aza-Michael addition were subjected to the SET oxidation/radical cyclization/oxygenation sequence in situ. A range of *N*,2,3,4-tetrasubstituted pyrrolidines **6** and **7** was synthesized by this tandem approach in moderate to good yields using ester acceptors **1a**–**1f**, lithium amides **2a**$^-$ and **2b**$^-$, ferrocenium hexafluorophosphate **4** as the SET oxidant, and persistent radical TEMPO **5** as the oxygenation reagent (Table 3). Better yields of pyrrolidines **6** and **7** were obtained using THF as the solvent than with DME (Table 3, entries 1 and 3 vs. 2 and 4). Therefore, THF was chosen for all subsequent reactions. Methyl esters gave yields somewhat lower than those obtained with *tert*-butyl esters, but still acceptable, with lithium amide **2a**$^-$ (Table 3, entries 7 and 8). When ethyl sorbate (**1e**) and 4-(benzyloxy)crotonate (**1f**) were used as the Michael acceptors with lithium amide **2a**$^-$, the yields were moderate (Table 3, entries 9–11); these yields improved somewhat with LiCl catalysis (Table 3, entry 10). The main side products were the easily separable noncyclized β-amino esters (i.e., **3**), which were isolated in 7–21 % yield (Table 3, entries 1–4, 6, and 10–11). The lithium amide derived from prenylamine **2b** reacted less selectively in the polar conjugate addition with **1d**, **1f** or ethyl (*E*)-4-{[(*tert*-butyl)dimethylsilyl]oxy}but-2-enoate; this translated into low yields of pyrrolidines **6** and **7**, and the formation of inseparable side products (not shown). Another factor contributing to the observed low yields was γ-deprotonation, which competed with the aza-Michael addition, resulting in the formation of γ-oxygenated esters, such as **8**, which formed in yields up to 30 %.

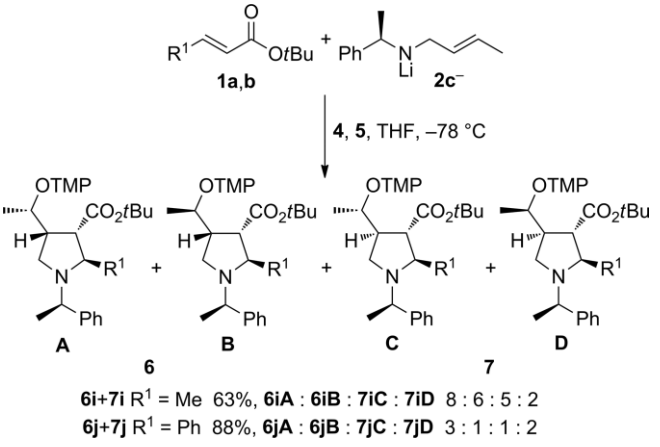


8

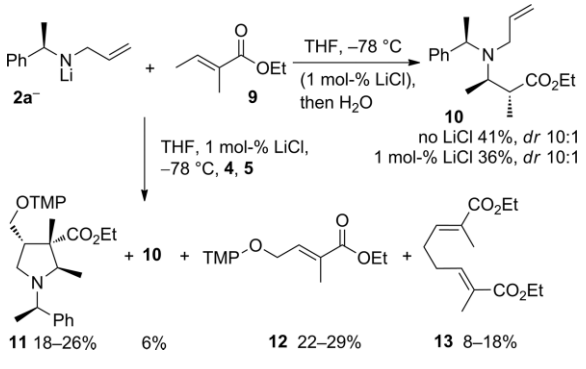
The absolute stereochemistry depends on the diastereoselectivity of the initial Michael addition, which was in most cases excellent. The absolute configuration of pyrrolidine **6c** was assigned earlier by X-ray crystallographic analysis, and the relative configurations of all other derivatives were assigned by the similarity of their NMR spectroscopic data.[35] The tandem sequence gave pyrrolidines **6** and **7** with an exclusive 2,3-*trans* diastereoselectivity. With lithium amide **2a**$^-$, the 3,4-*cis*/*trans* selectivity (i.e., the **6**/**7** ratio) ranged from 2.5 to 6:1, whereas with lithium amide **2b**$^-$, the **6**/**7** ratio remained low (Table 3, entries 5 and 6).

The use of lithium amide **2c**$^-$ bearing 1,2-disubstituted alkene units resulted in the formation of pyrrolidines with an exocyclic stereogenic center adjacent to C-4 (Scheme 2). Four inseparable diastereomers of **6iA**, **6iB**, **7iC**, and **7iD** (from **1a**) or **6jA**, **6jB**, **7jC**, and **7jD** (from **1b**) were formed in 63 and 88 % yields, respectively. The rather complex NMR spectra prohibited the assignment of the particular diastereomers at this stage. However, their configurations were assigned after reductive deprotection to the corresponding lactones and alcohols (vide infra).

Ethyl tiglate (**9**), an example of an α,β-disubstituted unsaturated ester, was also studied. The aza-Michael addition with lithium amide **2a**$^-$ gave the addition product (i.e., **10**) in moderate yield, but with excellent diastereoselectivity in the addition, and good diastereoselectivity in the protonation step (Scheme 3). For this example, the addition of LiCl did not increase the efficiency of the conjugate-addition step. The tandem aza-Michael addition/radical cyclization reaction gave the desired 3,3-disubstituted pyrrolidine (i.e., **11**) in a low 18–26 % yield, albeit with the best observed diastereoselectivity for the cyclization. Some aza-Michael adduct **10** was also isolated. Alkoxyamine **12** and dimer **13** were obtained as side products in 25–29 % and 8–18 % yields, respectively. Their formation can be attributed to significant γ-deprotonation of **9** by **2a**$^-$ competing with the aza-Michael addition, thus the yield of cyclization product **11** is reasonable based on the observed extent of the conjugate addition. Carrying out the Michael addition step at –40 °C and the oxidative cyclization at –20 °C led to a decrease in the yield of **11** to 18 %, and a decrease in the 3,4-diastereoselectivity to 5:1. Also, compounds **12** (22 %) and **10** (6 %) were isolated, but the formation of dimer **13** was not observed.



Scheme 2. Tandem conjugate addition of crotylamide **2c**$^-$/radical cyclization.



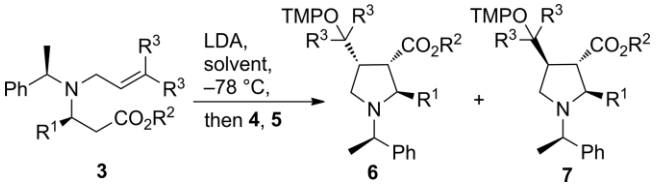
Scheme 3. The tandem aza-Michael addition/radical reaction with ethyl tiglate (**9**).

Oxidative Cyclizations of β-Substituted-β-Amino Esters 3

Isolated β-substituted β-amino esters **3** can be deprotonated with LDA (lithium diisopropylamide) in THF or DME at –78 °C, and subjected to oxidative cyclization conditions to give *N*,2,3,4-tetrasubstituted pyrrolidines **6** and **7** in 60–89 % yield

(Table 4). This broadly reflects the yields of the tandem processes (Table 4, entries 1–4). The outcome of the cyclization reaction of **3** was affected neither by the choice of solvent (Table 4, entry 2) nor by whether *tert*-butyl (entries 1 and 2), methyl (entries 3 and 4), or ethyl (entries 5 and 6) esters were used. The diastereoselectivity of the cyclization followed the preferred 3,4-*cis* orientation[24] for R^3 = H (Table 4, entries 1, 3, 4, and 5), with the **6**/**7** ratio ranging from 2:1 to 5.5:1. Both diastereomers had a 2,3-*trans* configuration exclusively, and were formed in enantiomerically pure form. For derivatives with $R^3 = CH_3$ (Table 4, entries 2 and 6), almost equal amounts of **6** and **7** were formed. Sometimes small amounts of starting material **3** were recovered (10–14 %; Table 4, entries 4 and 5). Interestingly, the cyclizations of substrates **3g** and **3h** also proceeded smoothly in 61–70 % yields (Table 4, entries 5 and 6).

Table 4. Oxidative radical cyclization reactions of chiral β-amino esters **3a**–**3h**.[a]

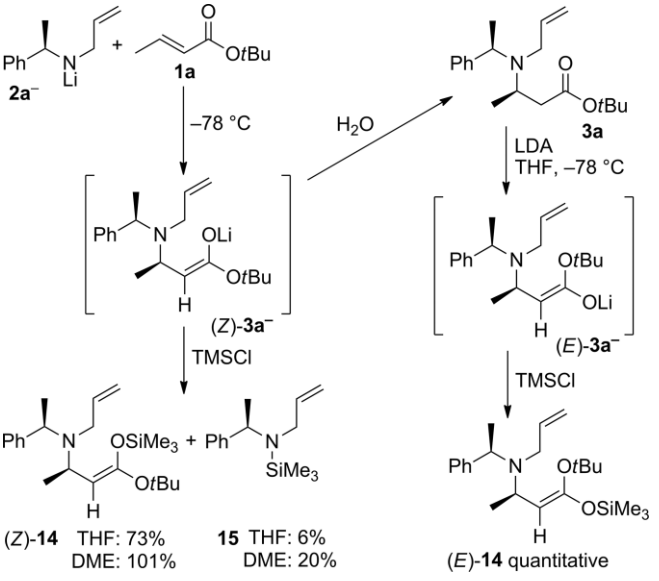


Entry	3	R^1	R^2	R^3	Solvent	6 + 7, yield [%]	6/7	Other products, yield [%]
1	**3a**	Me	*t*Bu	H	THF	**a**, 75	3.6:1	–
2	**3c**	Ph	*t*Bu	Me	DME	**d**, 73	1:1	–
3	**3d**	Me	Me	H	THF	**e**, 60	3:1	–
4	**3e**	Ph	Me	H	THF	**f**, 89	5.5:1	**3e**, 10
5	**3g**	MeCH=CH	Et	H	THF	**g**, 61	2:1	**3g**, 14
6	**3h**	MeCH=CH	Et	Me	THF	**k**, 70	1:1	–

[a] Standard conditions: **3** (1 mmol), LDA (1.25 mmol) at –78 °C, then **5** (0.2 mmol), followed by a homogenized mixture of **4** (1.0 mmol) and the remaining **5** (0.8 mmol). When the addition was complete, further **4** (0.3 to 0.5 mmol) was added in small portions.

Elucidation of the Geometry of Enolates 3^-

The conjugate addition of lithium amides **2a**$^-$, **2b**$^-$, and **2c**$^-$ to α,β-unsaturated esters **1** should result in the formation of the (*Z*)-enolates.[24,25a,33b] Indeed, conjugate addition of lithium amide **2a**$^-$ to ester **1a** and subsequent enolate trapping by chlorotrimethylsilane in THF gave silyl ketene acetal **14** with a (*Z*) configuration in 73 % yield (Scheme 4). No (*E*)-silyl ketene acetal was detected. In addition, *N*-silylated amine **15** (6 %) and recovered amine **2a** (36 %) were detected. The products were not purified, so the overall yield exceeded 100 %. Repeating the experiment in DME provided (*Z*)-**14**, **15**, and **2a** in more than quantitative yield in a 7:1.5:1 ratio. Enolate (*E*)-**3a**$^-$ was generated by protonation of (*Z*)-**3a**$^-$ and subsequent deprotonation with LDA. Quenching by chlorotrimethylsilane gave silyl ketene acetal (*E*)-**14** in a 120 % crude yield. No (*Z*)-**14** or **15**, which could potentially be formed by retro-Michael addition, were observed.

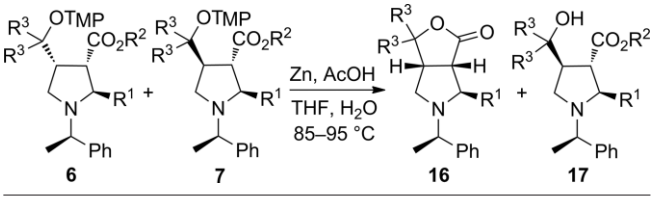


Scheme 4. Preparation of silyl ketene acetals **14** from enolates **3a**$^-$. TMS = trimethylsilyl.

Reductive Cleavage of the Alkoxyamine Units in Compounds 6 and 7

Reductive cleavage of the N–O bond in tetrasubstituted pyrrolidines **6** and **7** gave bicyclic lactones **16** from the 3,4-*cis* isomers and *trans*-(1-hydroxyalkyl)pyrrolidines **17** from the *trans*-congeners, respectively (Table 5). Complete lactonization occurred starting from 3,4-*cis* isomers **6**, i.e., no free alcohol *cis*-**17** was isolated. The reaction products were separable by column chromatography, thus diastereomeric mixtures of **6** and **7** can be resolved into individual and enantiomerically pure **16** and **17**. The combined yields of lactones **16**, formed from major pyrrolidine diastereomers **6**, and pyrrolidinols **17a**–**17d**, formed from the corresponding *trans*-isomers **7a**–**7d**, were with 71–94 % good to excellent (Table 5, entries 1–3, and 6). Diastereomeri-

Table 5. Reductive alkoxyamine cleavage of pyrrolidines **6**/**7**.[a]



Entry	6 + 7	6/7	Time [h]	16, yield [%]	17, yield [%]	Yield of 6 + 7[b] [%]
1	**a**	3.6:1	3	**16a**, 67	**17a**, 18	11
2	**b**	6:1	3	**16b**, 68	**17b**, 11	–
3	**b**	4.7:1	4	**16b**, 59	**17b**, 12	25
4	**c**	1:0	3	**16c**, 65	–	–
5	**c**	0:1	4	–	**17c**, 82	–
6	**d**	1:1.3	3	**16d**, 57	**17d**, 37	–
7	**f**	4.7:1	2.5	**16b**, 54	**17f**, 12	–
8	**g**	2.3:1	2.5	**16g**, 51	**17g**, 18	–

[a] General conditions: A mixture of **6** and **7** was heated with zinc powder (50 equiv.) in a AcOH/H_2O/THF mixture (3:1:1) until the reaction was complete. [b] Recovered starting material had the same **6**/**7** ratio.

cally pure starting materials **6c** and **7c** gave single products, thus epimerization did not occur under the reaction conditions (Table 5, entries 4 and 5). Some of the reactions were carried out on multigram scale (Table 5, entries 6 and 7). For methyl esters **6f**/**7f** and ethyl esters **6g**/**7g**, the combined yields of **16b**/**17f** and **16g**/**17g** ranged from 66 to 69 %, probably because of a small amount of ester hydrolysis under the acidic reaction conditions (Table 5, entries 7 and 8).

Lactones **16** are, in contrast to alcohols **17** or starting materials **6** and **7**, mostly crystalline compounds. The structure of compound **16b**, formed from the major component **6b** or **6f** was confirmed by X-ray crystallography (Figure 2), thus providing further evidence for the absolute configuration.

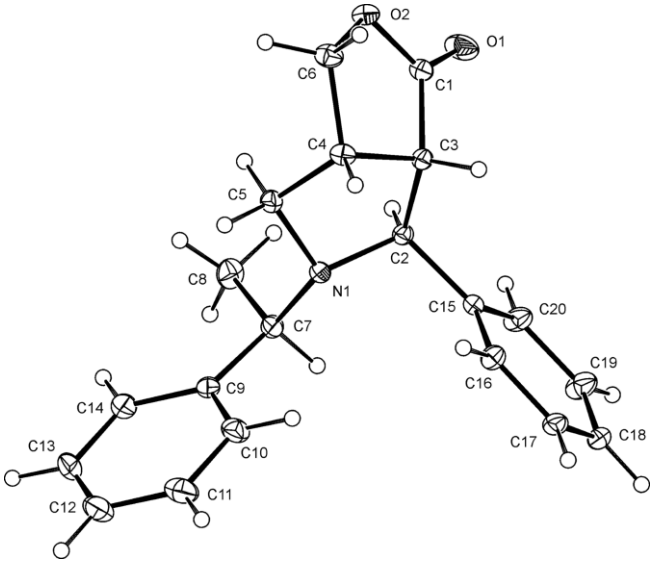


Figure 2. Crystal structure of **16b** with atom-numbering scheme. The displacement ellipsoids are drawn at the 30 % probability level.

Reductive cleavage of the TMP (2,2,6,6-tetramethylpiperidinyl) unit in the four inseparable diastereomers of pyrrolidines **6j** and **7j** also allowed them to be separated and their configurations to be assigned (Scheme 5). The deprotected products (i.e., **16j** and **17j**) were formed in 73 % overall yield as a separable mixture.

This allowed full assignment of the NMR resonances, and also determination of the absolute stereochemistry of (3*S*)-**16j** and [4(1*S*)]-**17j** by X-ray crystallographic analysis (Figure 3). This was crucial for determining the absolute configuration at the exocyclic stereocenter in **17j**, since it could not be assigned using NOE techniques. The crystal structure of (*3S*)-**16j** revealed an (*S*)-configuration at C-3, and a *trans* orientation of 6-H and 6a-H. In [4(1*S*)]-**17j**, the configuration at the 1-(hydroxyethyl) group was determined to be (*S*). Moreover, the *trans* orientation of the phenyl group at C-2 and the carboxylate at C-3, and the *trans* orientation of 3-H and 4-H were confirmed.

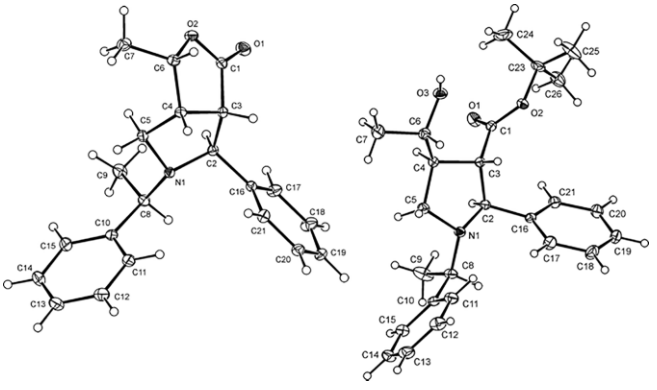
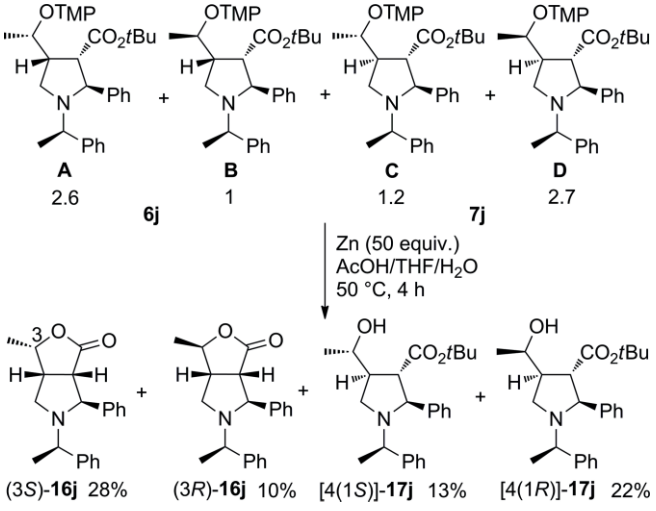


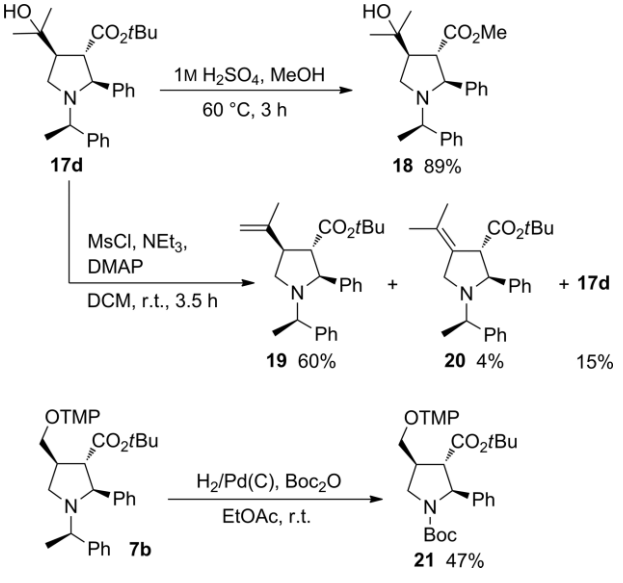
Figure 3. Crystal structures of lactone (3*S*)-**16j** (left) and hydroxyethyl pyrrolidine [4(1*S*)]-**17j** (right) with atom-numbering schemes. The displacement ellipsoids are drawn at the 30 % probability level.



Scheme 5. Reductive cleavage of the alkoxyamine unit in pyrrolidines **6j**/**7j**.

Transformations of Pyrrolidines 7 and 17

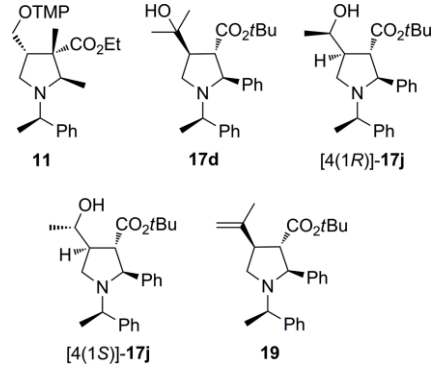
To illustrate possible synthetic applications, a simple carboxylate interconversion was carried out. Methyl ester **18** was synthesized in 89 % yield by acid-catalyzed transesterification of



Scheme 6. Synthetic modifications of pyrrolidines **7b** and **17d**.

17d. Furthermore, compound **17d** was subjected to mesylation/elimination using MsCl/DMAP (4-dimethylaminopyridine)/Et_3N (Scheme 6). The desired kinetic product, alkene **19**, was isolated in 60 % yield, along with a small amount of isomeric product **20** containing a C-4-exocyclic double bond. The *N*-protecting group was exchanged by hydrodebenzylation of **7b** in the presence of Boc_2O (Boc = *tert*-butoxycarbonyl) to give **21** in 47 % yield.

Table 6. Antiviral activity of compounds **11**–**19** against different HCV genotypes.



Compound	Replicon 1B[a] EC_{50} [μM]	Replicon 1A EC_{50} [μM]	Replicon 1A CC_{50} [μM]
11	3.5	2.8	16.5
17d	1.5	30.1	44.4
[4(1*R*)]-**17j**	2.6	13.6	29.2
[4(1*R*/1*S*)]-**17j**	2.0	38.7	44.4
19	2.9	21.0	44.4

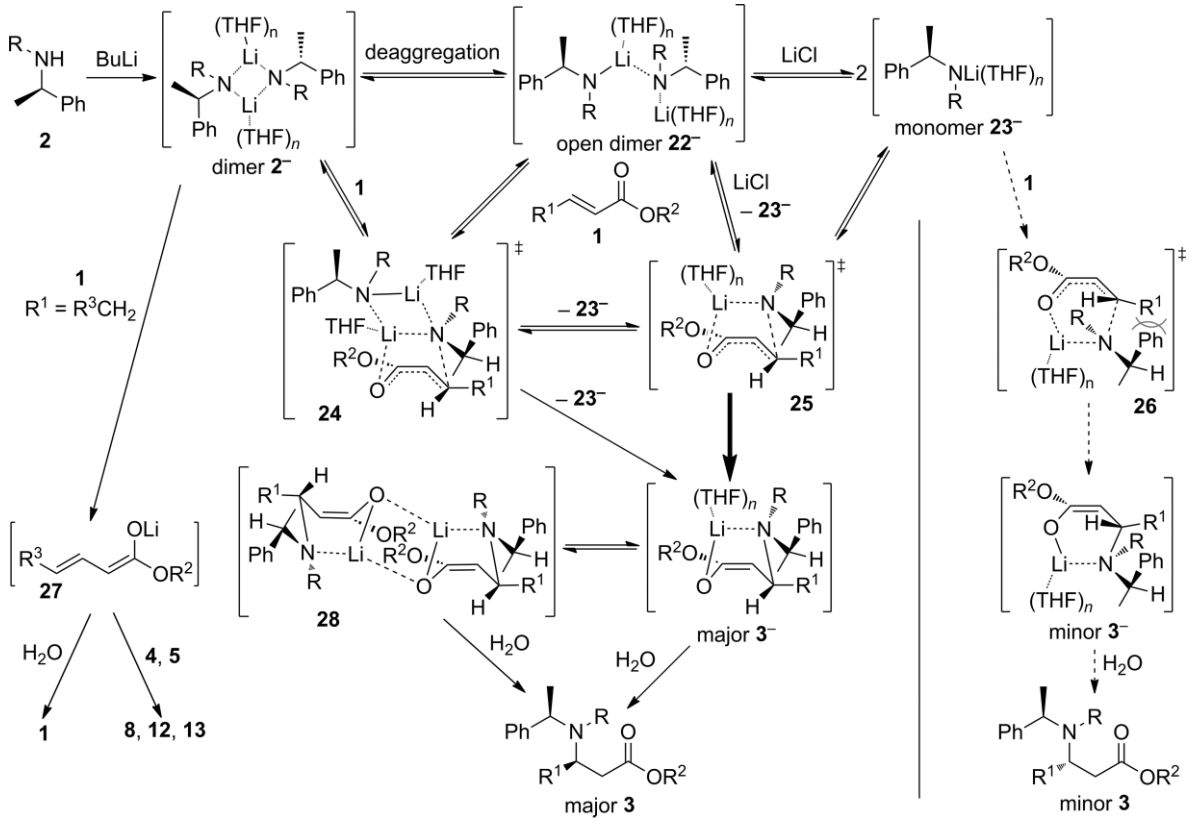
[a] CC_{50} values for the Replicon 1B were at the threshold value of 44.4 μM.

Activities Against the Hepatitis C Virus

All the newly synthesized heterocyclic compounds were tested against different genotypes of the hepatitis C (HCV) virus in 1A, 1B, and 2A replicon assays. Compounds **11** and **17d**, as well as both diastereomers of **17j** and **19**, were active in the replicon 1B assay in low micromolar concentrations (Table 6). However, no significant activity was observed for the replicon 2A HCV strain. Compound **11** was the only compound to show activity, at the low micromolar level, in the replicon 1A assay. The cytotoxicities of the tested compounds were measured using Huh-7 cells, and were found to be at or above the threshold value of 44.4 μM, except for compounds **11** and [4(1*R*)]-**17j** in the replicon 1A antiviral assay.

Discussion

The tandem reactions show some remarkable features. The asymmetric aza-Michael addition, pioneered by Davies,[25a,33] typically applies *N*-benzyl-*N*-(1-phenylethyl)amines, which thus serve as a chiral ammonia surrogate. In this paper, the reactivity of *N*-allylic amines **2** was explored to allow their application in one-pot C–N, C–C, and C–O bond-formation steps, thus adding



Scheme 7. Rationalization of the lithium amide conjugate addition results.

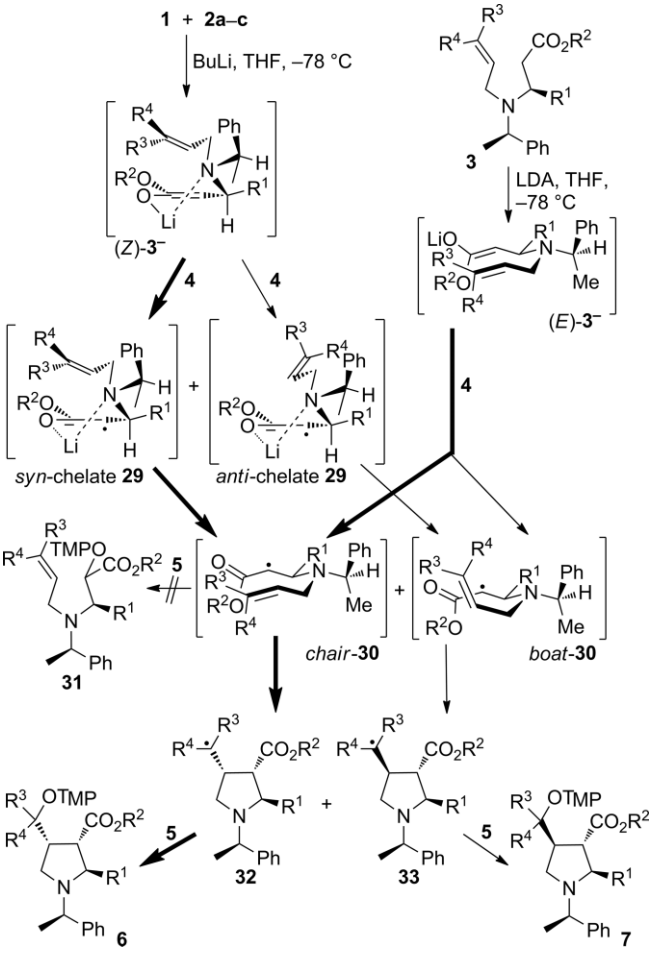
much value to the applications of lithium amides in organic chemistry.

Lithium amides **2**$^-$ typically exist as dimers in ethereal solutions (Scheme 7),[36] but they have to deaggregate to monomers **23**$^-$ via open dimers **22**$^-$ to undergo reasonably fast conjugate addition, as shown by Collum et al. in a recent study.[34] Catalytic amounts of lithium chloride promote deaggregation of **2**$^-$ and faster conjugate addition to unsaturated esters **1**, as demonstrated here for methyl ester **1d** and sorbate **1e**, which undergo the conjugate addition significantly less efficiently in the absence of LiCl (cf. Table 2 vs. Table 1). This can be attributed to the much faster conjugate addition of monomeric **23**$^-$ to **1** via cyclic transition state **25** than that of dimers **2**$^-$ or **22**$^-$ via sterically much more encumbered transition state **24**. In this way, the addition of LiCl partially limits competing anionic polymerization of **1**. However, γ-deprotonation to give dienolates **27**, which is detrimental to the yields of the subsequent radical cyclization step, cannot be prevented by the addition of LiCl (cf. Scheme 3). It must be also noted that esters **1** have to be substituted in the β position ($R^1 \neq H$), since acrylates polymerize faster than they undergo aza-Michael addition under identical conditions, irrespective of whether or not LiCl is present.[37]

The aza-Michael addition step via cyclic transition state **25** leads to the formation of (*Z*)-enolate **3**$^-$, as shown by the formation of silyl ketene acetal (*Z*)-**14** (cf. Scheme 5), which may exist as a chelate as shown, or in an open form. The resulting amino ester enolates (i.e., **3**$^-$) typically aggregate to form homodimers **28** or mixed aggregates with lithium amides (not shown). The high diastereoselectivity is based on the large difference in the steric demand of the 1-phenylethyl auxiliary in the transition states **25** vs. **26**, which effectively dictates the facial selectivity.[38]

Protonation of the resulting enolates (i.e., **3**$^-$) to give β-substituted β-amino esters **3** was used to determine the diastereoselectivity of the addition step and to synthesize substrates for oxidative radical cyclizations (cf. Table 4).

Chelated (*Z*)-enolates (*Z*)-**3**$^-$ are easily oxidized by ferrocenium hexafluorophosphate **4** to give chelated α-carbonyl radicals **29** (Scheme 8). According to very recent results, this single-electron oxidation process can also be carried out catalytically in **4**.[35] The resulting radicals can either remain chelated or transform into open radicals **30**. Alternatively, β-amino esters **3** give (*E*)-enolates (*E*)-**3**$^-$ on deprotonation with LDA (cf. Scheme 5). These enolates are also efficiently oxidized, but should only form nonchelated radicals **30**, since radicals with an ester group in the α position have been shown to have a significant rotational barrier, which should preserve the configuration of the precursor under the very mild reaction conditions.[39] Irrespective of the pathway by which they were generated, radicals **29** and/or **30** undergo efficient 5-*exo* cyclization to give diastereomeric radicals **32** and **33**. The radical cyclization must be very fast, since the formation of acyclic coupling products **31**, which is also fast,[40] does not compete under the reaction conditions. The introduction of the oxygen functionality proceeds by a final coupling step with persistent radical TEMPO **5**. Small amounts of β-amino esters **3** were recovered from some reactions. These products were probably formed from radicals **30** by hydrogen abstraction from THF. For esters **1f** or **9**, γ-oxygenated esters **8** or **12** are formed by SET oxidation of the competitively formed dienolate **27** (cf. Table 3, and Schemes 3 and 7).



Scheme 8. Diastereoselectivity of the radical cyclization leading to pyrrolidines **6** and **7**.

The diastereoselectivity of the radical cyclization can, in principle, be explained by considering chelated and nonchelated radicals **29** and **30**, respectively. Indeed, convincing evidence was previously provided that chelated radicals **29** cyclize, because the tandem reactions starting from **1** and **2** gave the opposite diastereoselectivity to that obtained in the oxidative cyclizations starting from **3**; this was attributed to the steric demand of the nitrogen-protecting group and the chelated (*Z*)- or nonchelated (*E*)-enolate geometry of enolates **3**$^-$.[24] However, with a 1-phenylethyl group at nitrogen, the acyclic radicals were found to cyclize with exclusive 2,3-*trans* and very similar 3,4-*cis* diastereoselectivity, irrespective of whether the (*Z*)-enolate resulting from conjugate addition or the (*E*)-enolate resulting from deprotonation of β-amino esters **3** by LDA was used (cf. Tables 3 and 4, and Scheme 4). This implies that chelated radical **29**, formed after SET oxidation, is probably destabilized by the bulk of the *N*-protecting group, and easily collapses to form open radical **30** to minimize strain. Therefore, the subsequent cyclization proceeds via the same open Beckwith–Houk

transition state for both starting enolate geometries (Scheme 8).[41]

For derivatives with $R^3 = R^4 = H$, *chair*-**31**, in which the substituent in the 2-position and the ester group are in an *anti* arrangement, is more populated; this leads predominantly to cyclic radical **32**, which couples with excess TEMPO **5** to give 2,3-*trans*-3,4-*cis* pyrrolidines **6**. The minor diastereomers must result from a cyclization via boat transition state *boat*-**30**, since the same relative 1,2,3-orientation is found in 2,3-*trans*-3,4-*trans*-pyrrolidines **7**. In derivatives bearing methyl substituents at the *N*-allyl unit, the cyclization transition states *chair*-**30** and *boat*-**30** have apparently similar energies, thus giving almost equal amounts of **6** and **7** after 5-*exo* radical cyclization and coupling with **5**.

Conclusions

Enantioselective tandem aza-Michael addition/radical cyclization sequences using allylic lithium amides and α,β-unsaturated esters gave *N*,2,3,4-tetrasubstituted pyrrolidines **6** and **7** in up to 78 % yield with up to 6:1 3,4-*cis*/3,4-*trans* diastereoselectivity. Single-electron transfer (SET) oxidation allowed facile lithium amide conjugate additions and 5-*exo* radical cyclizations to be combined. Ferrocenium hexafluorophosphate was used as a mild, nontoxic SET oxidant that is easy to prepare, easy to handle, and can be stored under ambient conditions. The tandem sequence leads to the formation of C–N, C–C, and C–O bonds, including three contiguous stereogenic centers, in a simple one-pot procedure. Exclusive 2,3-*trans* diastereoselectivity was observed in all the cyclization reactions. Pyrrolidines bearing an additional exocyclic stereogenic center can be synthesized using lithium (*E*)-but-2-en-1-ylamide **2c**$^-$. Oxidative radical cyclizations of β-amino esters **3** are an alternative to the tandem conjugate addition/radical cyclization sequences, especially for such cases where an aza-Michael addition may not be the method of choice for their preparation.

The reactivity of the pyrrolidines was briefly investigated. Reductive cleavage of the N–O bond of the alkoxyamine unit was successfully carried out; this helped to separate diastereomeric mixtures of pyrrolidines into enantiomerically pure lactones **16** and *trans*-hydroxyalkyl pyrrolidines **17**. The nitrogen-protecting group was removed, and the ester and alcohol groups could be selectively manipulated. Some of the derivatives showed promising activities against the HCV virus.

This tandem anionic/radical approach is currently being expanded to allow the synthesis of pentasubstituted pyrrolidines, and spiro- and bicyclic compounds containing pyrrolidine units. We are also working on synthetic approaches to alkaloids and their analogs containing these structural units; the antiviral activities of these target compounds will be investigated.

Experimental Section

***N*,2,3,4-Tetrasubstituted Pyrrolidine-3-carboxylates 6 and 7 Through Tandem Aza-Michael Additions/Oxidative Radical 5-*exo* Cyclizations (General Procedure):** *n*-Butyllithium (1.6 M in hexanes; 0.69 mL, 1.1 mmol) was added dropwise to a stirred solution of amine **2a**–**2c** (1.1 mmol) in dry THF (10 mL) at –78 °C. The reaction mixture turned bright orange during the addition. After 30 min, a solution of ester **1** (1.0 mmol) in dry THF (0.5–0.6 mL) was added dropwise. The reaction was run until TLC indicated the complete conversion of **1** (usually 30 min). TEMPO **5** (0.031 g, 0.2 mmol) was added, followed by thoroughly mixed **4** (0.331 g, 1.0 mmol) and **5** (0.125 g, 0.8 mmol) in small portions. After the complete consumption of **4**, further portions of **4** (0.100–0.165 g, 0.3–0.5 mmol) were added until the mixture stayed blue and inhomogeneous. The reaction mixture was stirred at –78 °C for 40–60 min, then it was quenched with saturated NH_4Cl solution (4 drops). The mixture was warmed to room temp., diluted with diethyl ether, and filtered through a pad of silica gel. Evaporation of the filtrate gave an orange inhomogeneous residue, which was adsorbed at silica gel, and purified by flash chromatography.

***N*,2,3,4-Tetrasubstituted Pyrrolidine-3-carboxylates 6 and 7 Through Oxidative Radical 5-*exo* Cyclizations of β-Amino Ester Enolates (General Procedure):** *n*-Butyllithium (1.6 M in hexanes; 0.78 mL, 1.25 mmol) was added dropwise to a stirred solution of dry diisopropylamine (0.18 mL, 1.25 mmol) in anhydrous DME or THF (10 mL; see Table 4) at –78 °C. After 20–30 min, a solution of β-amino ester **3a**–**3h** (1.0 mmol) in dry solvent (0.6 mL) was added dropwise. After 30 min, **5** (0.031 g, 0.2 mmol) was added as a solid. Subsequently a thoroughly homogenized mixture of **5** (0.125 g, 0.8 mmol) and **4** (0.331 g, 1.0 mmol) was added in small portions with vigorous stirring at –78 °C. Since discoloration of **4** still occurred, further **4** (0.10–0.15 g) was added in small portions, until a dark blue-green color persisted in the reaction mixture for 60 min. The reaction mixture was then quenched with saturated NH_4Cl solution (4 drops). The mixture was diluted with diethyl ether, and filtered through a pad of silica gel. The filtrate was evaporated, and the crude heterogeneous mixture was adsorbed at silica gel, and purified by flash chromatography.

General Procedure for the Reductive N–O Bond Cleavage of *N*,2,3,4-Tetrasubstituted Pyrrolidines 6 and 7: A diastereomeric mixture of **6** and **7** was dissolved in acetic acid (typically 6 mL/mmol of substrate), and water (2 mL/mmol of substrate) was added. THF was added dropwise to the resulting turbid solution until it became clear. Zinc dust (10 μm; 50 mmol/mmol of substrate) was added portionwise with vigorous stirring, and then the resulting mixture was heated at 85–95 °C until TLC indicated that the starting material had been consumed. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 to three times its volume, and filtered. The filtrate was neutralized with saturated K_2CO_3 solution to a pH of ca. 10. The layers were separated, and the organic phase was washed twice with water, dried with $MgSO_4$, and evaporated. The crude product was purified by flash chromatography to give lactones **16**, followed by *trans*-4-hydroxyalkyl-pyrrolidines **17**.

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Keywords: Tandem reactions · Nitrogen heterocycles · Michael addition · Radical reactions · Cyclization · Enolates

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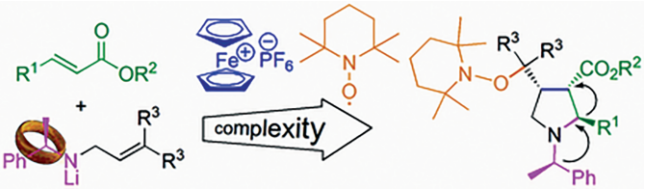
Tandem Reactions



Readily available chiral allylic amines and α,β-unsaturated esters are used to synthesize densely substituted pyrrolidines with exclusive 2,3-*trans* and up to 6:1 3,4-*cis*/*trans* configuration in a tandem polar lithium amide conjugate addition/radical cyclization/oxygenation sequence.

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