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N,3,4-Trisubstituted pyrrolidines by electron transfer-induced oxidative cyclizations of *N*-allylic β-amino ester enolates

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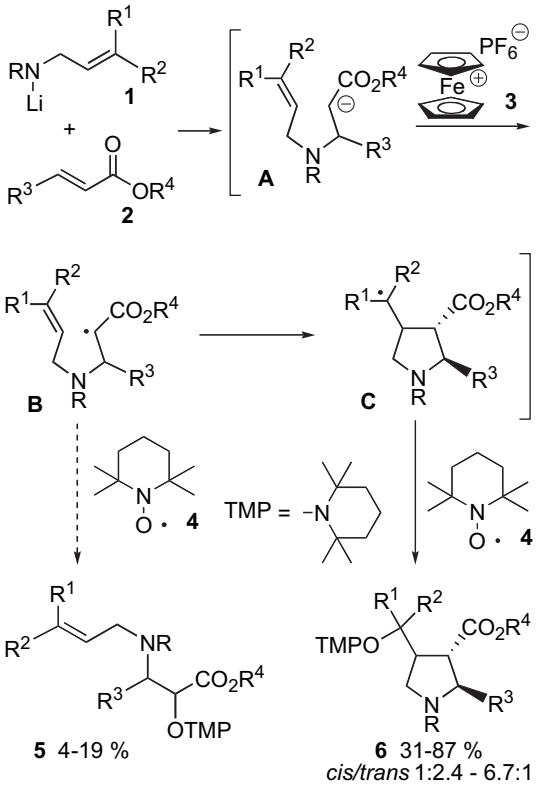
ABSTRACT

Oxidative radical cyclizations starting from easily accessible *N*-allylic β-alanine esters are reported. Deprotonation generates the corresponding enolates, which are transformed efficiently into α-ester radicals by single electron transfer mediated by ferrocenium hexafluorophosphate. The stereochemistry of the radical 5-*exo* cyclization can be switched by the configuration of the enolate precursor. First examples of asymmetric oxidative radical cyclizations using *N*-(1-phenylethyl)-substituted β-amino esters are reported. Only two of the four possible diastereomers are formed from the (*E*)-enolate with high *cis*-selectivity. From (*Z*)-enolates, an additional diastereomer is formed, which is likely to be formed only under chelation control.

1. Introduction

Pyrrolidines are important heterocyclic components of drugs and natural products.[1] They have gained importance as organocatalysts or ligands.[2] There are numerous methods for synthesizing pyrrolidines.[3] Common strategies include intramolecular alkylations, [3+2] cycloadditions,[4] intramolecular hydroaminations,[5] transition metal-catalyzed cycloisomerizations[6] and other cyclization approaches,[7] Tsuji–Trost-type reactions[8] or modifications of prolines and *N*-acylpyrrolidines[9] and aza-Michael additions.[10] Radical cyclizations constitute an important method for the access to pyrrolidines.[11] A number of reductive radical cyclization approaches exist for their synthesis, which require, however, the preparation of functionalized starting materials. There are also a few anionic cyclizations of *N*-homoallyl glycinates that lead to 3-substituted prolines.[12] The scope of this method is however limited. More recently approaches to pyrrolidine-3-carboxylates using metallo-ene reactions or radical cyclizations using organometallic initiators such as diorganozinc reagents have been developed.[13] Traces of oxygen promote a radical addition/5-*exo* cyclization process, in which the final radical is trapped by the organometallic species to give organozinc intermediates, which can be applied in a variety of subsequent polar reaction steps.

We have a longstanding interest in electron transfer-induced oxidative tandem reactions.[14] Recently, we developed an oxidative tandem anionic-radical methodology for the synthesis of pyrrolidines (Scheme 1).[15] In this process anionic conjugate additions of



Scheme 1. Tandem anion/radical sequence for the synthesis of pyrrolidines **6**.

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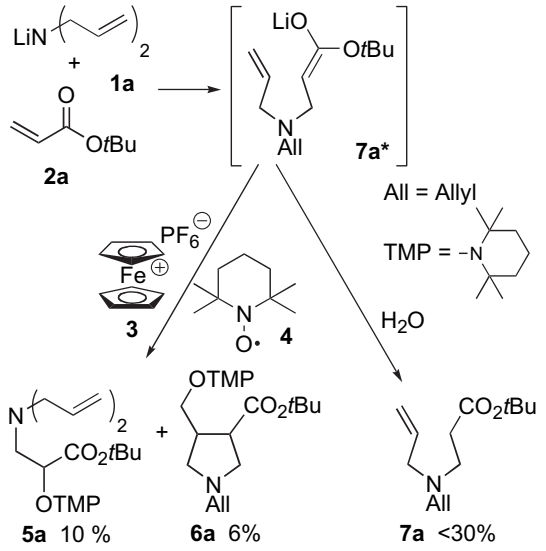
lithium *N*-allylic amides **1** to α,β-unsaturated esters **2**, oxidative radical 5-*exo* cyclizations mediated by the single electron transfer oxidant ferrocenium hexafluorophosphate **3** and oxygenations by the stable free radical TEMPO **4**[16] are combined. The pyrrolidines **6** were isolated in 31–87% yield with exclusive 2,3-*trans* and variable 3,4-diastereoselectivity.

Premature trapping of the initial α-ester radical **B** occurred only to a limited extent. An inherent advantage of the methodology compared to traditional radical-based approaches is that no prior functionalization is required. The enolate **A** generated in the addition step serves as the trigger for the radical cyclization step (**B**→**C**). Our interest in applying this methodology to the synthesis of natural products necessitated a more detailed investigation of the structural features that determine the outcome of such sequences.

Here we report our results on oxidative SET-mediated tandem addition/cyclization sequences and of oxidative radical 5-*exo* cyclization/oxygenation reactions of *N*-allylic β-alanine derivatives for the synthesis of 4-(piperidinyloxymethyl)pyrrolidine-3-carboxylates. We present an asymmetric version of these cyclizations using 1-phenylethylamine as the chiral auxiliary[17] and also a new catalytic method of preparing the starting esters.

2. Results and discussion

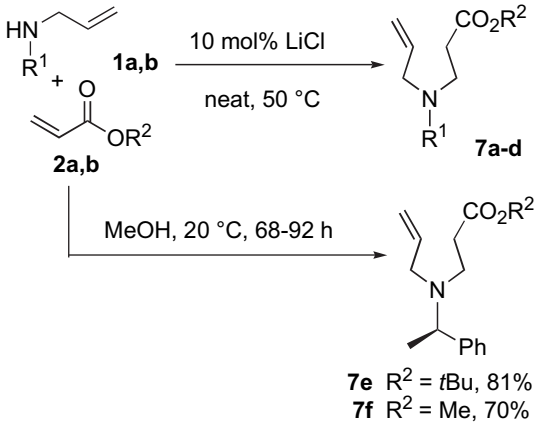
Attempts to adapt the tandem conjugate addition/SET oxidation/radical 5-*exo* cyclization/oxygenation reactions to lithium *N*,*N*-diallylamide **1a** and *tert*-butyl acrylate **2a**, in analogy to our initial conditions,[15] met very limited success (Scheme 2). On addition of **2a** to a solution of lithium *N*,*N*-diallylamide the reaction mixture became inhomogeneous, in contrast to all earlier reactions. In the following oxidation step, mediated by **3** in the presence of **4**, consumption of **3** was low. Products **5a** and **6a** were isolated in only 10% and 6% yield, respectively. To shed more light on the reaction course, the reaction mixture was hydrolyzed after consumption of **1a** and **2a**. The expected β-amino ester **7a** was obtained in a maximum yield of only 30% after exploring a variety of different reaction conditions and reagent ratios, but the mass balance of the reaction was always low. This indicated that Michael-type polymerization was the dominant pathway; thus Michael addition of **2a** to **7a*** was faster than aza-Michael addition of **1a** to **2a**. It can, however, be concluded that the radical cyclization step of **7*** may be a viable reaction step when decoupled from the conjugate addition.



Scheme 2. Attempted tandem addition/cyclization with **1a** and **2a**.

2.1. Synthesis of the starting β-amino esters 7

To explore this hypothesis, *N*-allyl-β-alaninates **7** were synthesized using an aza-Michael reaction of amines **1** themselves to **2** since they are less basic and enolate formation is not an issue. Initial attempts applying a literature method[18] failed for the reaction of **1a** with **2a**. Thus, a new method was devised to obtain **7**. Mixing *N*-allylamines **1a**–**b** with **2a** or methyl acrylate **2b** and 10 mol % of anhydrous lithium chloride and stirring the inhomogeneous reaction mixture vigorously until completion (by TLC) gave the β-alanine esters **7** (Scheme 3, Table 1). The reaction was slow at room temperature (entries 1,4), but it proceeded smoothly in high yield at 50 °C (entries 2,3,5,6). A control experiment under conditions identical to entry 1 but in the absence of lithium chloride gave only an 18% yield of **7a**. A simple dilution with ether and filtration to remove the catalyst gave the essentially pure β-amino esters **7a**–**d**.



Scheme 3. Preparation of *N*-allyl-β-alanine esters **7**.

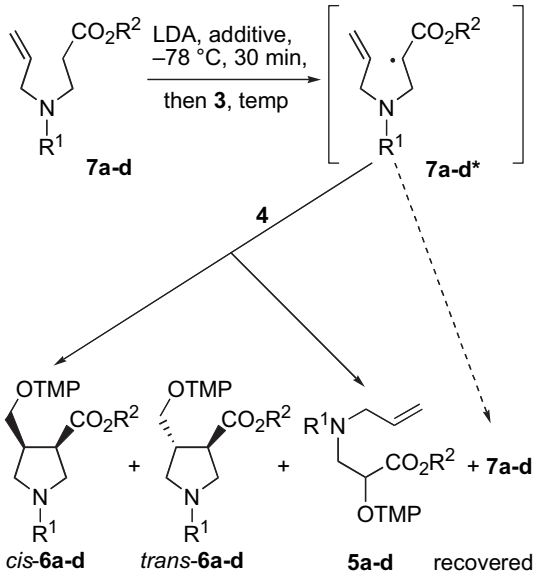
Table 1
N-Allylic β-alanine esters **7**

Entry	R^1	R^2	Ratio **1**:**2**	Temp (°C)	Time (h)	**7** (%)
1	All	*t*Bu	1:1	20	23	**7a** (69)
2	All	*t*Bu	1:1.2	50	29	**7a** (86)
3	All	Me	1:1.5	40	45	**7b** (94)
4	Bn	*t*Bu	1:1	20	50	**7c** (47)
5	Bn	*t*Bu	1:1.5	50	90	**7c** (90)
6	Bn	Me	1:1.5	40	50	**7d** (98)

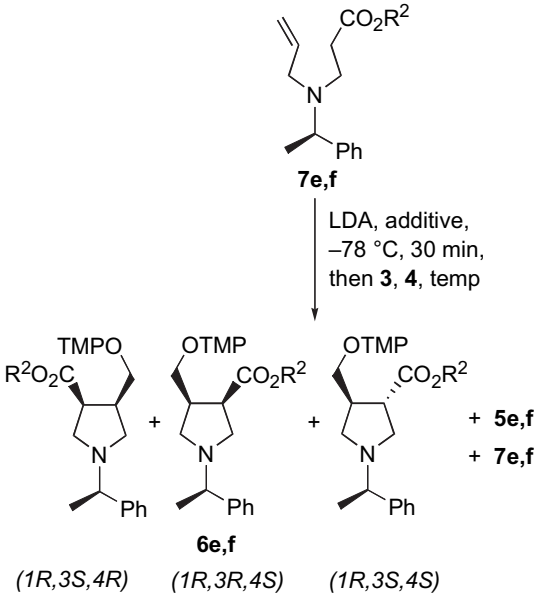
However, when the amine is branched at the α-position as in chiral *N*-allyl-1-phenylethylamines **1e**,**f**, this method failed. Compounds **7e** and **7f** were synthesized in 81 and 70% yield applying a method developed by Denes and co-workers.[19]

2.2. Oxidative radical cyclization/oxygenation reactions of β-amino esters 7a–f

The oxidative radical cyclizations were performed by deprotonation of *N*-allylic β-alanine esters **7a**–**f** with LDA in DME or THF for 30 min, subsequent addition of 0.2 equiv of TEMPO **4**, followed by addition of a homogenized mixture of **3** and the remaining **4** at −78 °C against a stream of argon with vigorous stirring (Schemes 4 and 5, Tables 2 and 3). When the addition was complete, further **3** was added in small portions until the mixture became blue and inhomogeneous. On average 1.5 equiv of **3** were necessary for complete oxidation. From the cyclization reactions of achiral esters **7a**–**d**, a diastereomeric mixture of the cyclized compounds *cis*- and *trans*-**6a**–**d** was isolated as the major product in 28–65% yield. In addition, the acyclic combination products **5a**–**f** were isolated in 0–49% yield, and in almost all cases starting ester **7** was recovered in



Scheme 4. Oxidative radical 5-*exo* cyclization/oxygenation sequences of β-amino ester enolates **7a**–**d***.



Scheme 5. Oxidative radical cyclizations of chiral β-alanine esters **7e**,**f**.

Table 2
Cyclization results of **7a**–**d***[a]

Entry	7	Solvent	Method[b]	T[c] (°C)	**5** (%)	**6** (%)	**7**[d] (%)	*cis*/*trans*
1[e]	**a**	DME	A	−78	46	38	3	3.9:1
2[e]	**a**	DME	A	−20	20	45	7	3.4:1
3[f]	**a**	THF	A	−78	26	35	18	4.3:1
4	**a**	DME	B	−78	3	65	22	1:2.8
5	**a**	DME	B	−20	—	53	27	1:1.5
6	**a**	DME	A[g]	−78	9	45	24	2:1
7	**b**	DME	B	−78	—	38	—	1:1.6
8	**b**	THF	C	−78	23	28	9	5.4:1
9[e]	**c**	DME	A	−78	49	39	4	5.8:1
10[h]	**c**	DME	A	−25	14	47	26	4.2:1
11[i]	**c**	DME	A	−78	19	38	10	7:1
12[j]	**c**	DME	A	−78	26	41	13	7:1
13[h]	**c**	DME	B	−78	18	44	21	1:1.1
14[f]	**c**	DME	C	−78	27	44	18	6:1
15[f]	**c**	DME	C	−20	22	42	27	9:1
16[f]	**d**	DME	A	−78	17	37	23	7:1

[a] Unless otherwise stated, **7** was deprotonated by 1.25 equiv of LDA at −78 °C for 30 min in the absence or presence of additives in the stated solvent (Methods A–C). TEMPO **4** (0.2 equiv) was added and a homogeneous mixture of 1.0 equiv of **3** and 0.8 equiv of **4** was added as a solid under a countercurrent of dry argon as **3** was consumed. If the reaction was not complete as seen by consumption, further **3** was added until the reaction mixture became blue and inhomogeneous.
[b] Method A: In the absence of additives. Method B: HMPA (6.0 equiv) was added before addition of ester. Method C: Anhydrous LiCl (7.0 equiv) was added from the beginning.
[c] Temperature for addition of **3**,**4**.
[d] Recovered **7**.
[e] TEMPO (1.0 equiv) was added first, followed by portion wise addition of **3** until the reaction mixture became blue and inhomogeneous.
[f] Reaction mixture was quenched by D_2O, no deuterium incorporation was detected in the products.
[g] HMPA (6.0 equiv) was added after deprotonation of **7** and just before oxidation.
[h] Experiment run in duplicate, outcome identical.
[i] Double concentration of **7**.
[j] An excess of 2.0 equiv of LDA was used.

Table 3
Cyclization results of **7e**,**f**[a]

Entry	7	Solvent	Method	T (°C)	**5** (%)	**6** (%)	**7**[b] (%)	(1*R*,3*S*,4*R*):(1*R*,3*R*,4*S*):(1*R*,3*S*,4*S*)
1	**e**	DME	A	−20	Trace	52	26	1.2:1:trace
2	**e**	DME	B	−78	8[c]	43	36	3:1:2
3	**e**	THF	C	−78	16[c]	59	11	1.4:1:trace
4	**f**	DME	A	−78	—	49	16	1.5:1:trace
5	**f**	DME	B	−78	—	39	26	3.2:2:1
6[d]	**f**	DME	C	−78	11[c]	50	10	1.7:1:trace

[a] Unless otherwise stated, reaction conditions were identical to those of the cyclization of achiral substrates **7a**–**d** (cf. Table 2).
[b] Recovered **7**.
[c] Diastereomeric ratio 1:1.
[d] Reaction mixture was quenched by D_2O, no deuterium incorporation was detected in the products.

0–27% yield. Several factors influenced the reaction course and the product ratios significantly. It proved useful to add only a part of **4** at the beginning and then add a mixture of **3** and **4**, since this kept the concentration of the persistent radical **4** lower and thus decreased the extent of premature trapping to **5**.[20]

The *tert*-butyl esters **7a** and **7c** gave better yields than the corresponding methyl esters **7b** and **7d** (entries 1–6, 9–15 vs 7,8,16). The yields were usually somewhat higher in DME than in THF, while the amount of recovered **7** was higher in THF (entries 1,2 vs 3). The use of HMPA as an additive increased the yield of cyclized products (entries 1,2 vs 4,5). Lithium chloride as an aggregate-breaking additive led in some cases to slightly better yields of **6** (entries 14,15). An increase in temperature led to increased yields of products **6** (entries 1 and 10 vs 2 and 11), while an increase of the concentration of the enolate of **7** from 0.05 M to 0.1 M had no significant effect on the product distribution (entry 11 vs 12). In an attempt to shed light on the origin of the rather large amounts of recovered ester **7**, several reaction mixtures were quenched by deuterium oxide (entry 3,14–16). However, no deuterium incorporation was found in recovered **7**.

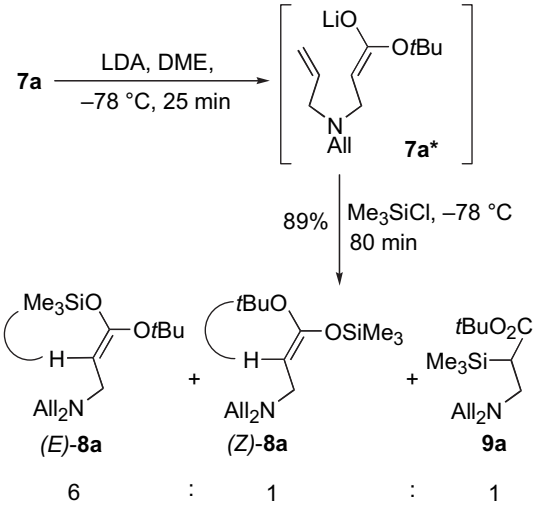
The stereoselectivity of the cyclization reaction proved to be dependent on the nitrogen substituent and the reaction conditions. From ester **7a** the 3,4-*cis* isomer predominated (entries 1–3). However, when HMPA was used as an additive prior to deprotonation, the diastereoselectivity was surprisingly reversed (entries 4,5). On the other hand no reversal of diastereoselectivity was observed, when HMPA was added after the deprotonation was complete (entry 6). Not surprisingly, the diastereoselectivity of the cyclization decreased when the reaction temperature was increased from −78 to −20 °C (entries 1,4,10 vs 2,5,11).

The 3,4-*cis* diastereoselectivity of the oxidative cyclizations was generally better using the *N*-benzyl substituent in **7c**,**d** (entries 9–16). The diastereoselectivity also changed on addition of HMPA, but

not as dramatically as in case of the *N*-allyl unit (entry 12 vs 13). In the presence of LiCl the diastereoselectivity increased with increasing temperature (entry 15 vs 14). This is attributed to an increased solubility of LiCl in DME at higher temperature and better formation of mixed aggregates.[21]

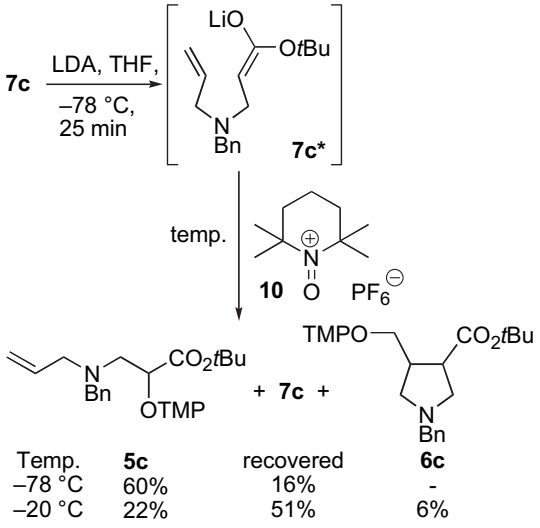
The cyclization results for the chiral esters **7e**,**f** are summarized in Scheme 5 and Table 3. The yields of cyclized products were also better for the *tert*-butyl ester **7e** than for methyl ester **7f** (entries 1–3 vs 4–6). When the cyclization was performed according to methods A and C, the simple cyclization diastereoselectivity was very high, since only two *cis*-isomers out of the possible four diastereomers were formed (entries 1,2,4,5). The (1*R*,3*S*,4*R*)-**6e**,**f**:(1*R*,3*R*,4*S*)-**6e**,**f** ratio was, however, low. In the presence of HMPA as an additive, a 3,4-*trans*-diastereomer was formed to a sizeable extent, to which the (1*R*,3*S*,4*S*)-configuration was assigned (entries 2,5). The acyclic oxygenation products **5e** and **5f** were isolated as a diastereomeric mixture in a 1:1 ratio. Their configuration was not assigned.

The change of diastereoselectivity that accompanied the use of HMPA as an additive was surprising and is potentially related to the enolate geometry after deprotonation. To gain more information, the enolate **7a*** generated by deprotonation in DME was subjected to trapping by chlorotrimethylsilane (Scheme 6). A mixture of silyl ketene acetals **8a** was isolated in 89% yield in a 6:1 (*E*/*Z*)-ratio. In addition 11% of *C*-silylated ester **9a** was detected. When the same experiment was repeated in the presence of HMPA, no **8a** was isolated. The reaction mixtures of several experiments under varying isolation conditions consisted only of *C*-silylated **9a** and starting material according to NMR analysis.



Scheme 6. Generation of silyl ketene acetals **8** after deprotonation of **7a** (Curves indicate NOE contacts).

Since several mechanisms for the SET oxidation and the further course of the oxidative cyclizations of **7a**–**f** can be envisaged, additional experiments were performed. It was determined in a control experiment that **4** does not act as an oxidant for the enolate **7a***. Both starting materials were recovered unchanged quantitatively. Furthermore, **4** may be oxidized by **3** to the *N*-oxopiperidinium ion **10** (cf. Scheme 7), which may subsequently act as the actual oxidant for **7a***. Since no interaction between **3** and **4** was noticeable in the solid state (vide supra), **4** was dissolved in DME and an equimolar amount of **3** was added. After 60 min at −78 °C and −20 °C, 91 and 95% of **3** was recovered unchanged by filtration from the blue inhomogeneous mixture under inert conditions, while 82 and 96% of **4** were reisolated after evaporation of the solvent. However, this does not prove definitely that **3** is not oxidizing **4** to a small extent in equilibrium thus driving the oxidative cyclization. To gain more detailed information 1.5 equiv of *N*-oxoiminium hexafluorophosphate **10**[22] was added to a solution of enolate **7c*** in the absence of **3** at −78 °C in THF (Scheme 7). It was indeed consumed instantaneously. After workup, 60% of **5c** was obtained and 16% of starting **7c** was recovered, but no trace of cyclized product **6c** was detected. When the reaction was run at −20 °C (in duplicate), only 22% of **5c** was obtained and a much larger amount of 51% of **7c** was recovered. A 6% yield of cyclized product **6c** and traces of an unknown compound, which was never observed in the cyclization experiments and does not contain the TMP unit, was also obtained from the reactions. Quenching by D_2O revealed no deuterium incorporation in **5c**–**7c**.



Scheme 7. Reaction between enolate **7c** and *N*-oxopiperidinium salt **10**.

The configuration of products **6a**–**f** was assigned in analogy to the diastereomers **D** and **E** obtained from the tandem amide conjugate addition/radical cyclization/oxygenation reactions reported earlier (Fig. 1, Table 4).[15] The relative *cis*-configuration was confirmed for the major diastereomers of **6a**, **6c** and the two major diastereomers (1*R*,3*S*,4*R*)-**6e** and (1*R*,3*R*,4*S*)-**6e** by ROESY analysis. A strong NOE effect between the *tert*-butyl and the piperidinyloxymethyl group was observed (Supplementary data). Such an NOE effect was, however, not detected for (1*R*,3*S*,4*S*)-**6e** with 3,4-*trans*-configuration. In addition, H5β showed a clear NOE to H6 in all investigated compounds.

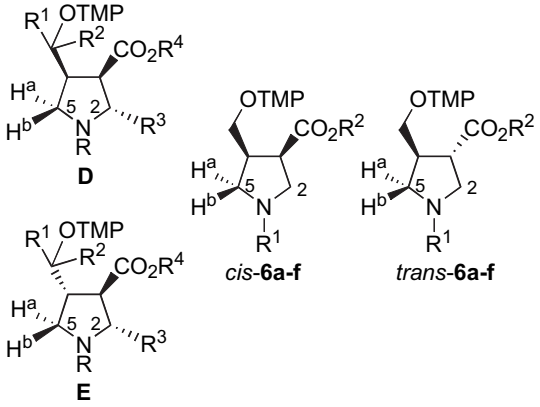


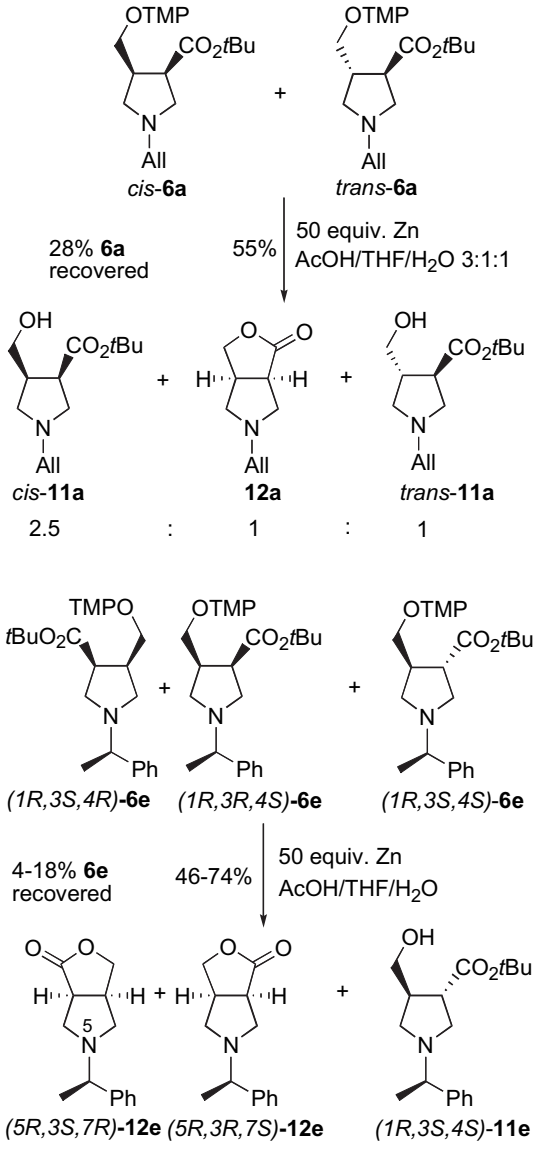
Figure 1. Structures and relative configurations of **6**.

The N–O bond of the alkoxyamine function in **6** can be cleaved reductively.[15] Heating a mixture of *cis*- and *trans*-**6a** with zinc and acetic acid to 80–90 °C gave a mixture of the free alcohols *cis*- and *trans*-**11a** and the bicyclic lactone **12a** in 55% yield (Scheme 8). In the

Table 4
Characteristic ^{1}H and ^{13}C NMR resonances of the diastereomeric **6** in ppm

Compound	H2	H2	H3	H4	H5α	H5β	H6	C6
D[a]	—	—	2.5–2.8	2.6–2.9	3.1–3.5	2.2–2.4	3.7/3.8	<77
cis-**6a**	2.54	2.94	2.94	2.61	3.04	2.29	3.62/3.80	76.7
cis-**6b**	2.57	3.03	3.03	2.69	3.03	2.23	3.59/3.74	76.2
cis-**6c**	2.61	2.87	2.96	2.61	2.96	2.41	3.66/3.78	76.6
cis-**6d**	2.61	2.95	3.06	2.69	2.95	2.31	3.61/3.73	76.2
(1*R*,3*S*,4*R*)-**6e**	2.58	2.73	2.93	2.69	3.16	2.41	3.73/3.82	76.5
(1*R*,3*S*,4*R*)-**6f**	2.58	2.79	3.06	2.78	3.20	2.36	3.70/3.80	75.7
(1*R*,3*R*,4*S*)-**6e**	2.73	2.93	3.02	2.60	2.68	2.56	3.71/3.78	76.1
(1*R*,3*R*,4*S*)-**6f**	2.71	3.17	3.18	2.68	2.72	2.35	3.64/3.76	75.5
E[a]	—	—	2.2–2.5	2.5–2.9	2.7–3.1	2.3–2.6	3.7/3.85	>78
trans-**6a**	2.61	2.72	2.61	2.54	2.69	2.41	3.72/3.72	78.7
trans-**6b**	2.69	3.03	2.69	2.69	2.69	2.40	3.74/3.74	78.4
trans-**6c**	2.68	2.87	2.61	2.54	2.68	2.45	3.72/3.72	78.7
trans-**6d**	2.69	3.06	2.69	2.69	2.69	2.45	3.60/3.73	78.5
(1*R*,3*S*,4*S*)-**6e**	2.71	2.74	2.93	2.58	2.75	2.60	3.78/3.78	78.3
(1*R*,3*S*,4*S*)-**6f**	2.67	2.75	2.75	2.70	2.72	2.62	3.76/3.76	78.1

[a] Average values over all compounds in Ref. 15.



Scheme 8. Reductive deprotection of the 2,2,6,6-tetramethylpiperidine unit in **6a** and **6e**.

case of **6e** resulting from cyclization according to method C, both major cyclized isomers led to lactones (5*R*,3*S*,7*R*)-**12e** and (5*R*,3*R*,7*S*)-**12e** in 74% yield in a 1.6:1 diastereomeric ratio. During deprotection of the three component mixture of (1*R*,3*S*,4*R*)-**6e**, (1*R*,3*R*,4*S*)-**6e**, and (1*R*,3*S*,4*S*)-**6e**, the same lactones (5*R*,3*S*,7*R*)-**12e** and (5*R*,3*R*,7*S*)-**12e** were formed in a 3:1 diastereomeric ratio in 28% yield, while the free *trans*-alcohol (1*R*,3*S*,4*S*)-**11e** was also obtained in 18% yield. Although corresponding experiments were not performed here, the *N*-allyl, *N*-benzyl and *N*-(1-phenylethyl) groups can be deprotected in principle under reductive conditions.[23]

The constitution and absolute configuration of the major lactone **12e** was proved unequivocally by X-ray crystallography (Fig. 2).[24] The butyrolactone ring of the bicyclic system is almost planar (mean deviation 0.006 Å), while the pyrrolidine ring prefers an envelope conformation, in which the carbon atoms C2–C5 are almost coplanar (mean deviation 0.014 Å) and the nitrogen lies 0.65 Å out of the plane thus defined. Since the 1-phenylethyl group in the starting material **7e** has an (*R*)-configuration the configurations of the bridge of the bicycle can be derived to (3*S*,7*R*). However, in this case the anomalous dispersion of oxygen is sufficient to determine the absolute configuration directly without recourse to a known center. This result provides further support for the assignment of the absolute configurations to the other diastereomers obtained in the oxidative cyclizations of **7e**,**f**.

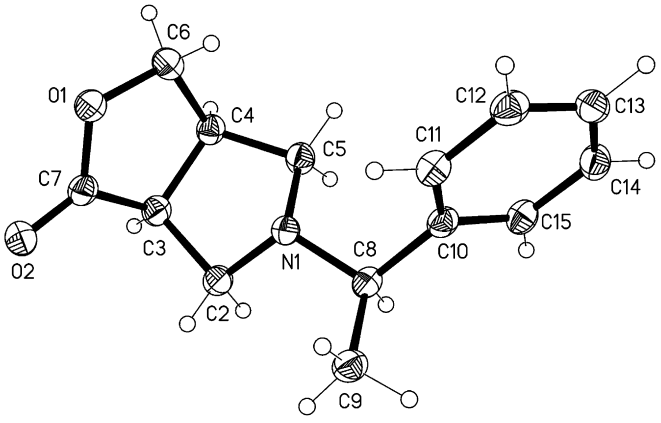
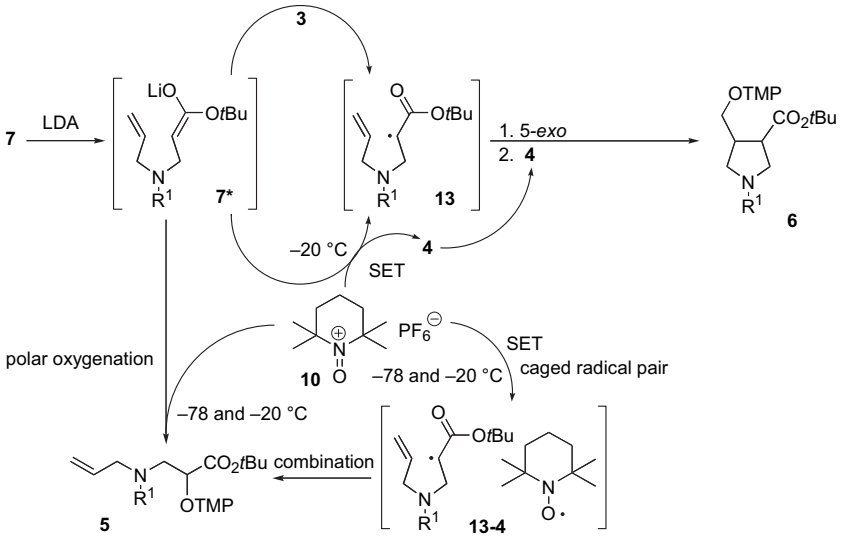


Figure 2. Structure of (5*R*,3*S*,7*R*)-**12e** in the crystal.

The results of the oxidative cyclizations can be rationalized as follows. Deprotonation of β-alanine esters **7a**–**f** by LDA alone or in the presence of lithium chloride gives predominately the (*E*)-enolate (*E*)-**7*** as seen by the configuration of the silyl ketene acetal (*E*)-**8a**.

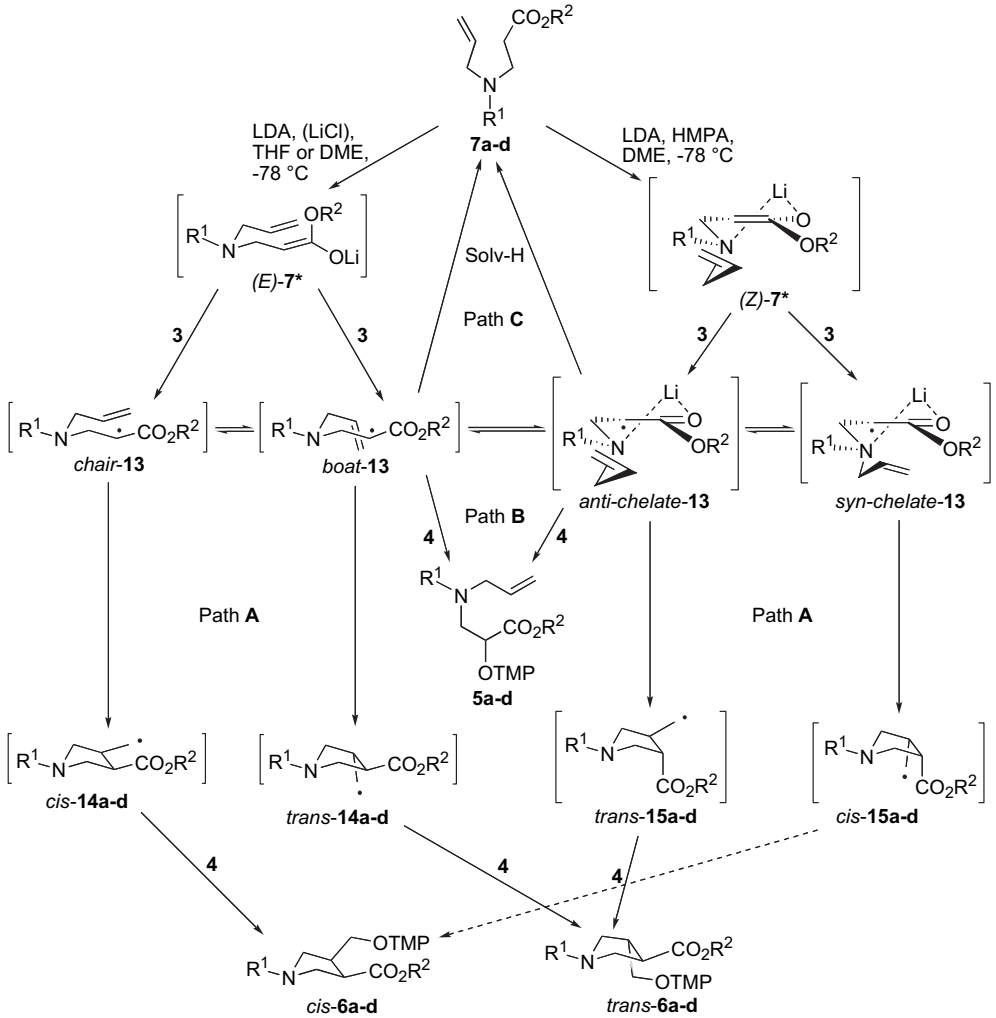
Two principal pathways are possible for the SET oxidation of **7*** (Scheme 9). The first consists of direct oxidation of **7*** mediated by ferrocenium hexafluorophosphate **3** giving an α-ester radical **13**,



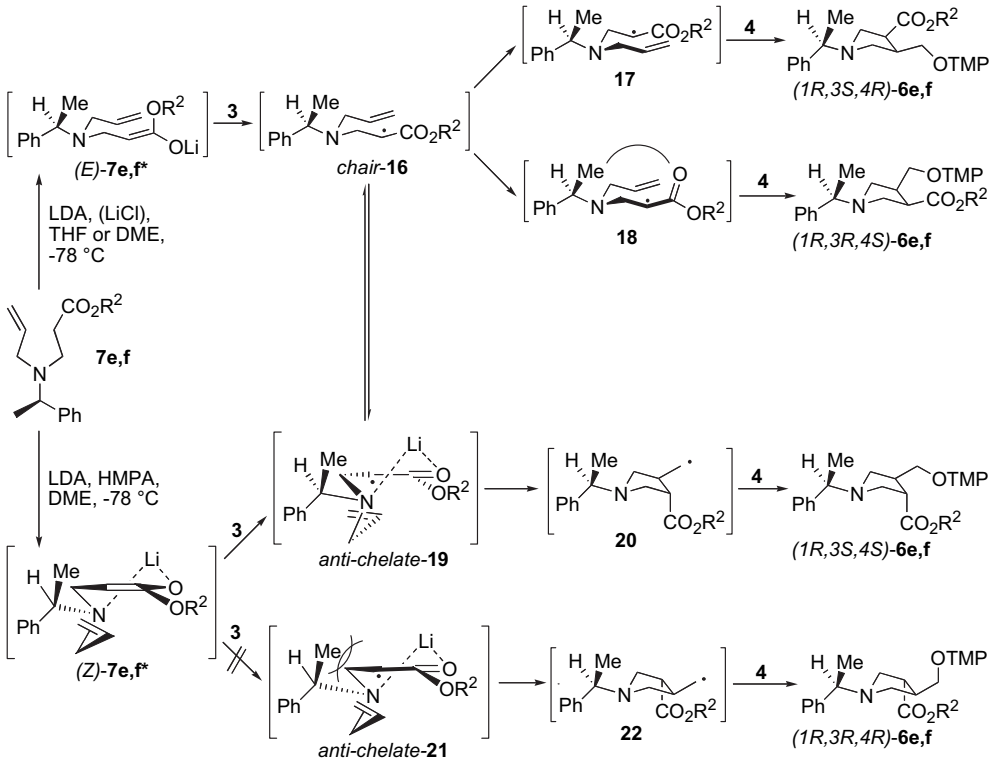
Scheme 9. Mechanism of SET oxidation of enolates **7***.

which cyclizes to **6**. This pathway is supported by a number of prior investigations, in which **3** was used to trigger efficient radical cyclizations in the absence of **4**.[14d,25] In the presence of TEMPO **4**, **3** may competitively act as an oxidant for **4** generating oxoiminium ion **10** as an intermediate. This compound can be envisaged as a SET oxidant for **7*** affording radical **13** that will ultimately cyclize to **6**.[26]

The latter pathway cannot be a significant contributor to the outcome of the cyclization reactions. First, oxidation of **4** by **3** to **10** is



Scheme 10. Mechanistic and stereochemical rationalization of the cyclizations of **7a**–**d**.



Scheme 11. Model for the formation of the stereoisomeric products **6e**,**f**.

very slow at −78 and −20 °C, if occurring at all, based on the control experiments. Using isolated **10** as the stoichiometric oxidant for **7*** in the absence of **3** at −78 °C gave only isoserine derivative **5** and not a trace of cyclized **6**. Compound **5** arises here either from a direct polar oxygenation of **7*** with **10**. Alternatively, a SET oxidation of **7*** to a caged radical pair **13**–**4** is possible, which combines to **5** before cage escape to free radicals **13** and **4** can occur. At −20 °C, the reaction between **10** and **7*** was much less efficient, though 6% of **6c** were indeed formed. The ratio of isolated **5**, **7** and **6** was, however, very different from the cyclization reactions mediated by **3**. Thus, **10** oxidizes **7*** only to a small extent at the higher temperature to free radical **13**, which cyclizes to **6**. Alternatively, cage escape from radical pair **13**–**4** leading to **6** may be a somewhat more facile at −20 °C compared to −78 °C. Taken these results together, direct oxidation of **7*** by **3** and subsequent cyclization to **6** is much more plausible than assuming a cyclization process invoking **10** as the oxidant.

Enolates (*E*)-**7*** are certainly aggregated in solution, but cannot be chelated by the amino group (Scheme 10). On SET oxidation by **3**, which is apparently quantitative, α-ester radicals **13** result, for which three reaction channels were observed. Most of radicals **13** undergo a 5-*exo* cyclization to radicals **14** followed by coupling with TEMPO **4** to give pyrrolidine derivatives **6** (Path **A**). Another portion of **13** is trapped by **4** prior to cyclization furnishing the protected isoserine derivatives **5** (Path **B**). A third portion of **13** is reduced leading to recovery of esters **7** (Path **C**). Path **C** cannot be related to incomplete deprotonation or oxidation and re-formation of **7** by protonation after the reaction, since considerable amounts of **7** were formed with even larger amounts of base. Furthermore, deuterium incorporation was never observed on hydrolyzing the reaction mixtures with deuterium oxide. Moreover, ferrocenium hexafluorophosphate is also unlikely as a source of moisture, since it is not hygroscopic.[27] Thus, recovered **7** is most probably produced by hydrogen atom transfer from the solvent or diisopropylamine, which should be reasonably fast.[28]

It was surprising that **5** and **7** were produced to a larger extent compared to the tandem lithium amide addition/cyclization/oxygenation sequences reported earlier.[15] Apparently, if a substituent is missing in the 2-position of the enolates, the cyclization is slowed down considerably so that intermolecular coupling with **4** and radical reduction of the α-ester radical compete to a more significant extent.

In contrast, deprotonation in the presence of HMPA is known to lead to predominant formation of the corresponding (*Z*)-enolates (*Z*)-**7***.[29] They are most probably chelated by the amino function in the molecule. Enolates (*Z*)-**7a**–**d*** give on oxidation essentially the same products **5a**–**d** and **6a**–**d** as the (*E*)-enolate. Interestingly, the stereoselectivity of the cyclization varies with the enolate geometry of **7a**–**d***. Enolates (*E*)-**7*** cyclize predominately via transition state *chair*-**13**, while the minor isomer may arise via *boat*-**13**. The significantly different diastereoselectivity observed in the cyclizations in the presence of HMPA suggests, that the chelate is at least to a reasonable extent conserved on oxidation from (*Z*)-**7*** to *chelate*-**13**. Cyclization to the major isomers *trans*-**6a**–**d** should occur via the sterically favored transition state *anti*-*chelate*-**13a**–**d** and coupling of resulting radicals *trans*-**15a**–**d** with **4**. The minor isomers *cis*-**6a**–**d** can arise either via cyclization of *syn*-*chelate*-**13** or via equilibration of radicals *chelate*-**13** to the open radicals *chair*- and *boat*-**13** and subsequent cyclization. An unambiguous determination of the actual pathways is, however, not possible for achiral substrates **7a**–**d**.

The cyclization of the chiral substrates **7e**,**f** provided valuable insight into the reaction course since the exocyclic stereocenter of the chiral *N*-(1-phenylethyl) group provides a bias for the radical cyclization steps (Scheme 11). The cyclization of the (*E*)-enolates **7e**,**f*** occurred with the best simple *cis*-cyclization diastereoselectivity and only two of the four possible isomers, namely (1*R*,3*S*,4*R*)-**6e**,**f** and (1*R*,3*R*,4*S*)-**6e**,**f**, were isolated. The chiral auxiliary differentiates the orientations of substituents in radical *chair*-**16**, thus the cyclization proceeds through two diastereomeric transition states **17** and **18**. The discrimination between them is, however, poor. Transition state **17** is apparently lower in energy, since it is free of steric interactions, while **18** seems to be slightly disfavored because of a *syn*-pentane-type interaction[30] between the methyl and ester groups.

Cyclization of the corresponding (*Z*)-enolates **7e**,**f*** leads in contrast to three diastereomers. This indicates clearly that a different pathway operates. On oxidation of chelated **7e**,**f*** a part of the radical *anti-chelate*-**19** cyclizes. In this case, however, only one diastereomer (1*R*,3*S*,4*S*)-**6e**,**f** is formed in large excess. Only *anti-chelate*-**19** has no unfavorable steric interactions during cyclization to **20**, while a strong steric interaction between the methyl group and the N–CH_2 group of the aminoester unit builds up in the alternative cyclizing radical *anti-chelate*-**21**, thus preventing cyclization to the alternative *trans*-diastereomer (1*R*,3*R*,4*R*)-**6e**,**f** via **22**. The formation of the two *cis*-isomers (1*R*,3*S*,4*R*)-**6e**,**f** and (1*R*,3*R*,4*S*)-**6e**,**f** cannot be attributed to cyclization via a chelated radical such as *syn-chelate*-**13** (cf. Scheme 10). In this case also one of the two diastereomers is expected to be formed in larger excess, since the same interactions as in *anti-chelate*-**19** and *anti-chelate*-**21** should affect the cyclizations. In the event, the *cis*-diastereomers (1*R*,3*S*,4*R*)-**6e**,**f** and (1*R*,3*R*,4*S*)-**6e**,**f** were isolated in a similar ratio as in the cyclizations of the corresponding (*E*)-enolates. Thus, it is more likely that radical *anti-chelate*-**19** relaxes to *chair*-**16**, which cyclizes via **17** and **18** to similar diastereomeric mixtures as those isolated from (*E*)-**7e**,**f***.

3. Conclusions

In the present study we showed that successful tandem lithium amide conjugate addition/radical 5-*exo* cyclization/oxygenation sequences require the presence of a substituent in 2-position of the forming ring to be efficient. However, the synthesis of pyrrolidines can nevertheless be accomplished by decoupling the tandem process into a two-step methodology. *N*-Allylic β-alanine derivatives were synthesized easily and in high yield by lithium chloride-catalyzed aza-Michael addition of allylic amines to acrylates. They can be transformed by an oxidative radical cyclization/oxygenation sequence into *N*-protected 4-oxymethylpyrrolidine-3-carboxylates in moderate to acceptable yields. It is surprising that for these rather unbiased systems diastereoselectivities up to 9:1 can be observed depending on the nitrogen protecting group. The selective generation of either (*E*)- or (*Z*)-enolates allows the control and the switch of the diastereoselectivity from a moderate to high *cis*-selectivity to a moderate *trans*-selectivity. The application of the 1-phenylethyl group allows the asymmetric synthesis of pyrrolidines. The cyclization proceeds with high *cis*-diastereoselectivity via two similar chair-type transition states. The knowledge gained will be applied in alkaloid synthesis by tandem lithium amide conjugate addition/radical cyclization reactions.

4. Experimental

4.1. *N*-Allylic β-amino esters 7a–d (General procedure)

Amine **1** (1.0 equiv) was mixed with acrylate ester **2a** or **b** (1.2–1.5 equiv; see Table 1) and flame-dried lithium chloride (0.1 equiv) under an argon atmosphere. The reaction mixture was heated to 50 °C with vigorous stirring until finished by TLC. The reaction mixture was cooled, diluted with ether and filtered through a pad of silica gel. The filtrate was evaporated and the crude product was purified by flash chromatography.

*4.1.1. tert-Butyl 3-(diallylamino)propanoate (**7a**).* Yield after flash chromatography (hexanes/EtOAc 15:1) as a colorless oil 967 mg (86%) [R_f(hexanes/EtOAc 20:1)=0.25]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 2978 (m), 2927 (m), 2808 (m), 1731 (s), 1367 (m), 1255 (m), 1157 (s), 918 (m). ^{1}H NMR (400 MHz, C_6D_6): δ=1.43 (s, 9H, C(C*H*$_3$)$_3$); 2.35 (t, *J*=7.4 Hz, 2H, C*H*$_2$CO); 2.74 (t, *J*=7.4 Hz, 2H, NC*H*$_2$CH$_2$); 3.07 (d, *J*=6.4 Hz, 4H, =CHC*H*$_2$); 5.12 (dd, *J*=1.0, 10.2 Hz, 2H, C*H*H=CH); 5.16 (dd, *J*=1.7, 17.1 Hz, 2H, CH*H*=CH); 5.82 (ddt, *J*=6.5, 10.2, 16.8 Hz, 2H, CH$_2$=C*H*). ^{13}C NMR (100 MHz, C_6D_6): δ=28.5 (q, C(*C*H$_3$)$_3$), 34.8 (t, CH$_2$CH$_2$CO), 49.9 (t, *C*H$_2$CH$_2$CO), 57.4 (t, *C*H$_2$CH=), 79.9 (s, *C*(CH$_3$)$_3$), 117.2 (t, CH=*C*H$_2$), 136.9 (d, *C*H=CH$_2$), 171.8 (s, *C*=O). MS *m*/*z*, (%): 225 (M^+, 40), 184 (85) [M^+ –CH$_2$=CHCH$_2$], 168 (80) [M^+ –C(CH$_3$)$_3$], 142 (70) [M^+ –(CH$_2$=CHCH$_2$)$_2$], 128 (100) [CH$_2$=CHCO$_2$*t*Bu$^+$], 110 (70) [All$_2$NCH$_2^+$], 81 (30), 68 (55). $C_{13}H_{23}NO_2$ (225.33): calcd C 69.29, H 10.29, N 6.22; found C 69.62, H 10.45, N 5.83.

*4.1.2. tert-Butyl 3-(N-allyl-N-benzylamino)propanoate (**7c**).* Yield after flash chromatography (hexanes/EtOAc 10:1) as a colorless oil 1.652 g (90%) [R_f (hexanes/EtOAc 10:1)=0.33]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3036 (m), 2977 (m), 2930 (m), 2801 (m), 1726 (s), 1366 (m), 1251 (m), 1152 (s), 918 (m), 739 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 9H, C(C*H*$_3$)$_3$); 2.34 (t, *J*=7.1 Hz, 2H, C*H*$_2$CO); 2.71 (t, *J*=7.2 Hz, 2H, NC*H*$_2$CH$_2$); 3.00 (d, *J*=6.2 Hz, 2H, =CHC*H*$_2$); 3.51 (s, 2H, PhC*H*$_2$N); 5.08 (m, 2H, C*H*$_2$=CH); 5.79 (ddt, *J*=6.4, 10.2, 16.7 Hz, 1H, CH$_2$=C*H*); 7.16–7.26 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.3 (q, C(*C*H$_3$)$_3$), 34.2 (t, CH$_2$CH$_2$CO), 49.5 (t, *C*H$_2$CH$_2$CO), 56.8 (t, *C*H$_2$CH=), 58.1 (t, PhCH$_2$N), 80.41 (s, *C*(CH$_3$)$_3$), 117.5 (t, CH=CH$_2$), 127.1 (d, *C*H$_{Ar}$), 128.4 (d, *C*H$_{Ar}$), 129.1 (d, *C*H$_{Ar}$), 135.9 (d, *C*H=CH$_2$), 139.6 (s, *C*$_{Ar}$), 172.2 (s, *C*=O). MS *m*/*z*, (%): 275 (M^+, 2), 218 (15) [M^+ –C(CH$_3$)$_3$], 184 (22) [M^+ –PhCH$_2$], 160 (80) [CH$_2$=N(All)Bn$^+$], 128 (55) [CH$_2$=CHCOO*t*Bu$^+$], 91 (100) [$C_7H_7^+$]. $C_{17}H_{25}NO_2$ (275.39): calcd C 74.14, H 9.15, N 5.09; found C 74.02, H 9.22, N 4.95.

*4.1.3. (R)-tert-Butyl 3-[N-allyl-N-(1-phenylethyl)amino]propanoate (**7e**).* Yield after flash chromatography (hexanes/EtOAc 5:1) as a colorless oil 1.00 g (81%) [R_f(hexanes/EtOAc 5:1)=0.38]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 2976 (m), 2930 (w), 2817 (w), 1728 (s), 1367 (m), 1256 (m), 1153 (s), 917 (m), 701 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (d, *J*=6.7 Hz, 3H, CHC*H*$_3$); 1.36 (s, 9H, C(C*H*$_3$)$_3$); 2.28 (t, *J*=7.3 Hz, 2H, C*H*$_2$CO); 2.66 (dt, *J*=7.3, 14.3 Hz, 1H, NC*H*HCH$_2$); 2.79 (dt, *J*=7.3, 14.3 Hz, 1H, NCH*H*CH$_2$); 2.91 (dd, *J*=6.3, 14.5 Hz, 1H, =CHC*H*HN); 3.02 (dd, *J*=6.3, 14.5 Hz, 1H, =CHCH*H*N); 3.79 (q, *J*=6.8 Hz, 1H, C*H*CH$_3$); 5.00 (dd, *J*=1.2, 10.2 Hz, 1H, C*H*H=CH); 5.07 (dd, *J*=1.6, 17.2 Hz, 1H, CH*H*=CH); 5.73 (ddt, *J*=6.3, 10.2, 16.6 Hz, 1H, CH$_2$=C*H*); 7.14–7.28 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.1 (q, CH*C*H$_3$), 28.4 (q, C(*C*H$_3$)$_3$), 34.7 (t, CH$_2$CH$_2$CO), 45.9 (t, *C*H$_2$CH$_2$CO), 53.4 (t, *C*H$_2$CH=), 59.2 (d, *C*HCH$_3$), 80.3 (s, *C*(CH$_3$)$_3$), 116.7 (t, CH=CH$_2$), 126.9 (d, *C*H$_{Ar}$), 127.9 (d, *C*H$_{Ar}$), 128.2 (d, *C*H$_{Ar}$), 137.1 (d, *C*H=CH$_2$), 144.1 (s, *C*$_{Ar}$), 172.4 (s, *C*=O). MS *m*/*z*, (%): 289 (M^+, 2), 218 (35) [M^+ –CH$_3$–(H$_3$C)$_2$C=CH$_2$], 174 (30) [M^+ –CH$_2$COO*t*Bu], 146 (40) [PhCH=NHAll$^+$], 128 (60) [CH$_2$=CHCOO*t*Bu$^+$], 105 (100) [PhCHCH$_3^+$], 70 (35). $C_{18}H_{27}NO_2$ (289.41): calcd C 74.70, H 9.40, N 4.84; found C 74.58, H 9.51, N 4.77.

4.2. Pyrrolidine-3-carboxylates 6 via oxidative radical 5-*exo* cyclizations of β-amino ester enolates (General procedures)

Method A. To a stirred solution of dry diisopropylamine (0.18 mL, 1.25 mmol) in 20 mL anhydrous DME or THF (See Table 2) butyllithium (1.6 *M* in hexanes, 0.78 mL, 1.25 mmol) was added dropwise at −78 °C. After 20 min, a solution of β-amino ester **7a–f** (1.0 mmol) in 0.6 mL of dry solvent was added dropwise. After 30 min, TEMPO **4** (0.031 g, 0.2 mmol) was added as a solid. Subsequently a thoroughly homogenized mixture of **4** (0.125 g, 0.8 mmol) and ferrocenium hexafluorophosphate **3** (0.331 g, 1.0 mmol) was added in small portions with vigorous stirring at the given temperature. Since discoloration of **3** was still fast at that stage, further **3** (100–150 mg) was added in small portions, until a dark blue-green color of reaction mixture persisted for 20 min. The reaction mixture was quenched by saturated NH_4Cl solution or D_2O (five drops), diluted with 20 mL of ether and filtered through a pad of silica gel. The filtrate was evaporated, the crude

inhomogeneous mixture was preadsorbed on silica gel and purified by flash chromatography.

Method B. To a stirred solution of dry diisopropylamine (0.18 mL, 1.25 mmol) in 20 mL anhydrous DME or THF (See Table 2) butyllithium (1.6 M in hexanes, 0.78 mL, 1.25 mmol) was added dropwise at −78 °C. After 20 min, HMPA (1.05 mL, 6.0 mmol) was added, followed by a solution of β-amino ester **7** (1.0 mmol) in 0.6 mL of dry solvent. After 30 min, TEMPO **4** (0.031 g, 0.2 mmol) was added as a solid. Subsequently a thoroughly homogenized mixture of **4** (0.125 g, 0.8 mmol) and **3** (0.331 g, 1.0 mmol) was added in small portions with vigorous stirring at the given temperature. Since discoloration of **3** was still fast at that stage, further **3** (100–150 mg) was added in small portions, until a dark blue-green color of reaction mixture persisted for 20 min. The reaction mixture was worked up and purified as described in method A.

Method C. Lithium chloride (0.297 g, 7.0 mmol) was flame-dried in a Schlenk flask. After cooling to room temperature the solvent was added and the reaction was performed as described in method A.

*4.2.1. tert-Butyl 1-allyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)-methyl]pyrrolidine-3-carboxylate (**6a**).* Isolated after flash chromatography (hexanes/EtOAc 50:1 to 1:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 2. [R_f (hexanes/EtOAc 5:1)=0.19]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 2975 (m), 2930 (m), 2794 (w), 1728 (s), 1367 (m), 1148 (s), 993 (m), 918 (m). MS (ESI) *m*/*z*, (%): 381 (M+H$^+$, 100), 325 (12) [M+H$^+$ –H$_2$C=C(CH$_3$)$_2$], 240 (5) [M$^+$ –TMP]. $C_{22}H_{40}N_2O_3$ (380.56): calcd C 69.43, H 10.59, N 7.36; found C 69.21, H 10.75, N 7.12. ^{1}H NMR (400 MHz, CDCl$_3$): δ=1.05–1.14 (m, 24H, TMP–C*H*$_3$, TMP–C*H*$_3$*); 1.23 (m, 4H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 1.34 (m, 8H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 1.37 (s, 9H, C(C*H*$_3$)$_3$*); 1.38 (s, 9H, C(C*H*$_3$)$_3$); 2.29 (t, *J*=8.9 Hz, 1H, H5); 2.41 (dd, *J*=6.1, 9.0 Hz, 1H, H5*); 2.54 (m, 2H, H2, H4*); 2.61 (m, 3H, H4, H2*, H3*); 2.69 (m, 1H, H5*); 2.72 (m, 1H, H2*); 2.94 (m, 3H, H2, H3, NC*H*$_2$CH=*); 3.04 (m, 3H, H5, NC*H*$_2$CH=, NC*H*$_2$CH=*); 3.13 (ddd, *J*=1.1, 6.3, 13.2 Hz, 1H, NC*H*$_2$CH=); 3.62 (dd, *J*=8.6, 10.7 Hz, 1H, H6); 3.72 (m, 2H, H6*); 3.80 (dd, *J*=4.7, 8.5 Hz, 1H, H6); 5.03 (dd, *J*=1.6, 10.2 Hz, 2H, CH=C*H*$_2$, CH=C*H*$_2$*); 5.14 (dd, *J*=1.6, 17.1 Hz, 2H, CH=C*H*$_2$, CH=C*H*$_2$*); 5.84 (ddt, *J*=6.5, 10.1, 16.7 Hz, 2H, C*H*=CH$_2$, C*H*=CH$_2$*). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.3 (t, TMP–CCH$_2$*C*H$_2$), 20.1 (q, TMP–*C*H$_3$), 20.2 (q, TMP–*C*H$_3$), 28.3 (s, C(*C*H$_3$)$_3$*), 28.4 (s, C(*C*H$_3$)$_3$), 33.4 (q, TMP–*C*H$_3$), 33.6 (q, TMP–*C*H$_3$), 39.9 (t, TMP–*C*CH$_2$), 40.1 (d, C4), 41.8 (d, C4*), 45.4 (d, C3), 46.7 (d, C3*), 56.1 (t, C2), 56.6 (t, C2*), 57.5 (t, C5*), 58.4 (t, C5), 59.1 (t, *C*H$_2$CH=*), 59.2 (t, *C*H$_2$CH=), 59.8 (s, TMP–*C*(CH$_3$)$_2$), 60.1 (s, TMP–*C*(CH$_3$)$_2$), 76.7 (t, C6), 78.7 (t, C6*), 80.5 (s, *C*(CH$_3$)$_3$*), 80.9 (s, *C*(CH$_3$)$_3$), 117.0 (t, CH=*C*H$_2$*), 117.1 (t, CH=*C*H$_2$), 135.96 (d, *C*H=CH$_2$*), 136.02 (d, *C*H=CH$_2$), 172.7 (s, *C*=O), 173.9 (s, *C*=O*). Resonances marked with * belong to 3,4-*trans*-**6a**.

*4.2.2. tert-Butyl 3-(N,N-diallylamino)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**5a**).* Pale yellow oil, for yields see Table 2. [R_f (hexanes/EtOAc 20:1)=0.28]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3070 (w), 2976 (m), 2931 (m), 1736 (s), 1365 (s), 1153 (s), 917 (s), 732 (s). MS (ESI) *m*/*z*, (%): 403 (M+Na$^+$, 100), 381 (M+H$^+$, 100), 347 (5) [M+Na$^+$ –H$_2$C=C(CH$_3$)$_2$], 325 (5) [M+H$^+$ –H$_2$C=C(CH$_3$)$_2$]. $C_{22}H_{40}N_2O_3$ (380.56): calcd C 69.43, H 10.59, N 7.36; found C 69.31, H 10.76, N 7.17. ^{1}H NMR (400 MHz, CDCl$_3$): δ=1.02–1.10 (m, 12H, TMP–C*H*$_3$); 1.22 (m, 2H, TMP–C*H*$_2$); 1.36 (m, 4H, TMP–C*H*$_2$); 1.40 (s, 9H, C(C*H*$_3$)$_3$); 2.72 (m, 2H, NC*H*$_2$CHCO); 2.93 (dd, *J*=7.1, 14.0 Hz, 2H, NC*H*$_2$CH=); 3.09 (dd, *J*=5.9, 14.0 Hz, 2H, NC*H*$_2$CH=); 4.18 (dd, *J*=5.7, 9.8 Hz, 1H, C*H*OTMP); 5.05 (ddd, *J*=1.1, 9.9, 17.2 Hz, 4H, CH=C*H*$_2$); 5.73 (ddt, *J*=7.1, 10.1, 16.9 Hz, 2H, C*H*=CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.4 (t, TMP–CCH$_2$*C*H$_2$), 20.2 (q, TMP–*C*H$_3$), 20.4 (q, TMP–*C*H$_3$), 28.3 (s, C(*C*H$_3$)$_3$), 33.6 (q, TMP–*C*H$_3$), 33.7 (q, TMP–*C*H$_3$), 40.6 (t, TMP–*C*CH$_2$), 55.0 (t, NCH$_2$CHCO), 57.6 (t, NCH$_2$CH=), 59.3 (s, TMP–*C*(CH$_3$)$_2$), 60.3 (s, TMP–*C*(CH$_3$)$_2$), 80.7 (s, *C*(CH$_3$)$_3$), 85.4 (d, *C*HOTMP), 117.5 (t, CH=*C*H$_2$), 135.9 (d, *C*H=CH$_2$), 172.8 (s, *C*=O).

*4.2.3. Methyl 1-allyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylate (**6b**).* Isolated after flash chromatography (hexanes/EtOAc 50:1 to 1:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 2. [R_f (hexanes/EtOAc 2:1)=0.21]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3078 (w), 2973 (m), 2929 (m), 2797 (w), 1736 (s), 1359 (m), 1194 (s), 1046 (m), 919 (m). MS (ESI) *m*/*z*, (%): 339 (M+H$^+$, 100), 198 (15) [M$^+$–TMP]. HRMS *m*/*z*, ($C_{19}H_{35}N_2O_3$; M+H$^+$): calcd 339.2642; found 339.2643. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.99–1.05 (m, 24H, TMP–C*H*$_3$, TMP–C*H*$_3$*); 1.19 (m, 4H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 1.35 (m, 8H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 2.23 (t, *J*=8.9 Hz, 1H, H5); 2.40 (m, 1H, H5*); 2.57 (m, 1H, H2); 2.69 (m, 5H, H4, H2*, H3*, H4*, H5*); 2.96 (m, 2H, NC*H*$_2$CH=*); 3.03 (m, 5H, H2, H3, H5, H2*, NC*H*$_2$CH=); 3.09 (m, 1H, NC*H*$_2$CH=); 3.59 (m, 7H, H6, OC*H*$_3$, OC*H*$_3$*); 3.74 (m, 3H, H6, H6*, H6*); 5.03 (d, *J*=10.2 Hz, 2H, CH=C*H*$_2$, CH=C*H*$_2$*); 5.14 (d, *J*=17.1 Hz, 2H, CH=C*H*$_2$, CH=C*H*$_2$*); 5.84 (ddt, *J*=6.6, 10.1, 17.0 Hz, 2H, C*H*=CH$_2$, C*H*=CH$_2$*). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.2 (t, TMP–CCH$_2$*C*H$_2$), 20.09 (q, TMP–*C*H$_3$), 20.10 (q, TMP–*C*H$_3$), 33.1 (q, TMP–*C*H$_3$), 33.2 (q, TMP–*C*H$_3$), 39.8 (t, TMP–*C*CH$_2$), 40.2 (d, C4), 41.5 (d, C4*), 44.2 (d, C3), 46.0 (d, C3*), 51.6 (q, OC*H*$_3$), 51.9 (q, OC*H*$_3$*), 56.2 (t, C2), 56.7 (t, C2*), 56.9 (t, C5*), 57.6 (t, C5), 58.8 (t, *C*H$_2$CH=*), 58.9 (t, *C*H$_2$CH=), 59.8 (s, TMP–*C*(CH$_3$)$_2$), 59.9 (s, TMP–*C*(CH$_3$)$_2$), 76.2 (t, C6), 78.4 (t, C6*), 116.0 (t, CH=*C*H$_2$*), 117.0 (t, CH=*C*H$_2$), 135.51 (d, *C*H=CH$_2$*), 135.55 (d, *C*H=CH$_2$), 173.6 (s, *C*=O), 174.8 (s, *C*=O*). Resonances marked with * belong to 3,4-*trans*-**6b**.

*4.2.4. Methyl 3-(N,N-diallylamino)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**5b**).* Pale yellow oil, for yields see Table 2. [R_f (hexanes/EtOAc 10:1)=0.65]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3077 (w), 2975 (m), 2930 (m), 1747 (s), 1362 (m), 1176 (m), 1041 (s), 918 (s). MS (ESI) *m*/*z*, (%): 361 (100, M+Na$^+$), 339 (45, M+H$^+$). HRMS *m*/*z*, ($C_{19}H_{35}N_2O_3$; M+H$^+$): calcd 339.2642; found 339.2639. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.94–1.11 (m, 12H, TMP–C*H*$_3$); 1.21 (m, 2H, TMP–C*H*$_2$); 1.35 (m, 4H, TMP–C*H*$_2$); 2.75 (m, 2H, NC*H*$_2$CHCO); 2.93 (dd, *J*=7.1, 14.0 Hz, 2H, NC*H*$_2$CH=); 3.07 (dd, *J*=5.8, 14.0 Hz, 2H, NC*H*$_2$CH=); 3.63 (s, 3H, OC*H*$_3$), 4.31 (dd, *J*=5.8, 10.2 Hz, 1H, C*H*OTMP); 5.04 (m, 4H, CH=C*H*$_2$); 5.69 (ddt, *J*=7.1, 10.1, 17.0 Hz, 2H, C*H*=CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.1 (t, TMP–CCH$_2$*C*H$_2$), 19.9 (q, TMP–*C*H$_3$), 20.2 (q, TMP–*C*H$_3$), 32.7 (q, TMP–*C*H$_3$), 33.2 (q, TMP–*C*H$_3$), 40.3 (t, TMP–*C*CH$_2$), 51.1 (q, OC*H*$_3$), 54.1 (t, NCH$_2$CHCO), 57.5 (t, NCH$_2$CH=), 59.3 (s, TMP–*C*(CH$_3$)$_2$), 60.5 (s, TMP–*C*(CH$_3$)$_2$), 84.9 (d, *C*HOTMP), 117.2 (t, CH=*C*H$_2$), 135.6 (d, CH=CH$_2$), 173.4 (s, *C*=O).

*4.2.5. tert-Butyl 1-benzyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)-methyl]pyrrolidine-3-carboxylate (**6c**).* Isolated after flash chromatography (hexanes/EtOAc 50:1 to 2:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 2. [R_f (hexanes/EtOAc 7:1)=0.15]. IR (film); $\tilde{\nu}$[cm^{-1}]: 2974 (m), 2930 (m), 2790 (w, br), 1726 (s), 1366 (m), 1147 (s), 735 (m), 698 (s). MS (ESI) *m*/*z*, (%): 431 (M+H$^+$, 100), 375 (3) [M+H$^+$ –H$_2$C=C(CH$_3$)$_2$]. $C_{26}H_{42}N_2O_3$ (430.62): calcd C 72.52, H 9.83, N 6.51; found C 72.79, H 10.01, N 6.21. ^{1}H NMR (400 MHz, CDCl$_3$): δ=0.96–1.05 (m, 24H, TMP–C*H*$_3$, TMP–C*H*$_3$*); 1.18 (m, 4H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 1.32 (m, 8H, TMP–C*H*$_2$, TMP–C*H*$_2$*); 1.36 (s, 9H, C(C*H*$_3$)$_3$*); 1.37 (s, 9H, C(C*H*$_3$)$_3$); 2.41 (dd, *J*=8.3, 8.7 Hz, 1H, H5); 2.45 (m, 1H, H5*); 2.54 (m, 1H, H4*); 2.61 (m, 3H, H2, H4, H3*); 2.68 (m, 2H, H2*, H5*); 2.87 (m, 2H, H2, H2*); 2.96 (m, 2H, H5, H3); 3.47 (d, *J*=13.2 Hz, 1H, PhC*H*$_2$*); 3.53 (d, *J*=12.9 Hz, 1H, PhC*H*$_2$); 3.66 (m, 3H, PhC*H*$_2$, PhCH$_2$*, H6); 3.72 (m, 2H, H6*); 3.78 (dd, *J*=4.7, 8.4 Hz, 1H, H6); 7.16–7.27 (m, 10H, Ar*H*, Ar*H**). ^{13}C NMR (100 MHz, CDCl$_3$): δ=17.4 (t, TMP–CCH$_2$*C*H$_2$), 20.1 (q, TMP–*C*H$_3$), 20.3 (q, TMP–*C*H$_3$), 28.3 (s, C(*C*H$_3$)$_3$*), 28.4 (s, C(*C*H$_3$)$_3$), 33.4 (q, TMP–*C*H$_3$), 33.6 (q, TMP–*C*H$_3$), 39.9 (t, TMP–*C*CH$_2$), 40.1 (d, C4), 41.7 (d, C4*), 45.5

(d, C3), 46.9 (d, C3*), 56.0 (t, C2), 56.7 (t, C2*), 57.4 (t, C5*), 58.6 (t, C5), 59.8 (s, TMP–$C(CH_3)_2$), 60.07 (s, TMP–$C(CH_3)_2$), 60.10 (t, PhCH_2*), 60.6 (t, PhCH_2), 76.6 (t, C6), 78.7 (t, C6*), 80.4 (s, $C(CH_3)_3$*), 80.8 (s, $C(CH_3)_3$), 127.0 (d, CH_{Ar}*), 127.1 (d, CH_{Ar}), 128.38 (d, CH_{Ar}*), 128.43 (d, CH_{Ar}), 128.8 (d, CH_{Ar}*), 128.9 (d, CH_{Ar}), 139.3 (s, C_{Ar}*), 139.5 (s, C_{Ar}), 172.7 (s, C=O), 174.0 (s, C=O*). Resonances marked with * belong to 3,4-*trans*-**6c**.

*4.2.6. tert-Butyl 3-(N-allyl-N-benzylamino)-2-(2,2,6,6-tetramethyl piperidin-1-yloxy)propanoate (**5c**).* Colorless oil, for yields see Table 2. [R_f (hexanes/EtOAc 20:1)=0.41]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3064 (w), 2975 (m), 2930 (m), 1734 (s), 1365 (s), 1154 (s), 741 (m), 699 (m). MS (ESI) *m*/*z*, (%): 453 ($M+Na^+$, 70), 431 ($M+H^+$, 100), 160 (70) [CH_2=N(All)Bn^+]. $C_{26}H_{42}N_2O_3$ (430.62): calcd C 72.52, H 9.83, N 6.51; found C 72.73, H 9.99, N 6.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.01–1.09 (m, 12H, TMP–CH_3); 1.21 (m, 2H, TMP–CH_2), 1.35 (m, 4H, TMP–CH_2); 1.43 (s, 9H, C(CH_3)$_3$); 2.74 (dd, *J*=5.0, 12.4 Hz, 1H, NC*H*HCHCO); 2.82 (m, 2H, NC*H*HCHCO, NCH*H*CH=); 3.02 (dd, *J*=5.9, 14.1 Hz, 1H, NCH*H*CH=); 3.43 (d, *J*=13.5 Hz, 1H, PhC*H*HN); 3.62 (d, *J*=13.5 Hz, 1H, PhC*H*HN); 4.21 (dd, *J*=5.0, 9.9 Hz, 1H, C*H*OTMP); 5.03 (m, 2H, CH=CH_2); 5.74 (m, 1H, C*H*=CH_2); 7.14–7.25 (m, 5H, Ar*H*). ^{13}C (100 MHz, $CDCl_3$): δ=17.3 (t, TMP–CCH_2CH_2), 20.3 (q, TMP–CH_3), 20.4 (q, TMP–CH_3), 28.4 (q, C(CH_3)$_3$), 33.7 (q, TMP–CH_3), 33.8 (q, TMP–CH_3), 40.6 (t, TMP–CCH_2), 55.6 (t, NCH_2CHCO), 57.1 (t, NCH_2CH=), 58.9 (t, PhCH_2), 59.5 (s, TMP–$C(CH_3)_2$), 60.5 (s, TMP–$C(CH_3)_2$), 80.9 (s, $C(CH_3)_3$), 85.4 (d, *C*HOTMP), 117.8 (t, CH=CH_2), 127.0 (d, CH_{Ar}), 128.2 (d, CH_{Ar}), 129.4 (d, CH_{Ar}), 135.5 (d, *C*H=CH_2), 139.2 (s, C_{Ar}), 172.6 (s, *C*=O).

*4.2.7. Methyl 1-benzyl-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)-methyl]pyrrolidine-3-carboxylate (**6d**).* Isolated after flash chromatography (hexanes/EtOAc 50:1 to 2:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 2. [R_f (hexanes/EtOAc 5:1)=0.23]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 2973 (m), 2932 (m), 2792 (w, br), 1735 (s), 1362 (m), 1139 (s), 702 (m). MS (ESI) *m*/*z*, (%): 389 ($M+H^+$, 100), 288 (5). HRMS *m*/*z*, ($C_{23}H_{37}N_2O_3$; $M+H^+$): calcd 389.2799; found 389.2798. $C_{23}H_{36}N_2O_3$ (388.54): calcd C 71.10, H 9.34, N 7.21; found C 71.54, H 9.21, N 6.92. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96–1.04 (m, 24H, TMP–CH_3, TMP–CH_3*); 1.18 (m, 4H, TMP–CH_2, TMP–CH_2*); 1.35 (m, 8H, TMP–CH_2, TMP–CH_2*); 2.31 (t, *J*=8.7 Hz, 1H, H5); 2.45 (dd, *J*=9.7, 12.9 Hz, 1H, H5*); 2.61 (dd, *J*=8.1, 9.4 Hz, 1H, H2); 2.69 (m, 5H, H4, H2*, H3*, H4*, H5*); 2.95 (m, 2H, H2, H5); 3.06 (dt, *J*=7.9, 9.9 Hz, 2H, H3, H2*); 3.48 (d, *J*=13.0 Hz, 1H, PhCH_2*); 3.59 (s, 3H, OCH_3); 3.60 (m, 8H, PhCH_2, PhCH_2*, H6, H6*, OCH_3*); 3.73 (dd, *J*=6.2, 8.7 Hz, 2H, H6, H6*); 7.16–7.27 (m, 10H, Ar*H*, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.3 (TMP–CCH_2CH_2), 20.16 (q, TMP–CH_3), 20.18 (q, TMP–CH_3), 33.2 (q, TMP–CH_3), 33.3 (q, TMP–CH_3), 39.9 (t, TMP–CCH_2), 40.3 (d, C4), 41.5 (d, C4*), 44.4 (d, C3), 46.1 (d, C3*), 51.5 (q, OCH_3*), 51.7 (q, OCH_3), 56.4 (t, C2), 56.86 (t, C2*), 56.91 (t, C5*), 57.9 (t, C5), 59.91 (s, TMP–$C(CH_3)_2$), 59.92 (s, TMP–$C(CH_3)_2$), 60.0 (t, PhCH_2*), 60.5 (t, PhCH_2), 76.2 (t, C6), 78.5 (t, C6*), 127.08 (d, CH_{Ar}*), 127.13 (d, CH_{Ar}), 128.37 (d, CH_{Ar}*), 128.43 (d, CH_{Ar}), 128.8 (d, CH_{Ar}*), 128.9 (d, CH_{Ar}), 139.3 (s, C_{Ar}*), 139.4 (s, C_{Ar}), 173.8 (s, *C*=O), 174.0 (s, *C*=O*). Resonances marked with * belong to 3,4-*trans*-**6d**.

*4.2.8. Methyl 3-(N-allyl-N-benzylamino)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**5d**).* Colorless oil, for yields see Table 2. [R_f (hexanes/EtOAc 10:1)=0.63]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3064 (w), 2975 (m), 2930 (w), 1744 (s), 1361 (m), 1040 (s), 740 (s), 698 (s). MS (ESI) *m*/*z*, (%): 411 ($M+Na^+$, 80), 389 ($M+H^+$, 100), 160 (80) [CH_2=N(All)Bn^+]. HRMS *m*/*z*, ($C_{22}H_{36}N_2O_3Na$; $M+Na^+$): calcd 411.2618; found 411.2616. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.94–1.09 (m, 12H, TMP–CH_3); 1.22 (m, 2H, TMP–CH_2), 1.35 (m, 4H, TMP–CH_2); 2.78 (dd, *J*=5.4, 12.4 Hz, 1H, NC*H*HCHCO); 2.87 (m, 2H, NC*H*HCHCO, NCH*H*CH=); 3.03 (dd, *J*=5.8, 14.2 Hz, 1H, NCH*H*CH=); 3.39 (d, *J*=13.5 Hz, 1H, PhC*H*HN); 3.62 (s, 3H, OCH_3); 3.64 (d, *J*=13.0 Hz, 1H, PhC*H*HN); 4.34 (dd, *J*=5.4, 10.4 Hz, 1H, C*H*OTMP); 5.05 (m, 2H, CH=CH_2); 5.71 (ddt, *J*=6.5, 10.2, 17.6 Hz, 1H, C*H*=CH_2); 7.12–7.23 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.3 (t, TMP–CCH_2CH_2), 20.2 (q, TMP–CH_3), 20.4 (q, TMP–CH_3), 32.9 (q, TMP–CH_3), 33.5 (q, TMP–CH_3), 40.4 (t, TMP–CCH_2), 51.3 (q, OCH_3), 54.7 (t, NCH_2CHCO), 57.1 (t, NCH_2CH=), 59.1 (t, PhCH_2N), 59.6 (s, TMP–$C(CH_3)_2$), 60.7 (s, TMP–$C(CH_3)_2$), 85.0 (d, *C*HOTMP), 117.8 (t, CH=CH_2), 127.1 (d, CH_{Ar}), 128.3 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 135.4 (d, *C*H=CH_2), 139.3 (s, C_{Ar}), 173.5 (s, *C*=O).

*4.2.9. tert-Butyl 1-(1-phenylethyl)-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylates (**6e**).* Isolated after flash chromatography (hexanes/EtOAc 50:1–7:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 3. [R_f (hexanes/EtOAc 10:1)=0.19].

*4.2.9.1. (1R,3S,4R)-**6e** and (1R,3R,4S)-**6e**.* IR (film); $\tilde{\nu}$ [cm^{-1}]: 2973 (m), 2930 (m), 2780 (w, br), 1727 (s), 1367 (m), 1146 (s), 701 (m). MS (ESI) *m*/*z*, (%): 445 ($M+H^+$, 100). $C_{27}H_{44}N_2O_3$ (444.65): calcd C 72.93, H 9.97, N 6.30; found 73.14, H 10.19, N 5.92. ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.98–1.17 (m, 24H, TMP–CH_3, TMP–CH_3*); 1.29 (m, 2H, TMP–CH_2, TMP–CH_2*); 1.37 (d, *J*=6.6 Hz, 3H, CHCH_3*); 1.39 (d, *J*=6.6 Hz, 3H, CHCH_3); 1.38–1.45 (m, 8H, TMP–CH_2, TMP–CH_2*); 1.42 (s, 9H, C(CH_3)$_3$); 1.44 (s, 9H, C(CH_3)$_3$*); 1.52 (m, 2H, TMP–CH_2, TMP–CH_2*); 2.41 (dd, *J*=7.8, 9.0 Hz, 1H, H5); 2.56 (dd, *J*=6.5, 8.7 Hz, 1H, H5*); 2.58 (dd, *J*=7.3, 9.9 Hz 1H, H2); 2.60 (m, 1H, H4*); 2.68 (dd, *J*=5.9, 8.7 Hz, 1H, H5*); 2.69 (m, 1H, H4); 2.73 (dd, *J*=7.9, 9.9 Hz 1H, H2); 2.73 (dd, *J*=8.4, 9.7 Hz, 1H, H2*); 2.93 (ddd, *J*=7.3, 7.9, 10.0 Hz, 1H, H3); 2.93 (dd, *J*=9.1, 9.7 Hz, 1H, H2*); 3.02 (ddd, *J*=7.4, 8.4, 9.1 Hz, 1H, H3*); 3.16 (dd, *J*=6.5, 9.0 Hz, 1H, H5); 3.31 (d, *J*=6.6 Hz, 1H, C*H*CH$_3$); 3.34 (d, *J*=6.6 Hz, 1H, C*H*CH$_3$*); 3.71 (dd, *J*=5.5, 8.4 Hz, 1H, H6*); 3.73 (dd, *J*=6.1, 8.5 Hz, 1H, H6); 3.78 (dd, *J*=4.6, 8.4 Hz, 1H, H6*); 3.82 (dd, *J*=4.7, 8.5 Hz, 1H, H6); 7.19–7.35 (m, 10H, Ar*H*, Ar*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ=17.3 (t, TMP–CCH_2CH_2), 20.1 (q, TMP–CH_3), 20.2 (q, TMP–CH_3), 23.2 (q, CHCH_3*), 23.4 (q, CHCH_3), 28.31 (q, C(CH_3)$_3$), 28.33 (q, C(CH_3)$_3$*), 33.3 (q, TMP–CH_3), 33.6 (q, TMP–CH_3), 39.8 (t, TMP–CCH_2), 39.9 (d, C4*), 40.1 (d, C4), 45.3 (d, C3), 45.5 (d, C3*), 54.4 (t, C2*), 55.2 (t, C2), 56.3 (t, C5*), 56.7 (t, C5), 59.8 (s, TMP–$C(CH_3)_2$), 60.0 (s, TMP–$C(CH_3)_2$), 65.3 (d, CHCH$_3$*), 65.7 (d, CHCH$_3$), 76.1 (t, C6*), 76.5 (t, C6), 78.6 (s, $C(CH_3)_3$*), 80.7 (s, $C(CH_3)_3$), 126.93 (d, CH_{Ar}*), 126.96 (d, CH_{Ar}), 127.3 (d, CH_{Ar}*), 127.4 (d, CH_{Ar}), 128.38 (d, CH_{Ar}*), 128.41 (d, CH_{Ar}), 145.7 (s, C_{Ar}*), 145.8 (s, C_{Ar}), 172.6 (s, *C*=O*), 172.7 (s, *C*=O). Resonances marked with * belong to (1*R*,3*R*,4*S*)-**6e**.

*4.2.9.2. (1R,3S,4S)-**6e**.* ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.07 (s, 3H, TMP–CH_3); 1.09 (s, 3H, TMP–CH_3); 1.15 (s, 3H, TMP–CH_3); 1.16 (s, 3H, TMP–CH_3); 1.30 (m, 1H, TMP–CH_2); 1.34 (d, *J*=6.7 Hz, 3H, CHCH_3); 1.39–1.45 (m, 4H, TMP–CH_2); 1.41 (s, 9H, C(CH_3)$_3$); 1.53 (m, 1H, TMP–CH_2); 2.58 (m, 1H, H4); 2.60 (m, 1H, H5); 2.71 (m, 1H, H2); 2.74 (m, 1H, H2); 2.75 (m, 1H, H5); 2.93 (dt, *J*=10.0, 7.6 Hz, 1H, H3); 3.21 (q, *J*=6.7 Hz, 1H, C*H*CH$_3$); 3.78 (m, 2H, H6); 7.19–7.35 (m, 5H, Ar*H*). ^{13}C NMR (151 MHz, $CDCl_3$): δ=17.0 (t, TMP–CCH_2CH_2), 20.06 (q, TMP–CH_3), 20.10 (q, TMP–CH_3), 23.04 (q, CHCH_3), 28.0 (q, C(CH_3)$_3$), 33.02 (q, TMP–CH_3), 33.06 (q, TMP–CH_3), 39.5 (t, TMP–CCH_2), 41.2 (d, C4), 46.4 (d, C3), 55.41 (t, C2 or C5), 55.47 (t, C2 or C5), 59.5 (s, TMP–$C(CH_3)_2$), 59.6 (s, TMP–$C(CH_3)_2$), 65.0 (d, CHCH$_3$), 78.3 (t, C6), 80.2 (s, $C(CH_3)_3$), 126.8 (d, CH_{Ar}), 127.1 (d, CH_{Ar}), 128.2 (d, CH_{Ar}), 145.6 (s, C_{Ar}), 173.9 (s, *C*=O).

*4.2.10. (R,R- and R,S)-tert-Butyl 3-[N-allyl-N-(1-phenylethyl)amino]-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoates (**5e**).* Colorless oil, for yields see Table 3. [R_f (hexanes/EtOAc 10:1)=0.49]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3062 (w), 2975 (m), 2931 (m), 1734 (s), 1365 (s), 1148 (s), 916 (m), 701 (s). MS (ESI) *m*/*z*, (%): 467 ($M+Na^+$, 100), 445 ($M+H^+$, 50), 174 (70) [CH_2=NAll(PhCHCH_3)$^+$]. HRMS *m*/*z*, ($C_{27}H_{44}N_2O_3Na$; $M+Na^+$): calcd 467.3244; found 467.3243. ^{1}H

NMR (400 MHz, $CDCl_3$): δ=0.99–1.04 (m, 24H, TMP–CH_3, TMP–CH_3*); 1.19 (m, 4H, TMP–CH_2, TMP–CH_2*); 1.26 (d, J=6.8 Hz, 3H, CHCH_3*); 1.27 (d, J=6.8 Hz, 3H, CHCH_3); 1.34 (m, 8H, TMP–CH_2, TMP–CH_2*); 1.43 (s, 9H, C(CH_3)$_3$); 1.44 (s, 9H, C(CH_3)$_3$*); 2.58 (dd, J=5.2, 12.4 Hz, 1H, NCHHCHCO*); 2.80 (dd, J=7.4, 14.3 Hz, 1H, NCHHCH=); 2.83 (d, J=7.5 Hz, 2H, NCH_2CHCO); 2.89 (m, 1H, NCHHCHCO*); 2.93 (m, 1H, NCHHCH=); 3.01 (dd, J=7.2, 14.3 Hz, 1H, NCHHCH=*); 3.08 (ddt, J=1.4, 5.4, 14.3 Hz, 1H, NCHHCH=); 3.84 (q, J=6.8 Hz, 2H, CHCH$_3$, CHCH$_3$*); 4.14 (dd, J=7.4, 7.9 Hz, 1H, CHOTMP); 4.21 (dd, J=5.3, 10.6 Hz, 1H, CHOTMP*); 5.03 (m, 4H, CH=CH_2, CH=CH_2*); 5.70 (m, 2H, CH=CH$_2$, CH=CH$_2$); 7.13–7.30 (m, 10H, ArH, ArH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.8 (q, CHCH_3*), 17.3 (t, TMP–CCH$_2$CH_2), 18.4 (q, CHCH_3), 20.3 (q, TMP–CH_3), 20.4 (q, TMP–CH_3), 28.40 (q, C(CH_3)$_3$*), 28.44 (q, C(CH_3)$_3$), 33.6 (q, TMP–CH_3), 33.9 (q, TMP–CH_3), 40.6 (t, TMP–CCH$_2$), 51.6 (t, NCH$_2$CHCO*), 52.4 (t, NCH$_2$CHCO), 53.5 (t, NCH$_2$CH=*), 54.4 (t, NCH$_2$CH=), 59.2 (d, CHCH$_3$*), 59.4 (d, CHCH$_3$), 59.5 (s, TMP–C(CH$_3$)$_2$), 60.5 (s, TMP–C(CH$_3$)$_2$), 80.8 (s, C(CH$_3$)$_3$*), 80.9 (s, C(CH$_3$)$_3$), 85.4 (d, CHOTMP), 85.8 (d, CHOTMP*), 117.0 (t, CH=CH$_2$*), 117.1 (t, CH=CH$_2$), 126.9 (d, CH$_{Ar}$), 127.0 (d, CH$_{Ar}$*), 128.06 (d, CH$_{Ar}$), 128.12 (d, CH$_{Ar}$*), 128.3 (d, CH$_{Ar}$), 128.4 (d, CH$_{Ar}$), 136.7 (d, CH=CH$_2$*), 136.9 (d, CH=CH$_2$), 142.2 (s, C$_{Ar}$), 143.6 (s, C$_{Ar}$*), 172.8 (s, C=O), 172.9 (s, C=O*). Resonances marked with * belong to one diastereomer (configuration not assigned).

*4.2.11. Methyl 1-(1-phenylethyl)-4-[(2,2,6,6-tetramethylpiperidin-1-yloxy)methyl]pyrrolidine-3-carboxylates (**6f**).* Isolated after flash chromatography (hexanes/EtOAc 50:1 to 2:1) as a pale yellow oil. For yields and diastereomeric ratios see Table 3. [R_f(hexanes/EtOAc 3:1)=0.41].

*4.2.11.1. (1R,3S,4R)-**6f** and (1R,3R,4S)-**6f**.* IR (film); $\tilde{\nu}$ [cm^{-1}]: 2973 (m), 2931 (m), 2782 (w, br), 1736 (s), 1454 (m), 1164 (s), 702 (s). MS (ESI) m/z, (%): 403 (M+H$^+$, 100). HRMS m/z, ($C_{24}H_{39}N_2O_3$; M+H$^+$): calcd 403.2955; found 403.2954. ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.01–1.15 (m, 24H, TMP–CH_3); 1.30 (m, 4H, TMP–CH_2, TMP–CH_2*); 1.38 (d, J=6.6 Hz, 3H, CHCH_3*); 1.40 (d, J=6.6 Hz, 3H, CHCH_3); 1.43 and 1.54 (2 m, 8H, TMP–CH_2, TMP–CH_2*); 2.35 (dd, J=7.2, 9.1 Hz, 1H, H5*); 2.36 (t, J=8.7 Hz, 1H, H5); 2.58 (dd, J=7.9, 9.8 Hz, 1H, H2); 2.68 (m, 1H, H4*); 2.71 (m, 1H, H2*); 2.72 (m, 1H, H5*); 2.78 (m, 1H, H4); 2.79 (dd, J=7.9, 9.8 Hz, 1H, H2); 3.06 (dt, J=7.9, 10.0 Hz, 1H, H3); 3.17 (m, 1H, H2*); 3.18 (m, 1H, H3*); 3.20 (dd, J=6.9, 8.7 Hz, 1H, H5); 3.32 (d, J=6.6 Hz, 1H, CHCH$_3$); 3.34 (d, J=6.6 Hz, 1H, CHCH$_3$*); 3.64 (s, 3H, CH$_3$O); 3.64 (dd, J=7.7, 8.8 Hz, 1H, H6*); 3.69 (s, 3H, CH$_3$O*); 3.70 (t, J=8.6 Hz, 1H, H6); 3.76 (dd, J=6.4, 8.8 Hz, 1H, H6*); 3.80 (dd, J=6.1, 8.6 Hz, 1H, H6); 7.21–7.36 (m, 10H, ArH, ArH*). ^{13}C NMR (151 MHz, $CDCl_3$): δ=16.8 (t, TMP–CCH$_2$CH_2), 19.67 (q, TMP–CH_3), 19.72 (q, TMP–CH_3), 22.7 (q, CHCH_3*), 22.9 (q, CHCH_3), 32.6 (q, TMP–CH_3), 32.8 (q, TMP–CH_3), 39.3 (t, TMP–CCH$_2$), 39.7 (d, C4*), 39.8 (d, C4), 43.6 (d, C3), 43.9 (d, C3*), 51.3 (q, OCH_3), 51.4 (q, OCH_3*), 54.4 (t, C2*), 55.2 (t, C2), 55.80 (t, C5), 55.81 (t, C5*), 59.4 (s, TMP–C(CH$_3$)$_2$), 59.5 (s, TMP–C(CH$_3$)$_2$), 65.0 (d, CHCH$_3$*), 65.3 (d, CHCH$_3$), 75.5 (t, C6*), 75.7 (t, C6), 126.7 (d, CH$_{Ar}$* and CH$_{Ar}$), 126.80 (d, CH$_{Ar}$*), 126.86 (d, CH$_{Ar}$), 128.04 (d, CH$_{Ar}$), 128.05 (d, CH$_{Ar}$*), 144.9 (s, C$_{Ar}$*), 145.1 (s, C$_{Ar}$), 173.48 (s, C=O*), 173.52 (s, C=O). Resonances marked with * belong to (1*R*,3*R*,4*S*)-**6f**.

*4.2.11.2. (1R,3S,4S)-**6f**.* ^{1}H NMR (600 MHz, $CDCl_3$): δ=1.08 (s, 3H, TMP–CH_3); 1.12 (s, 3H, TMP–CH_3); 1.15 (s, 3H, TMP–CH_3); 1.16 (s, 3H, TMP–CH_3); 1.30 (m, 1H, TMP–CH_2); 1.37 (d, J=6.6 Hz, 3H, CHCH_3); 1.40–1.45 (m, 4H, TMP–CH_2); 1.53 (m, 1H, TMP–CH_2); 2.62 (m, 1H, H5); 2.67 (m, 1H, H2); 2.70 (m, 1H, H4); 2.72 (m, 1H, H5); 2.75 (m, 2H, H2, H3); 3.24 (q, J=6.7 Hz, 1H, CHCH$_3$); 3.76 (m, 2H, H6); 7.21–7.36 (m, 5H, ArH). ^{13}C NMR (151 MHz, $CDCl_3$): δ=16.8 (t, TMP–CCH$_2$CH_2), 19.7 (q, TMP–CH_3), 19.8 (q, TMP–CH_3), 22.7 (q, CHCH_3), 32.6 (q, TMP–CH_3), 32.8 (q, TMP–CH_3), 39.3 (t, TMP–CCH$_2$), 40.7 (d, C4), 45.7 (d, C3), 51.5 (OCH_3); 54.8 (t, C5), 55.5 (t, C2), 59.4 (s, TMP–C(CH$_3$)$_2$), 59.5 (s, TMP–C(CH$_3$)$_2$), 64.8 (d, CHCH$_3$), 78.1 (t, C6), 126.6 (d, CH$_{Ar}$), 126.8 (d, CH$_{Ar}$), 128.0 (d, CH$_{Ar}$), 145.0 (s, C$_{Ar}$), 174.8 (s, C=O). Traces of the other *trans*-diastereomer were detected.

*4.2.12. (R,R-nand R,S)-Methyl 3-[N-allyl-N-(1-phenylethyl)amino]-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**5f**).* Pale yellow oil, for yields see Table 3. [R_f(hexanes/EtOAc 10:1)=0.49]. IR (film); $\tilde{\nu}$ [cm^{-1}]: 3064 (w), 2973 (m), 2932 (m), 1745 (s), 1200 (m), 1042 (m), 700 (m). MS (ESI) m/z, (%): 403 (M+H$^+$, 100), 174 (45) [CH$_2$=NAll(PhCHCH$_3$)$^+$]. HRMS m/z, ($C_{24}H_{39}N_2O_3$; M+H$^+$): calcd 403.2955; found 403.2965. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92–1.08 (m, 24H, TMP–CH_3, TMP–CH_3*); 1.20 (m, 4H, TMP–CH_2, TMP–CH_2*); 1.25 (d, J=6.8 Hz, 3H, CHCH_3*); 1.26 (d, J=6.9 Hz, 3H, CHCH_3); 1.34 (m, 8H, TMP–CH_2, TMP–CH_2*); 2.68 (dd, J=5.4, 12.8 Hz, 1H, NCHHCHCO*); 2.84 (m, 2H, NCH_2CHCO); 2.89 (m, 1H, NCHHCHCO*); 2.96 (m, 4H, NCH_2CH=, NCH_2CH=*); 3.56 (s, 3H, OCH_3); 3.65 (s, 3H, OCH_3*); 3.83 (q, J=6.9 Hz, 2H, CHCH$_3$, CHCH$_3$*); 4.31 (m, 2H, CHOTMP, CHOTMP*); 5.01 (m, 4H, CH=CH_2, CH=CH_2*); 5.67 (m, 2H, CH=CH$_2$, CH=CH$_2$*); 7.13–7.25 (m, 10H, ArH, ArH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.7 (q, CHCH_3*), 17.0 (q, CHCH_3), 17.3 (t, TMP–CCH$_2$CH_2), 20.2 (q, TMP–CH_3), 20.5 (q, TMP–CH_3), 33.0 (q, TMP–CH_3), 33.4 (q, TMP–CH_3), 40.4 (t, TMP–CCH$_2$), 40.5 (t, TMP–CCH$_2$), 51.1 (t, NCH$_2$CHCO*), 51.24 (q, OCH_3*), 51.25 (q, OCH_3), 51.9 (t, NCH$_2$CHCO), 53.8 (t, NCH$_2$CH=*), 54.3 (t, NCH$_2$CH=), 58.6 (d, CHCH$_3$*), 59.5 (s, TMP–C(CH$_3$)$_2$), 60.1 (d, CHCH$_3$), 60.8 (s, TMP–C(CH$_3$)$_2$), 85.2 (d, CHOTMP*), 85.8 (d, CHOTMP), 116.9 (t, CH=CH$_2$*), 117.1 (t, CH=CH$_2$), 126.9 (d, CH$_{Ar}$), 127.0 (d, CH$_{Ar}$*), 128.0 (d, CH$_{Ar}$), 128.09 (d, CH$_{Ar}$*), 128.14 (d, CH$_{Ar}$), 128.2 (d, CH$_{Ar}$*), 136.8 (d, CH=CH$_2$), 137.0 (d, CH=CH$_2$*), 142.7 (s, C$_{Ar}$*), 143.7 (s, C$_{Ar}$), 173.5 (s, C=O), 173.7 (s, C=O*). Resonances marked with * belong to one diastereomer (configuration not assigned).

*4.2.13. Silyl ketene acetals (**8a**) by trapping of the enolate resulting from deprotonation of **7a**.* To a stirred solution of dry diisopropylamine (0.18 mL, 1.25 mmol) in 15 mL anhydrous DME butyllithium (1.6 *M* in hexanes, 0.78 mL, 1.25 mmol) was added dropwise at −78 °C. After 20 min a solution of *tert*-butyl 3-(*N*,*N*-diallylamino)propanoate **7a** (0.226 g, 1.0 mmol) in 0.9 mL of dry DME was added at −78 °C. After 25 min chlorotrimethylsilane (0.16 mL, 1.25 mmol) was added and the mixture was stirred at −78 °C for 80 min. The solvent was carefully removed under high vacuum. The solid white residue was washed with dry hexane (5×5 mL) and filtered under inert conditions. The solvent was removed in high vacuum and the remaining highly sensitive colorless oil (0.344 g) was dissolved in C_6D_6, transferred to an NMR tube and analyzed.

*4.2.14. (E)-1-tert-Butoxy-3-(N,N-diallylamino)-1-(trimethylsilyloxy)-propene (**E**–**8a**).* ^{1}H NMR (500 MHz, C_6D_6): δ=0.13 (s, 9H, Si(CH_3)$_3$); 1.26 (s, 9H, C(CH_3)$_3$); 3.10 (ddd, J=1.5, 1.8, 6.4 Hz, 4H, CH_2CH=CH$_2$); 3.17 (d, J=7.2 Hz, 2H, NCH_2CH=); 4.05 (t, J=7.2 Hz, 1H, All$_2$NCH$_2$CH=); 5.04 (ddt, J=1.5, 2.3, 10.2 Hz, 2H, CH$_2$CH=CHH); 5.16 (ddt, J=1.8, 2.3, 17.2 Hz, 2H, CH$_2$CH=CHH); 5.91 (ddt, J=6.4, 10.2, 17.2 Hz, 2H, CH$_2$CH=CH$_2$). ^{13}C NMR (125 MHz, C_6D_6): 0.0 (q, Si(CH$_3$)$_3$), 29.3 (q, C(CH$_3$)$_3$), 49.8 (t, NCH$_2$CH=C), 56.8 (t, CH$_2$CH=CH$_2$), 78.4 (s, C(CH$_3$)$_3$), 87.80 (d, NCH$_2$CH=C), 116.6 (t, CH$_2$CH=CH$_2$), 137.4 (d, CH$_2$CH=CH$_2$), 154.4 (s, NCH$_2$CH=C).

*4.2.15. (Z)-1-tert-Butoxy-3-(N,N-diallylamino)-1-(trimethylsilyloxy)-propene (**Z**–**8a**).* ^{1}H NMR (500 MHz, C_6D_6): δ=0.17 (s, 9H, Si(CH_3)$_3$); 1.21 (s, 9H, C(CH_3)$_3$); 3.09 (m, 4H, CH_2CH=CH$_2$); 3.18 (d, J=7.2 Hz, 2H, NCH_2CH=C); 4.10 (t, J=7.2 Hz, 1H, NCH$_2$CH=C); 4.99 (ddt, J=1.5, 2.3, 10.1 Hz, 2H, CH$_2$CH=CHH); 5.08 (ddt, J=1.8, 2.3, 17.1 Hz, 2H, CH$_2$CH=CHH); 5.81 (dddd, J=5.7, 6.9, 10.1, 17.1 Hz, 2H,

$CH_2CH{=}CH_2$). ^{13}C NMR (125 MHz, C_6D_6): 1.4 (q, Si(CH_3)$_3$), 28.7 (q, C(CH_3)$_3$), 49.6 (t, $NCH_2CH{=}C$), 57.0 (t, $CH_2CH{=}CH_2$), 79.0 (s, $C(CH_3)_3$), 87.75 (d, $NCH_2CH{=}C$), 117.0 (t, $CH_2CH{=}CH_2$), 137.3 (d, $CH_2CH{=}CH_2$), 153.8 (s, $NCH_2CH{=}C$).

*4.2.16. tert-Butyl 3-(N,N-diallylamino)-2-(trimethylsilyl)propanoate (**9a**).* ^1H NMR (500 MHz, C_6D_6): δ=0.03 (s, 9H, Si(CH_3)$_3$); 1.39 (s, 9H, C(CH_3)$_3$); 2.22 (dd, J=3.6, 11.1 Hz, 1H, CHSi(CH_3)$_3$); 2.43 (dd, J=3.6, 13.0 Hz, 1H, CHHCHSi); 2.92 (ddt, J=1.3, 7.1, 15.4 Hz, 2H, CHHCH=CH_2); 3.08 (dd, J=11.1, 13.0 Hz, 1H, NCHHCHSi); 3.10 (m, 2H, CHHCH=CH_2); 4.99 (ddt, J=1.3, 2.3, 10.1 Hz, 2H, $CH_2CH{=}CH$H); 5.08 (ddt, J=1.3, 2.3, 17.1 Hz, 2H, $CH_2CH{=}CH$H); 5.77 (ddt, J=7.1, 10.1, 17.1 Hz, 2H, $CH_2CH{=}CH_2$). ^{13}C NMR (125 MHz, C_6D_6): −2.3 (q, Si(CH_3)$_3$), 28.4 (q, C(CH_3)$_3$), 37.8 (d, CHSi), 51.6 (t, NCH_2CHSi), 56.80 (t, $CH_2CH{=}CH_2$), 78.2 (s, $C(CH_3)_3$), 116.9 (t, $CH{=}CH_2$), 136.7 (d, $CH{=}CH_2$), 173.4 (s, $C{=}O$).

*4.2.17. tert-Butyl 3-(N-allyl-N-benzylamino)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propanoate (**5c**) by oxygenation of **7c** with 2,2,6,6-tetramethyl-1-oxopiperidinium hexafluorophosphate (**10**).* To a stirred solution of dry diisopropylamine (0.18 mL, 1.25 mmol) in 10 mL anhydrous THF, butyllithium (1.4 M in hexanes, 0.90 mL, 1.25 mmol) was added dropwise at −78 °C. After 15 min, a solution of **7c** (0.276 g, 1.0 mmol) in 0.6 mL of dry THF was added dropwise. After 30 min, **10** (0.302 g, 1.0 mmol) was added in portions and after its dissolution further 0.150 g (0.5 mmol) of **10**. The reaction mixture was stirred at −78 °C for 60 min, quenched with saturated NH_4Cl solution (four drops), diluted with ether (20 mL) and filtered through a pad of silica gel. Evaporation of the filtrate yielded 0.558 g of an orange oil, which was preadsorbed on silica gel and purified by flash chromatography (hexanes/EtOAc 20:1 gradient to 5:1) to give 0.259 g (60%) of **5c** and 0.044 g (16%) of **7c**.

4.3. Reductive N–O bond cleavage of 6a

The diastereomeric mixture of **6a** (0.222 g, 0.58 mmol; 3.5:1 *cis*/*trans*) was dissolved in a mixture of 1.2 mL THF and 1.2 mL water. Then, 3.6 mL of acetic acid was added and the mixture was warmed at 70 °C. Zinc dust (1.89 g, 29.0 mmol) was added with vigorous stirring. The temperature was increased to 80–85 °C and stirring was continued. According to TLC (hexanes/EtOAc/Et_3N 100:100:1) the starting material appeared to be consumed after 60 min. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (20 mL) and filtered. The filtrate was neutralized with saturated K_2CO_3 solution until a pH of ca. 10 was reached. The layers were separated. The organic layer was washed twice with water, dried over $MgSO_4$ and evaporated to give 0.151 g of a yellow oil, which was purified by flash chromatography (hexanes/iPrOH/Et_3N 200:100:1). At first 62 mg (28%) of **6a** was recovered as a 3.2:1 *cis*/*trans*-diastereomeric mixture [R_f(hexanes/iPrOH/Et_3N 200:100:1)=0.75], followed by 72 mg (55%) of an inseparable mixture of alcohols *cis*- and *trans*-**11a** and lactone **12a** in a ratio of 2.5:1:1 [R_f (hexanes/iPrOH/Et_3N 200:100:1)=0.3–0.4 (streaky)].

*4.3.1. tert-Butyl 1-allyl-4-(hydroxymethyl)pyrrolidine-3-carboxylates (**11a**).* ^1H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 9H, C(CH_3)$_3$*); 1.41 (s, 9H, C(CH_3)$_3$); 2.33 (m, 1H, H2*); 2.43 (m, 1H, H2); 2.46 (m, 2H, H4*, H5*); 2.58 (m, 1H, H4); 2.79 (m, 5H, H2, H5α, H5β, H2*, H3*); 3.01 (m, 6H, $NCH_2CH{=}$, $NCH_2CH{=}$*, H3, H5*); 3.17 (br s, 2H, OH); 3.57 (dd, J=4.8, 10.3 Hz, 1H, H6*); 3.64 (m, 3H, H6, H6*); 5.04 (m, 2H, $CH{=}CH$H, $CH{=}CH$H*); 5.13 (m, 2H, $CH{=}CH$H, $CH{=}CH$H*); 5.80 (m, 2H, $CH{=}CH_2$, $CH{=}CH_2$*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.2 (q, C(CH_3)$_3$*), 28.3 (q, C(CH_3)$_3$), 42.8 (d, C4), 43.8 (d, C4*), 45.7 (d, C3), 46.9 (d, C3*), 55.9 (t, C5), 56.7 (t, C5*), 57.40 (t, C2*), 57.68 (t, C2), 58.6 (t, $CH_2CH{=}$*), 58.8 (t, $CH_2CH{=}$), 63.3 (t, C6), 66.6 (t, C6*), 81.1 (s, $C(CH_3)_3$*), 81.5 (s, $C(CH_3)_3$), 117.3 (t, $CH{=}CH_2$*), 117.46 (t, $CH{=}CH_2$), 135.33 (d, $CH{=}CH_2$*), 135.45 (d, $CH{=}CH_2$), 172.9 (s, $C{=}O$), 173.9 (s, $C{=}O$*). Resonances marked with * belong to minor 3,4-*trans*-**11a**.

*4.3.2. N-Allylhexahydrofuro[3,4-c]pyrrol-1-one (**12a**).* ^1H NMR (400 MHz, $CDCl_3$): δ=2.33 (m, 1H, H2); 2.58 (m, 1H, H5); 2.79 (m, 1H, H5); 3.01 (m, 4H, $NCH_2CH{=}$, H3, H4); 3.17 (d, J=9.4 Hz, 1H, H2); 4.03 (dd, J=3.5, 9.2 Hz, 1H, H6); 4.43 (t, J=9.2 Hz, 1H, H6); 5.04 (m, 1H, $CH{=}CH$H); 5.13 (m, 1H, $CH{=}CH$H); 5.80 (m, 1H, $CH{=}CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=37.8 (d, C4), 43.9 (d, C3), 57.35 (t, $NCH_2CH{=}$), 57.70 (t, C5), 60.8 (t, C2), 74.0 (t, C6), 117.40 (t, $CH{=}CH_2$), 135.41 (d, $CH{=}CH_2$), 179.8 (s, $C{=}O$). The same numbering as in monocyclic compounds was used for assignment.

4.4. Reductive N–O bond cleavage of 6e obtained according to method C

A 1.8:1 diastereomeric mixture of (1*R*,3*S*,4*R*)-**6e** and (1*R*,3*R*,4*S*)-**6e** (0.207 g, 0.47 mmol) was dispersed in a mixture of 2.9 mL acetic acid and 1.0 mL water. THF was added dropwise until a homogeneous solution was formed (3.0 mL). Zinc dust (1.53 g, 23.30 mmol, 50 equiv) was added with vigorous stirring and the reaction mixture was heated at 85–90 °C for 7 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered. The filtrate was neutralized with saturated K_2CO_3 solution to a pH of ca. 10. The organic layer was separated, washed twice with water, dried over $MgSO_4$ and evaporated to give 118 mg of colorless oil. The aqueous layer and washing solutions were combined, treated with 2 M NaOH solution to pH 13 and extracted with ether (3×10 mL). The ethereal extract was washed with brine and dried over $MgSO_4$. Evaporation yielded 2 mg of colorless semi-solid residue, which was combined with main product. The crude product was purified by flash chromatography (hexanes/EtOAc 5:1 gradient to EtOAc) to give 8 mg (4%) recovered (1*R*,3*S*,4*R*)-**6e** and (1*R*,3*R*,4*S*)-**6e**, followed by 81 mg (74%) of a partly separable 1.6:1 diastereomeric mixture of lactones (5*R*,3*S*,7*R*)-**12e** and (5*R*,3*R*,7*S*)-**12e**.

*4.4.1. N-((R)-1-phenylethyl)hexahydrofuro[3,4–c]pyrrol-1-ones (**12e**).* IR (film); $\tilde{\nu}$ [cm^{-1}]: 2973 (m), 2918 (m), 2798 (m), 1766 (s), 1476 (m), 1362 (m), 1132 (s), 1046 (m), 1002 (s), 765 (m), 702 (m). MS (ESI) *m*/*z*, (%): 254 ($M+Na^+$, 17), 232 ($M+H^+$, 100). HRMS *m*/*z*, ($C_{14}H_{18}NO_2$; $M+H^+$): calcd 232.1332; found 232.1331. To simplify assignment, hydrogen and carbon numbers identical to those of the monocyclic derivatives are applied. ^1H NMR (400 MHz, $CDCl_3$): δ=1.29 (d, J=6.7 Hz, 3H, CH_3CH and CH_3CH*); 2.16 (dd, J=6.5, 9.8 Hz, 1H, H5); 2.27 (dd, J=7.1, 9.6 Hz, 1H, H2*); 2.37 (dd, J=7.7, 9.1 Hz, 1H, H2); 2.38 (m, 1H, H5*); 2.51 (d, J=9.9 Hz, 1H, H5); 2.90 (m, 5H, H4, H2*, H3*, H4*, H5*); 2.99 (ddd, J=1.2, 7.8, 9.5 Hz, 1H, H3); 3.14 (q, J=6.7 Hz, 1H, CH_3CH); 3.18 (q, J=6.6 Hz, 1H, CH_3CH*); 3.40 (d, J=9.1 Hz, 1H, H2); 3.90 (dd, J=4.2, 9.1 Hz, 1H, H6); 4.08 (dd, J=3.5, 9.1 Hz, 1H, H6*); 4.37 (t, J=9.0 Hz, 1H, H6); 4.43 (dd, J=8.1, 9.1 Hz, 1H, H6*); 7.12–726 (m, 10H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.1 (q, CH_3CH*), 23.4 (q, CH_3CH), 37.5 (d, C4), 37.8 (d, C4*), 43.7 (d, C3*), 43.9 (d, C3), 55.8 (t, C2), 56.2 (t, C2*), 59.0 (t, C5*), 60.0 (t, C5), 64.1 (d, CH_3CH*), 64.3 (d, CH_3CH), 74.0 (t, C6*), 74.2 (t, C6), 127.1 (d, CH_{Ar}* and CH_{Ar}), 127.30 (d, CH_{Ar}), 127.33 (d, CH_{Ar}*), 128.65 (d, CH_{Ar}), 128.67 (d, CH_{Ar}*), 144.6 (s, C_{Ar}*), 145.2 (s, C_{Ar}), 179.8 (s, $C{=}O$*), 180.1 (s, $C{=}O$). Resonances marked with an * belong to minor (5*R*,3*R*,7*S*)-**12e**.

4.5. Reductive N–O bond cleavage of 6e obtained according to method B

A 3:1:2 diastereomeric mixture of (1*R*,3*S*,4*R*)-**6e**, (1*R*,3*R*,4*S*)-**6e**, and (1*R*,3*S*,4*S*)-**6e** (0.130 g, 0.29 mmol) was dispersed in a mixture of 1.8 mL acetic acid and 0.6 mL water. THF was added dropwise

until a homogeneous solution was formed (3.0 mL). Zinc dust (0.95 g, 14.6 mmol, 50 equiv) was added with vigorous stirring and the reaction mixture was heated at 85 °C for 3 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered. The filtrate was neutralized with saturated K_2CO_3 solution to a pH of ca. 10. The organic layer was separated, washed twice with water, dried over $MgSO_4$ and evaporated to give 87 mg of an oil, which was purified by flash chromatography (hexanes/EtOAc 7:1 to EtOAc) to give a 3:1:2 mixture of (1*R*,3*S*,4*R*)-**6e**, (1*R*,3*R*,4*S*)-**6e** and (1*R*,3*S*,4*S*)-**6e** (23 mg, 18%) and a partly separable 3:1 diastereomeric mixture of lactones (5*R*,3*S*,7*R*)-**12e** and (5*R*,3*R*,7*S*)-**12e** (19 mg, 28%) and (1*R*,3*S*,4*S*)-**11e** (16 mg, 18%).

*4.5.1. tert-Butyl 4-(hydroxymethyl)-1-(1-phenylethyl)pyrrolidine-3-carboxylate (**11e**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (d, *J*=6.7 Hz, 3H, C*H*$_3$CH); 1.35 (s, 9H, C(C*H*$_3$)$_3$); 2.36 (dd, *J*=6.4, 8.3 Hz, 1H, H2); 2.47 (m, 1H, H4); 2.51 (dd, *J*=7.3, 8.2 Hz, 1H, H5); 2.60 (br s, 1H OH); 2.74 (dt, *J*=4.2, 8.3 Hz, 1H, H3); 2.78 (t, *J*=8.4 Hz, 1H, H2); 2.83 (dd, *J*=2.4, 8.5 Hz, 1H, H5); 3.14 (q, *J*=6.6 Hz, 1H, CH$_3$C*H*); 3.58 (ddd, *J*=0.6, 4.2, 10.2 Hz, 1H, H6); 3.70 (dd, 1H, *J*=4.5, 10.2 Hz, H6); 7.13–7.27 (m, 5H, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.2 (q, *C*H$_3$CH), 28.2 (q, C(*C*H$_3$)$_3$), 43.6 (d, C4), 46.8 (d, C3), 56.0 (t, C2 or C5), 56.1 (t, C2 or C5), 65.2 (d, CH$_3$*C*H), 67.2 (t, C6), 81.1 (s, *C*(CH$_3$)$_3$), 127.2 (d, *C*H$_{Ar}$), 127.33 (d, *C*H$_{Ar}$), 128.6 (d, *C*H$_{Ar}$), 144.9 (s, *C*$_{Ar}$), 174.1 (s, *C*=O).

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.10.034.

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24. Crystal data for (5*R*,3*S*,7*R*)-**12e**: $C_{14}H_{17}NO_2$, orthorhombic, $P2_12_12_1$, a=5.5570(2), b=11.8157(3), c=18.5313(4) Å, Z=4, T=100 K. A colorless tablet 0.25×0.15×0.06 mm was used to record a total of 23458 data to 2θ(max) 151° using Cu $K\alpha$ radiation on an Oxford Diffraction Nova O diffractometer. The structure was refined using the program SHELXL-97 (G.M. Sheldrick, *Acta Cryst.* 2008, *A*64, 112–122) to *wR*2 0.080, *R*1 0.030 (all data) for 2512 independent data and 155 parameters. The Flack parameter refined to 0.06(18), thus determining the absolute configuration on the basis of the anomalous dispersion of oxygen. Complete crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 747054. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) 1 44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk].
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26. We thank a referee for the suggestion of **10** acting as a SET oxidant for enolates **7***.
27. Reagent **3** is stable to storage on the bench for more than 6 months. A gain of weight was not observed during storage. However, **3** is dried routinely prior to use in high vacuum at room temperature for 1–2 h. For the preparation of **3**, see: Ref. 25a.
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