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Transition Metal-Catalyzed Chlorine Transfer Cyclizations of Carbon-Centered Glycine Radicals; A Novel Synthetic Route to Cyclic α-Amino Acids

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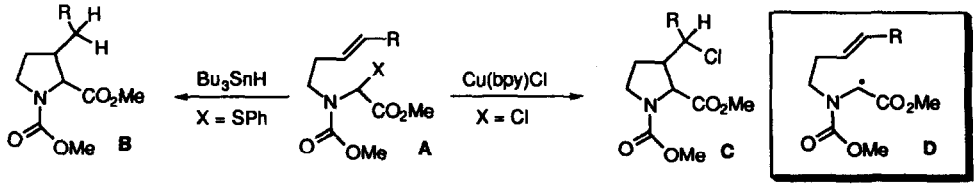
Abstract: Copper(I)-catalyzed chlorine transfer radical cyclizations of several α-chloroglycine derivatives with a 3-alkenyl substituent at nitrogen are reported. These reactions proceed via 2-aza-5-alken-1-yl radicals as intermediates which bear electron-withdrawing carbonyl substituents at the radical center and at nitrogen. These radicals can be considered as relatively stable captodative radicals, which are easily generated in the presence of Cu(bpy)Cl, but are reactive enough for olefin cyclization. The main products usually arise from 5-*exo* cyclization and are structurally interesting analogues of proline. An X-ray crystal structure of one of the cyclization products is presented.

INTRODUCTION

The development of radical cyclization reactions for synthetic purposes has been an area of active research since the early eighties. Although the tin hydride-mediated cyclization reactions in particular have proven very useful in organic synthesis,[1] the search for techniques which avoid the reductive step of the tin hydride process still continues. One of these techniques is the transition metal-catalyzed atom transfer radical cyclization, a method which is now well established.[2]

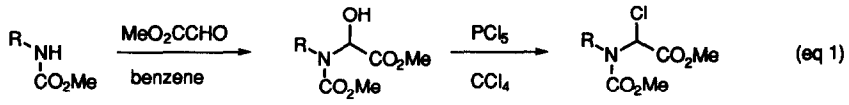


Recently,[3] we described the Bu_3SnH-mediated cyclization of α-(phenylthio)glycine derivatives **A** (X = SPh) to 3-substituted proline derivatives **B**. It was shown, that in spite of the presence of a pair of captodatively stabilizing substituents,[4,5] the 2-aza-5-hexenyl radical **D** is reactive enough for olefin cyclization. In this paper, we report on the efficient Cu(bpy)Cl-catalyzed chlorine transfer radical cyclization of α-chloroglycine derivatives **A** (X=Cl), leading to 3-(1-chloroalkyl)-substituted prolines **C**.[6] The structural features of radical **D** are important, as initial studies[7] on the use of Cu(bpy)Cl for these cyclization reactions indicated. Thus, we found that no products of radical cyclizations were formed, if the potential radical centre did not bear an ester substituent.

RESULTS AND DISCUSSION

Synthesis of radical cyclization precursors

The chlorides **1-7** (Table 1) were selected as substrates for the radical cyclizations. In addition to six 2-aza-5-hexenyl systems (**1-6**) we included a 2-aza-6-heptenyl system (**7**). These rather sensitive glycine derivatives were prepared as shown in eq 1. Addition of the appropriate *N*-monosubstituted carbamates (or 2-pyrrolidinone in the case of **2**) to methyl glyoxylate provided the stable hemiacetals, which have been described before.[3,8] Treatment of these glyoxylate adducts with PCl_5 in CCl_4[9] gave the required radical precursors in good yields (84 - 100%) as sensitive oils, virtually pure according to NMR.



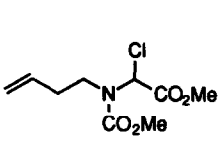
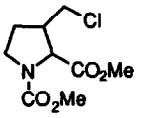
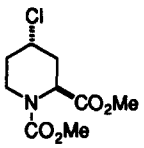
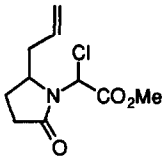
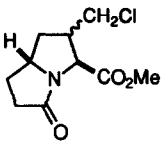
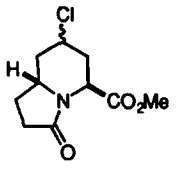
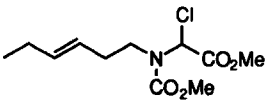
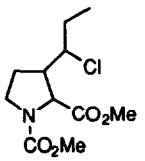
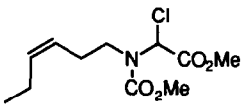
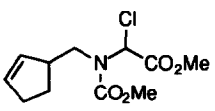
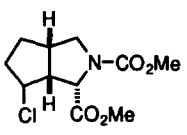
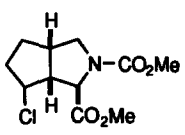
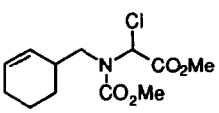
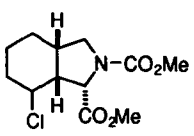
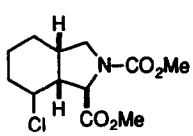
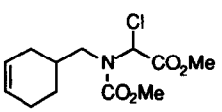
(eq 1)

Copper - catalyzed radical cyclizations

The radical cyclizations of precursors **1-7** were carried out in 1,2-dichloroethane solutions under a nitrogen atmosphere. The reactions were conducted in the presence of 30 mol% of a 1 : 1 molar mixture of copper(I) chloride and bpy in 0.3 M solutions with respect to the substrate. The cyclization conditions were optimized for the cyclization of the parent compound **1** (Table 1). Best results were obtained when the reaction was performed at 80 °C for 18 h. Cyclization took also place at lower temperatures (40 °C), but longer reaction times were then required. The reaction was carried out in a variety of other solvents. Tetrahydrofuran, dimethoxyethane and acetone were also suitable media for the the cyclization but these solvents gave rise to the formation of substantial amounts of the undesired reduced cyclization product **B** (R = H). Apparently, abstraction of a hydrogen atom from these solvents by the intermediate cyclized radical is competing with the the delivery of a chlorine atom by the copper complex.[10]

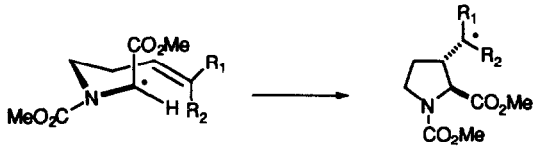
Table I summarizes the results of the cyclization reactions. In general, two types of regioisomeric cyclization products were obtained, i.e. those resulting from *endo*- and *exo*- cyclization modes. Only the monosubstituted alkenes **1** and **2** gave rise to the formation of 6-*endo* cyclization products. The Cu(bpy)Cl-catalyzed cylization of **1** gave a mixture of proline derivative **8** and the pipecolic acid derivative **9** with the 5-*exo* cyclization product predominating, while cyclization of the pyrrolidinone derivative **2** gave the six-membered ring product **11** as the major product. The regioselectivity for the cyclization of the disubstituted alkenes **3-6** was much higher, exclusive formation of the 5-*exo* cyclization products **12-14** being observed.

Table 1. Cu(bpy)Cl-catalyzed Radical Cyclization.

precursor	yield	products		
 **1**	86 %	 **8a,b** cis:trans = 40:60	71 : 29	 **9**
 **2**	66 %	 **10a,b** cis:trans = 17:83	18 : 82	 **11a,b** cis:trans = 39:61
 **3**	78 %	 **12a,b** cis:trans = 20:80		
 **4**	86 %	**12a,b** cis:trans = 34:66		
 **5**	75 %	 **13a**	12 : 88	 **13b**
 **6**	53 %	 **14a**	30 : 70	 **14b**
 **7**	–	no cyclization observed		

The nature of the double bond (*E* in **3** or *Z* in **4**) appeared of little importance for the stereochemical outcome of the cyclization, as was the ring size in **5** and **6**. The copper-catalyzed radical cyclizations to the proline derivatives gave the 2,3- *trans*-substituted pyrrolidines as the major products in all cases. This result is in agreement with the rules advanced by Beckwith and coworkers[11], if one assumes as the most favourable situation a quasi-axial orientation of the ester substituent in a chair-like transition state of cyclization (equation 2). The axial orientation of the ester group is a result of pseudo-allylic 1,3-strain caused by the *N*-carbonyl function.[3,12] The corresponding cyclizations to the oxygen heterocycles (O instead of NCO_2Me) mainly give the *cis*-products as expected.[6,13]

The formation of a single isomer for the six-membered ring product **9** may be understood by considering an efficient shielding by the ester group of the axial face of the cyclized radical in the delivery of a chlorine atom by the copper complex. The formation of two diastereomers of **11** is not readily explained in a similar way, and indicates that other transition state geometries play a role in the 6-*endo* cyclization of **2**.



(eq 2)

Both **12a** and **12b** were formed as about 1 : 1 mixtures of diastereomers, revealing little stereoselectivity in the delivery of the chlorine atom to the intermediate radical by the copper complex. For the bicyclic fused prolines **13** and **14**, about 1 : 1 mixtures of diastereomers were obtained for **13b** and **14a**, while **13a** and **14b** were found as single isomers. Apparently, the stereoselectivity in the chlorine atom transfer from the copper complex to the radical intermediate is depending on the ring size.

In addition to cyclizations of 2-aza-5-hexenyl systems **1-6**, we also investigated the cyclization of a 2-aza-6-heptenyl system. Treatment of **7** with the copper catalyst did not lead to the formation of the desired 3-azabicyclo[3.3.1]nonane system. After the reaction, only uncyclized compounds, still containing the alkene function, were detected in the crude mixture. This failure may be explained in terms of a slower rate of cyclization for the 2-aza-6-heptenyl radical derived from **7** as compared to the 2-aza-5-hexenyl radicals derived from **1-6**. A similar difference in the rates of cyclization was also observed in the tin hydride-mediated radical cyclizations of the corresponding phenylthio analogues of **1-7**[3] (*vide infra*).

The stereochemistry at C-2 in the proline analogues **8**, **10**, **12**, **13** and **14** was inferred from the relative chemical shifts of the C-2 hydrogens in the *cis*- and *trans*-isomers in combination with their coupling constants. In the *cis*-isomers this hydrogen was found at relatively low field and it showed relatively large coupling constants, compared with the corresponding *trans*-isomers. Comparison with literature data on analogues of these proline derivatives obtained via Bu_3SnH-mediated radical cyclizations confirmed the assignments in these cases.[3] Furthermore, the stereochemistry of the major *trans*-diastereomer of **12b** was proven via an X-ray crystal structure determination (Figure 1). The bicyclic system **10** posed an additional problem. While the *cis*/*trans* relationship between ester and chloromethyl substituents is clear in both isomers, the orientation of the angular hydrogen in **10** remains tentative. The 6-*endo* cyclization products **9** and **11a** were already known in literature.[8] The stereochemistry of the chlorine substituent in **11b** was inferred from the NMR data of H-7, which showed a quintet with $J = 3.1$ Hz, thus indicating an equatorial orientation.

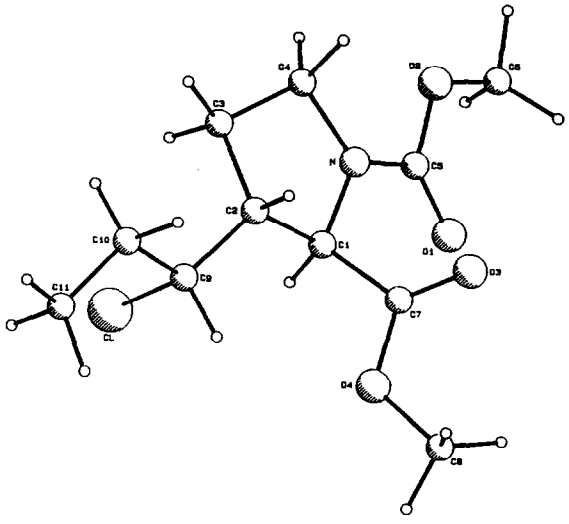
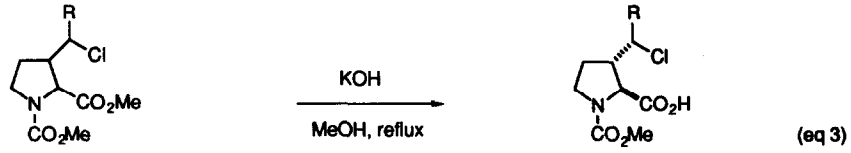


Figure 1. ORTEP diagram of **12b**.

The stereochemistry of the cyclization products was further elucidated after saponification of the cyclization products. Treatment of *cis/trans* mixtures of **8** or **12** with KOH in MeOH (equation 3) gave only the *trans*-substituted carboxylic acids **15** and **16**. Apparently, isomerization took place under these conditions, leading to the more stable *trans*-substituted proline derivative.[14] The complete *cis* to *trans* isomerisation of these cyclization products further enhances the synthetic utility of the novel route to proline analogues.



8a,b (R = H) *cis/trans* = 30 : 70
12a,b (R = Et) *cis/trans* = 20 : 80

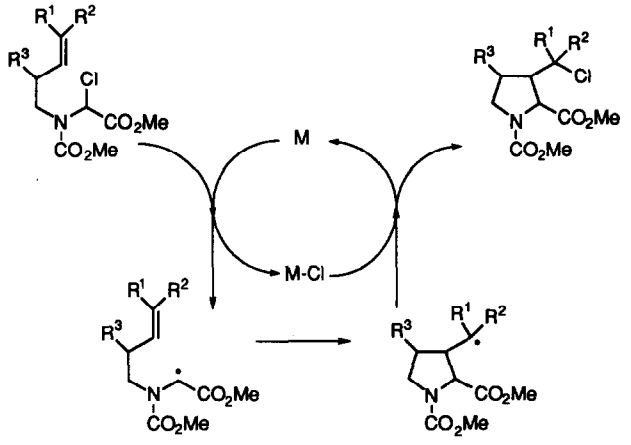
15 (R = H, 88 % yield)
16 (R = Et, 88 % yield)

(eq 3)

Comparison of the Cu(I)-catalyzed cyclization with the Bu_3SnH-mediated cyclizations

Earlier, we reported the Bu_3SnH-mediated cyclization of the phenylthio analogues of **1-7**.[3] The regioselectivity of these reductive cyclizations appears comparable to the copper-mediated radical cyclization of this paper, giving mainly *trans*-2,3-substituted proline derivatives. Similarly, the phenylthio analogues of **1** and **2** gave substantial amounts of 6-*endo* cyclization products. Cyclization of the phenylthio analogue of **7** was reported to give the desired 3-aza-[3.3.1]bicyclononane system in only 29 % yield, which reflects the difficulty of cyclization for this 2-aza-6-heptenyl system. In this respect, the failure to cyclize **7** with the copper catalyst is not unexpected.

The great similarities in regio- and stereoselectivity for both types of cyclization suggest that the reactive intermediates in the copper-catalyzed cyclization are the same as those in the free radical cyclization. This implies the generation of an incipient free radical which cyclizes unaffected by the copper complex. The catalyst acts as a carrier of the chlorine atom by way of a redox reaction between Cu(I) and Cu(II), as shown in Scheme 1. The generation of the incipient radical is probably facilitated by the presence of a pair of captodatively stabilizing substituents.[4,5] The use of bpy as a ligand probably enhances the ability of the copper centre to abstract a chlorine atom,[2e] resulting in relatively mild cyclization conditions.



Scheme 1. Transition metal-catalyzed radical cyclization.

In conclusion, the copper(I)-catalyzed cyclizations of 1,2-di(methoxycarbonyl)-2-aza-5-hexenyl radicals proceed with similar regio- and stereoselectivity as Bu_3SnH-mediated cyclizations of these captodative radicals. The use of Cu(bpy)Cl allows smooth cyclization to various new proline analogues, containing an extra halogen atom as compared to the products of the reductive cyclization method.

EXPERIMENTAL

General information. Experimental techniques and analytical measurements were applied as previously described.[15] IR spectral data are reported in cm^{-1} and NMR chemical shifts in ppm with $CDCl_3$ as a solvent (unless stated otherwise). CuCl was purified according to a literature procedure.[16]

General procedure for the conversion of alcohols to chlorides. To a solution of the alcohol (see eq 1) in CCl_4 (0.2 M) was added PCl_5 (1.03 equiv). The reaction mixture was stirred for 20 min. The excess PCl_5 was filtered off on a glas filter and the filtrate was concentrated in vacuo. The residue was dissolved in a small amount of EtOAc, and hexane (excess) was added. After stirring for 10 min, the white solid was filtered off on a glas filter and the solvent was removed in vacuo to give the chloride.

(But-3-enyl-methoxycarbonyl-amino)-chloro-acetic acid methyl ester (1). (But-3-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[8] (137.1 mg, 0.63 mmol) was treated with PCl_5 (135 mg, 0.648 mmol) in CCl_4 (3 ml) to give 1 as a light yellow oil (147.8 mg, 0.628 mmol, 100%). IR ($CHCl_3$) 3070, 3020, 3000, 2950, 1750, 1705, 1635, 1465, 1445, 1435, 1400. ^{1}H-NMR (200 MHz) 2.25-2.50 (m, 2H), 3.24-3.64 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 5.00-5.13 (m, 2H),

5.63-5.80 (m, 1H), 6.41 (s, 1H, CHCl).^{13}C-NMR (63 MHz) 32.92, 45.54, 53.42, 53.54, 70.10 (CHCl), 116.79, 134.51, 155.32 (NC=O), 165.55 (C=O).

(2-Allyl-5-oxo-pyrrolidin-1-yl)-chloro-acetic acid methylester (2). (2-Allyl-5-oxo-pyrrolidin-1-yl)-hydroxy-acetic acid methyl ester[8] (453 mg, 2.13 mmol) was treated with PCl_5 (456 mg, 2.19 mmol) in CCl_4 (10.7 ml) to give **2** as a light yellow oil (416.4 mg, 1.80 mmol, 84%). IR ($CHCl_3$) 3080, 3000, 2950, 1755, 1705, 1435, 1395. ^{1}H-NMR (200 MHz, 1:1 mixture of diastereomers) 1.75-1.95 (m, 1H), 2.05-2.70 (m, 5H), 3.77 (s) and 3.80 (s, 3H), 3.85-4.00 (m, 1H, NCH-allyl), 5.00-5.20 (m, 2H, $=CH_2$), 5.55-5.85 (m, 1H, CH=), 6.26 (s, 0.5H) and 6.43 (s, 0.5H, CHCl).

Chloro-(hex-3-(*E*)-enyl-methoxycarbonyl-amino)-acetic acid methyl ester (3). (Hex-3-(*E*)-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[8] (483.0 mg, 1.97 mmol) was treated with PCl_5 (423 mg, 2.03 mmol) in CCl_4 (7 ml) to give **3** as a light yellow oil (512.2 mg, 1.94 mmol, 99%). IR ($CHCl_3$) 3020, 2950, 1755, 1710, 1465, 1435, 1400. ^{1}H-NMR (200 MHz) 0.96 (t, J = 7.5 Hz, 3H), 2.00 (q, J = 7.1 Hz, 2H), 2.19-2.35 (m, 2H), 3.19-3.43 (m, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 5.28-5.58 (m, 2H), 6.41 (s, 1H, CHCl).

Chloro-(hex-3-(*Z*)-enyl-methoxycarbonyl-amino)-acetic acid methyl ester (4). (Hex-3-(*Z*)-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[8] (467.7 mg, 1.91 mmol) was treated with PCl_5 (409 mg, 1.97 mmol) in CCl_4 (6.4 ml) to give **4** as a light yellow oil (499 mg, 1.89 mmol, 99%). IR ($CHCl_3$) 3020, 2950, 1755, 1710, 1465, 1435, 1400. ^{1}H-NMR (200 MHz) 0.95 (t, J = 7.5 Hz, 3H), 2.05 (q, J = 7.4 Hz, 2H), 2.25-2.45 (m, 2H), 3.20-3.45 (m, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 5.20-5.35 (m, 1H), 5.42-5.55 (m, 1H), 6.44 (s, 1H, CHCl).

Chloro-(cyclopent-2-enyl-methoxycarbonyl-amino)-acetic acid methyl ester (5). (Cyclopent-2-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[3] (450 mg, 1.85 mmol) was treated with PCl_5 (397.1 mg, 1.91 mmol) in CCl_4 (9.3 ml) to give **5** as a light yellow oil (460.7 mg, 1.76 mmol, 95%). IR ($CHCl_3$) 3020, 2950, 2840, 1760, 1710, 1460, 1435. ^{1}H-NMR (200 MHz, 1:1 mixture of diastereomers) 1.40-1.65 (m, 1H), 1.90-2.15 (m, 1H), 2.20-2.50 (m, 2H), 2.95-3.15 (m, 1H, C*H*CH_2N), 3.10-3.55 (m, 2H, CH_2N), 3.77 (s) and 3.78 (s, 3H), 3.81 (s) and 3.83 (s, 3H), 5.55-5.85 (m, 2H, CH=CH), 6.08 (s, 0.5H) and 6.18 (s, 0.5H, CHCl).

Chloro-(cyclohex-2-enyl-methoxycarbonyl-amino)-acetic acid methyl ester (6). (Cyclohex-2-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[3] (317.7 mg, 1.24 mmol) was treated with PCl_5 (267.3 mg, 1.28 mmol) in CCl_4 (6.2 ml) to give **6** as a light yellow oil (341.7 mg, 1.24 mmol, 100%). IR ($CHCl_3$) 3020, 2950, 2910, 2830, 1760, 1710, 1465, 1435. ^{1}H-NMR (200 MHz, 1:1 mixture of diastereomers) 1.20-1.85 (m, 4H, CH_2), 1.85-2.05 (m, 2H, CH_2), 2.35-2.55 (m, 1H, C*H*-CH=), 3.05-3.25 (m, 1H, CH_2N), 3.30-3.45 (m, 1H, CH_2N), 3.74 (s, 3H), 3.78 (s) and 3.79 (s, 3H) 5.40-5.60 (m, 1H, CH=), 5.65-5.80 (m, 1H, CH=), 6.03 (s, 0.5H) and 6.11 (s, 0.5H, CHCl).

Chloro-(cyclohex-3-enyl-methoxycarbonyl-amino)-acetic acid methyl ester (7). (Cyclohex-3-enyl-methoxycarbonyl-amino)-hydroxy-acetic acid methyl ester[3] (735 mg, 2.86 mmol) was treated with PCl_5 (613 mg, 2.94 mmol) in CCl_4 (14 ml) to give **7** as a light yellow oil (807 mg, 2.93 mmol, 100%). IR ($CHCl_3$) 3020, 2950, 2910, 2830, 1760, 1710, 1465, 1435. ^{1}H-NMR (200 MHz, 1:1 mixture of diastereomers) 1.10-1.35 (m, 1H), 1.55-2.20 (m, 6H), 3.05-3.30 (m, 1H), 3.30-3.50 (m, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 5.65 (s, 2H), 6.09 (s, 0.5H) and 6.11 (s, 0.5H, CHCl).

General Procedure for the Cuprous Chloride Catalyzed Cyclization. To a solution of the precursor in 1,2-dichloroethane (0.3 M) in a dry nitrogen atmosphere was added first 0.3 equiv of bpy and then 0.3 equiv of CuCl. The resulting clear, reddish brown solution was heated at reflux for at least 18 h. The crude reaction mixture was directly brought on a column for flash chromatography.

Cyclization of 1. To a solution of **1** (105.2 mg, 0.447 mmol) in 1.5 mL of 1,2-dichloroethane was added bpy (21 mg, 0.13 mmol) and CuCl (13 mg, 0.13 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave three fractions. The first fraction consisted of **(2R*, 4R*)-4-chloro-piperidine-1,2-dicarboxylic acid dimethyl ester (9)**

(26.5 mg, 0.113 mmol, 25%) as a colourless oil. R_f 0.40 (EtOAc/hexane 1:4). Spectroscopic data of **9** were identical to literature data.[8] The second fraction consisted of a 50:50 mixture of **8a** and **8b** (52 mg, 0.221 mmol, 49%) as a colourless oil. R_f 0.10 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2950, 2890, 1745, 1690, 1450. Spectroscopic data derived from this mixture for **(2R*, 3R*)-3-chloromethyl-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (8a)**: ^{1}H-NMR (300 MHz, selected signals) 2.70-2.95 (m, 1H, H-3), 4.40 (d, J = 8.2 Hz) and 4.45 (d, J = 8.2 Hz, H-2 two rotamers). ^{13}C-NMR (50 MHz, selected signals) 60.8 and 61.1 (C-2, two rotamers). The third fraction consisted of **(2R*, 3S*)-3-chloromethyl-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (8b)** as a colourless oil (12.3 mg, 0.052 mmol, 12%). R_f 0.10 (EtOAc/hexane 1:4). IR ($CHCl_3$) 3000, 2950, 2890, 1745, 1690, 1450. ^{1}H-NMR (300 MHz) 1.82-1.97 (m, 1H), 2.08-2.22 (m, 1H), 2.59-2.71 (m, 1H, H-3), 3.50-3.70 (m, 4H, H-5 and CH_2Cl), 3.67 (s) and 3.72 (s, 3H, OCH_3 two rotamers), 3.76 (s) and 3.77 (s, 3H, OCH_3 two rotamers), 4.22 (d, J = 4.6 Hz) and 4.25 (d, J = 4.8 Hz, 1H, H-2 two rotamers). ^{13}C-NMR (50 MHz, most carbons show two peaks because of rotamers) 27.5 and 28.3 (C-4), 45.2 and 45.6 (C-5), 45.5 (CH_2Cl), 45.4 and 46.5 (C-3), 52.4 (OCH_3), 52.7 (OCH_3), 61.7 and 62.1 (C-2), 154.9 and 155.3 (NC=O), 172.1 (C=O). HRMS calculated for $C_9H_{14}NO_4Cl$ 235.0611, found 235.0623.

Cyclization of 2. To a solution of **2** (403.2 mg, 1.74 mmol) in 5.8 mL of 1,2-dichloroethane was added bpy (82 mg, 0.52 mmol) and CuCl (52 mg, 0.52 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave three fractions. The first fraction consisted of **(5R*, 7R*, 8aS*)-7-chloro-3-oxo-octahydro-indolizine-5-carboxylic acid methyl ester (11a)** (65.5 mg, 0.283 mmol, 16.3%). as a colourless oil. R_f 0.33 (EtOAc/hexane 4:1). Spectroscopic data for **11a** were identical to literature data.[8] The second fraction consisted of a 6:20:49:25 mixture of **10a**, **10b**, **11a** and **11b**, (137 mg, 0.592 mmol, 34%). R_f 0.33, 0.28 and 0.25 (EtOAc/hexane 4:1). IR ($CHCl_3$) 2990, 2950, 1740, 1680, 1435. Spectroscopic data derived from this mixture for **(2R*, 3S*, 7aR*)-2-chloromethyl-5-oxo-hexahydro-pyrrolizine-3-carboxylic acid methyl ester (10a)**: ^{1}H-NMR (200 MHz, selected signals) 4.68 (d, J = 7.9 Hz, 1H, H-3). ^{13}C-NMR (50 MHz) 28.8 (C-7), 33.9 (C-6), 35.5 (C-1), 43.4 (CH_2Cl), 45.7 (C-2), 52.2 (OCH_3), 56.7 and 57.8 (C-3 and C-7a), 170.2 (C=O), 175.5 (C-5). HRMS calculated for $C_{10}H_{14}NO_3Cl$ 231.0662, found 231.0673. The third fraction consisted of a 18:82 mixture of **10b** and **11b** (62.0 mg, 0.268 mmol, 15.4%). R_f 0.28 and 0.25 (EtOAc/hexane 4:1). IR ($CHCl_3$) 2990, 2950, 1740, 1680, 1435. Spectroscopic data derived from this mixture for **(2S*, 3S*, 7aR*)-2-chloromethyl-5-oxo-hexahydro-pyrrolizine-3-carboxylic acid methyl ester (10b)**: ^{1}H-NMR (250 MHz, selected signals) 2.82-2.97 (m, 1H), 4.24 (d, J = 4.6 Hz, 1H, H-3). ^{13}C-NMR (50 MHz) 26.1 (C-7), 33.7 (C-6), 37.2 (C-1), 46.0 (CH_2Cl), 48.8 (C-2), 52.6 (OCH_3), 57.4 and 61.1 (C-3 and C-7a), 171.4 (C=O), 174.3 (C-5). Spectroscopic data derived from this mixture for **(5R*, 7S*, 8aS*)-7-chloro-3-oxo-octahydro-indolizine-5-carboxylic acid methyl ester (11b)**: ^{1}H-NMR (250 MHz, selected signals) 4.45 (quintet, J = 3.1 Hz, 1H, H-7eq), 4.72 (d, J = 7.1 Hz, 1H, H-5eq). ^{13}C-NMR (50 MHz) 25.2 (C-1), 29.9 (C-2), 33.2 (C-6), 39.9 (C-8), 47.9 (C-5), 48.7 (C-7), 52.4 (OCH_3), 54.5 (C-8a), 170.7 (C=O), 174.8 (C-3). HRMS calculated for $C_{10}H_{14}NO_3Cl$ 231.0662, found 231.0680.

Cyclization of 3. To a solution of **3** (434.6 mg, 1.650 mmol) in 5.5 mL of 1,2-dichloroethane was added bpy (77.3 mg, 0.495 mmol) and CuCl (49.0 mg, 0.495 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave three fractions. The first fraction consisted of a 87:13 mixture of **(2R*, 3R*)-3-(1-chloro-propyl)-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (12a1 and 12a2)** (47.6 mg, 0.181 mmol, 11%) as a colourless oil. R_f 0.25 (EtOAc/hexane 1:3). IR 2950, 1740, 1690, 1450, 1390. Spectral data derived from this mixture for **12a1**: ^{1}H-NMR (250 MHz) 1.02 (t, J = 7.2 Hz, 3H), 1.63-1.79 (m, 1H), 1.93-2.26 (m, 3H), 2.53-2.70 (m, 1H, H-3), 3.26-3.44 (m, 1H), 3.58-3.76 (m, 2H), 3.62 (s), 3.62 (s), 3.69 (s) and 3.71 (s, 6H), 4.33 (d) and 4.40 (d, J = 7.9 Hz, 1H, H-2 two rotamers). ^{13}C-NMR (63 MHz, most carbons show two peaks because of rotamers) 10.86, 27.24 and 28.40 (C-4), 30.88, 45.21 and 45.62 (C-5), 48.71 and 49.52 (C-3), 52.21, 52.61, 60.78 and 60.99 (C-2), 64.11 and 64.34 (CCl), 154.62 and 155.28 (NC=O), 171.04 (C=O). Spectral data derived from this mixture for **12a2**: ^{1}H-NMR (250 MHz, characteristic signals) 4.54 (d) and 4.60 (d, J = 7.6 Hz, H-2 two rotamers). HRMS calculated for $C_{11}H_{18}NO_4Cl$ 263.0924, found 263.0916. The second fraction consisted of a 14:86 mixture of **12a2 and**

12b (138.0 mg, 0.524 mmol, 32%) as a colourless oil. According to ^{1}H-NMR, **12b1:12b2** = 65:35. The third fraction consisted of a 53:47 mixture of **(2R*, 3S*)-3-(1-chloro-propyl)-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (12b1 and 12b2)** (152.2 mg, 0.577 mmol, 35%) as a colourless oil containing white cristals. R_f 0.20 (EtOAc/hexane 1:3). IR 2950, 1740, 1690, 1450, 1390. Spectroscopic data derived from this mixture for **12b2**: ^{1}H-NMR (200 MHz, characteristic signals) 2.60-2.74 (m, 1H, H-3), 3.80-3.91 (m, 1H, CHCl), 4.38-4.41 (m, 1H, H-2). ^{1}H-NMR (200 MHz, benzene-*d*, characteristic signals) 4.54 (d) and 4.61 (d, J = 4.7 Hz, 1H, H-2 two rotamers). ^{13}C-NMR (50 MHz, characteristic signals, most carbons show two peaks because of rotamers) 27.21 and 28.18 (C-4), 29.07, 45.49 and 45.82 (C-5), 61.02 and 61.33 (C-2), 66.09 (CCl), 154.58 (NC=O), 172.42 (C=O). HRMS calculated for $C_{11}H_{18}NO_4Cl$ 263.0924, found 263.0903. Recrystallization from diisopropyl ether (twice) gave a sample of **(2R*, 3S*, 6R*)-3-(1-chloropropyl)-pyrrolidine-1,2-dicarboxylic acid dimethyl ester (12b1)**. Mp = 78-79 °C. IR 2950, 1740, 1690, 1450, 1390. ^{1}H-NMR (200 MHz) 1.07 (t, J = 7.2 Hz, 3H), 1.66-2.14 (m, 4H), 2.35-2.65 (m, 1H, H-3), 3.38-3.52 (m, 1H), 3.65-3.85 (m, 1H), 3.67 (s), 3.71 (s), 3.75 (s) and 3.77 (s, 6H), 3.95-4.08 (m, 1H, CHCl), 4.27 (d) and 4.32 (d, J = 6.7 Hz, 1H, H-2 two rotamers). ^{13}C-NMR (63 MHz, most carbons show two peaks because of rotamers) 11.33 and 11.40 (alkyl-CH_3), 25.34 and 25.43 (C-4), 30.03, 45.79 and 46.30 (C-5), 49.42 and 50.54 (C-3), 52.38, 52.66, 61.62 and 62.16 (C-2), 65.43 (CHCl), 155.18 (NC=O), 172.75 (s, C=O). Anal. calcd. for $C_{11}H_{18}NO_4Cl$: C, 50.10; H, 6.88; found: C, 50.16; H, 6.82. The X-ray crystal structure of this major diastereomer was determined (see Figure 1).[17] Crystallographic data: triclinic, P-1; a = 7.0235(4) Å, b = 9.3030(4) Å, c = 11.4165(5) Å; α = 103.354(4) °, β = 101.578(9) °, γ = 106.669(5) °; V = 666.16(9) Å^3; Z = 2; CuK-α-radiation, λ = 1.5418 Å. Final R = 0.049 for 2411 reflections.

Cyclization of 4. To a solution of **3** (448.5 mg, 1.702 mmol) in 5.7 mL of 1,2-dichloroethane was added bpy (79.8 mg, 0.511 mmol) and CuCl (50.5 mg, 0.511 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave three fractions. The first fraction consisted of a 87:13 mixture of **12a1 and 12a2** (73.3 mg, 0.278 mmol, 16.3%) as a colourless oil. R_f 0.25 (EtOAc/hexane 1:3). The second fraction consisted of a 38:62 mixture of **12a and 12b** (147.4 mg, 0.5594 mmol, 32.9%) as a colourless oil. According to ^{1}H-NMR, **12a1:12a2** = 38:62 and **12b1:12b2** = 69:31). R_f 0.25 and 0.20 (EtOAc/hexane 1:3). The third fraction consisted of a 50:50 mixture of **12b1 and 12b2** (163.3 mg, 0.620 mmol, 36.4%) as a colourless oil containing white cristals. R_f 0.20 (EtOAc/hexane 1:3).

Cyclization of 5. To a solution of **5** (430.8 mg, 1.65 mmol) in 5.5 mL of 1,2-dichloroethane was added bpy (77 mg, 0.49 mmol) and CuCl (49 mg, 0.49 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave two fractions. The first fraction consisted of a 83:17 mixture of **13b1** and **13a** as a colourless oil (225 mg, 0.86 mmol, 53%). R_f 0.27 (EtOAc/hexane 1:3). IR ($CHCl_3$) 3000, 2950, 2870, 1740, 1690, 1450. *Spectroscopic data derived from this mixture for* **(1R*, 3aR*, 6aS*)-6-chloro-hexahydro-cyclopenta[c]pyrrole-1,2-dicarboxylic acid dimethyl ester (13b1)**: ^{1}H-NMR (200 MHz) 1.40-1.60 (m, 1H), 1.80-2.35 (m, 3H), 2.75-3.15 (m, 2H, H-3a and H-6a), 3.30-3.50 (m, 1H, H-3), 3.64 (s) and 3.67 (s, 3H, OCH_3 two rotamers), 3.72 (s, 3H), 3.60-3.80 (m, 1H, H-3), 4.05-4.25 (m, 2H, H-1 and H-6). ^{1}H-NMR (200 MHz, benzene-*d*) 0.75-0.95 (m, 1H), 1.30-1.80 (m, 3H), 2.10-2.40 (m, 1H, H-3a), 2.55-2.70 (m, 1H, H-6a), 3.00-3.75 (m, 3H, H-3 and H-6), 3.28 (s, 3H), 3.42 (s) and 3.44 (s, OCH_3 two rotamers), 4.18 (d, J = 2.0 Hz) and 4.33 (d, J = 2.9 Hz, 1H, H-1 two rotamers). ^{13}C-NMR (63 MHz, most carbons show two peaks because of rotamers) 30.3 and 35.9 (C-4 and C-5), 39.5 and 40.7 (C-3a), 52.4, 52.7, 53.3 and 53.7 (C-3), 58.0 and 59.2 (C-6a), 63.2 and 63.6 (C-1), 64.1 (C-6), 155.0 and 155.5 (NC=O), 171.9 (C=O). Spectroscopic data derived from this mixture for **(1R*, 3aS*, 6aR*)-6-chloro-hexahydro-cyclopenta[c]pyrrole-1,2-dicarboxylic acid dimethyl ester (13a)**: ^{1}H-NMR (200 MHz, characteristic signals) 3.00-3.20 (m, 1H), 4.51 (d, J = 8.8 Hz, 1H, H-1). ^{13}C-NMR (63 MHz, characteristic signals) 27.4 and 37.1 (C-4 and C-5), 52.1 (OCH_3), 52.5 (C-3), 59.4 (CH), 61.2 (CH), 170.1 (C=O). HRMS calculated for $C_{11}H_{16}NO_4Cl$ 261.0768, found 261.0758. The second fraction consisted of **(1R*, 3aR*, 6aS*)-6-chloro-hexahydro-cyclopenta[c]pyrrole-1,2-dicarboxylic acid dimethyl ester (13b2)** as a colourless oil (93.5 mg, 0.357 mmol, 22%). R_f 0.13 (EtOAc/hexane 1:3). IR ($CHCl_3$) 3000, 2950, 2870, 1740, 1685, 1450. ^{1}H-

NMR (200 MHz) 1.60-1.80 (m, 1H), 1.85-2.15 (m, 3H), 2.70-2.95 (m, 2H, H-3a and H-6a), 3.25-3.50 (m, 1H), 3.85 (s) and 3.68 (s, 3H, OCH_3 two rotamers), 3.71 (s, 3H), 3.70-3.85 (m, 1H), 4.30-4.45 (m, 1H, H-6), 4.62 (broad s) and 4.66 (broad s, 1H, H-1 two rotamers). ^{13}C-NMR (63 MHz, most carbons show two peaks because of rotamers) 30.2 and 36.8 (C-4 and C-5), 40.1 and 41.2 (C-3a), 52.3, 52.6, 53.2 and 54.1 (C-6a), 54.3 and 54.6 (C-3), 61.1 and 61.5 (C-1), 62.2 (C-6), 154.7 and 155.1 (NC=O), 172.8 (C=O). HRMS calculated for $C_{11}H_{16}NO_4Cl$ 261.0768, found 261.0758.

Cyclization of 6. To a solution of **6** (320.0 mg, 1.16 mmol) in 3.9 mL of 1,2-dichloroethane was added bpy (54 mg, 0.35 mmol) and CuCl (35 mg, 0.35 mmol). The reaction mixture was heated at reflux for 18 h. Flash chromatography gave a 70:11:19 mixture of **14b**, **14a1** and **14a2** as a colourless oil (168 mg, 0.61 mmol, 53%). R_f 0.23 and 0.20 (EtOAc/hexane 1:3) IR ($CHCl_3$) 3000, 2950, 2870, 1740, 1690, 1450. Spectroscopic data derived from this mixture for **(1R*, 3aS*, 7aR*)-7-chloro-octahydro-isoindole-1,2-dicarboxylic acid dimethyl ester (14b)**: ^{1}H-NMR (200 MHz, benzene-*d*, characteristic signals) 2.20-2.40 (m, 1H), 4.58 (d, *J* = 1.2 Hz) and 4.67 (d, *J* = 2.2 Hz, 1H, H-7 two rotamers). ^{13}C-NMR (63 MHz, most carbons show two peaks because of rotamers) 20.3 and 20.4, 23.5 and 23.7 (C-4 and C-5), 34.1 and 34.5 (C-6), 35.4 and 36.1 (C-3a), 48.1 and 48.2 (C-3), 51.3 and 52.1 (C-7a), 52.2 (OCH_3), 52.5 (OCH_3), 58.7 and 59.0, 62.5 and 62.6 (C-1 and C-7), 155.2 and 155.7 (NC=O), 171.7 (C=O). Spectroscopic data derived from this mixture for **(1R*, 3aR*, 7aS*)-7-chloro-octahydro-isoindole-1,2-dicarboxylic acid dimethyl ester (14a1)**: ^{1}H-NMR (200 MHz, benzene-*d*, characteristic signals) 4.14 (d, *J* = 7.9 Hz) and 4.32 (d, *J* = 7.9 Hz, 1H, H-1 two rotamers). Spectroscopic data derived from this mixture for **(1R*, 3aR*, 7aS*)-7-chloro-octahydro-isoindole-1,2-dicarboxylic acid dimethyl ester (14a2)**: ^{1}H-NMR (200 MHz, benzene-*d*, characteristic signals) 2.55-2.70 (m, 1H), 4.34 (d, *J* = 8.0 Hz) and 4.47 (d, *J* = 8.0 Hz, 1H, H-1 two rotamers), 4.15-4.30 (m, 1H, H-7). HRMS calculated for $C_{12}H_{18}NO_4Cl$ 275.0924, found 275.0901.

Attempted cyclization of 7. To a solution of 7 (752.1 mg, 2.73 mmol) in 9 mL of 1,2-dichloroethane was added bpy (128 mg, 0.82 mmol) and CuCl (81 mg, 0.81 mmol). The reaction mixture was heated at reflux for 18 h. A ^{1}H-NMR spectrum of the crude reaction mixture was obtained after filtration through a short silica column (eluting with EtOAc). All starting material was gone, but no cyclization product could be detected.

Saponification of 8. A 30:70 mixture of **8a** and **8b** (50 mg, 0.21 mmol) was dissolved in 0.7 ml of 2% KOH in methanol. The mixture was heated at reflux for 18 h. After evaporation of the volatiles, water (5 ml) was added and the pH was adjusted to pH = 1 with 2M HCl. The water layer was extracted with CH_2Cl_2 (3x 10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. This gave **(2R*, 3S*)-3-chloromethyl-pyrrolidine-1,2-dicarboxylic acid 1-methyl ester (15)** (41 mg, 0.185 mmol, 88%) as a colourless oil. IR 3500-2500 (broad, CO_2H), 1720 (C=O), 1690 (NC=O). ^{1}H-NMR (200 MHz) 1.84-2.21 (m, 2H, H-4),), 2.69-2.82 (m, 1H, H-3), 3.43-3.76 (m, 4H, H-5 and CH_2Cl), 3.69 (s) and 3.74 (s, 3H, OCH_3), 4.24 (d, *J* = 6.4 Hz) and 4.27 (d, *J* = 5.1 Hz, 1H, H-2 two rotamers), 9.20 (broad s, 1H, COOH). ^{13}C-NMR (50 MHz, most carbons show two peaks because of rotamers) 27.4 and 28.2 (C-4), 45.0 and 46.5 (C-3), 45.4 (CH_2Cl), 45.6 (broad, C-5), 52.9 and 53.1 (OCH_3), 61.4 and 61.9 (broad, C-2), 155.2 and 156.1 (NC=O), 175.1 and 176.2 (broad, C=O). MS EI 178 (33) and 176 ((M^+-CO_2H), 100).

Saponification of 12. A 20:80 mixture of **12a** and **12b** (23.2 mg, 0.088 mmol; **12a1/12a2** = 62:38, **12b1/12b2** = 58:42) was dissolved in 0.3 ml of 2% KOH in methanol. The mixture was heated at reflux for 3 h. After evaporation of the volatiles, water (5 ml) was added and the pH was adjusted to pH = 1 with 2M HCl. The water layer was extracted with CH_2Cl_2 (3x 10 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. This gave **(2R*, 3S*)-3-(1-chloro-propyl)-pyrrolidine-1,2-dicarboxylic acid 1-methyl ester (16)** (19.4 mg, 0.0778 mmol, 88%) as a colourless oil, a 60:40 mixture of diastereomers. IR 3500-2500 (broad, CO_2H), 1720 (C=O), 1690 (NC=O). ^{1}H-NMR (200 MHz) 1.07 (t, *J* = 7.2 Hz) and 1.08 (t, *J* = 7.2 Hz, 3H), 1.73-2.15 (m, 4H), 2.60-2.95 (m, 1H, H-3), 3.39-3.75 (m, 2H, H-5), 3.70 (s) and 3.75 (s, 3H, OCH_3), 3.80-3.95 (m, 0.4H, CHCl), 4.04-4.11 (m, 0.6H, CHCl), 4.30-4.40 (m, 0.6H, H-2), 4.45-4.50 (m, 0.4H, H-2), 8.00 (bs,

1H, COOH). ^{1}H-NMR (200 MHz, benzene-*d*) 0.80 (t, *J* = 7.1 Hz, 3H), 1.27-1.70 (m, 4H), 2.31-2.37 (m, 1H, H-3), 3.12-3.85 (m, 3H), 3.42 (s) and 3.45 (s, 3H, OCH_3), 4.46 (d, *J* = 6.7 Hz) and 4.52 (d, *J* = 6.7 Hz, 0.4H, H-2), 4.59 (d, *J* = 4.1 Hz) and 4.64 (d, *J* =4.1 Hz, 0.6H, H-2), 9.66 (bs, 1H, COOH). ^{13}C-NMR (50 MHz, characteristic signals, most carbons show two signals because of rotamers) 60.96 and 61.02 (C-2 minor isomer), 61.33 and 61.98 (C-2 major isomer), 65.40 (CCl major isomer), 66.38 and 66.51 (CCl minor isomer), 154.96 and 156.26 (NC=O), 175.50 and 175.54 (C=O major isomer), 175.82 and 175.84 (C=O minor isomer). MS EI 206 (33) and 204 ((M^+-CO_2H), 100).

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REFERENCES AND NOTES

1. For reviews of radical cyclizations including atom transfer methods, see: (a) Giese, B. *Radicals in Organic Synthesis: formation of carbon-carbon bonds;* Pergamon: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Jasperse, C.P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715-832.
2. For recent references to atom transfer cyclizations, see: (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem.Soc.* **1988**, *110*, 7536. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Mori, M.; Kubo, Y.; Ban, Y. *Heterocycles* **1990**, *31*, 433. (e) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985. (f) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281. (g) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933. (h) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9410. (i) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (j) Belvisi, L.; Gennari, C.; Poli, G; Scolastico, C.; Salom, B. Vassallo, M. *Tetrahedron* **1992**, *48*, 3945. (k) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682. (l) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141. (m) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R.; Ónega, M. G.; Ruíz, M. *Tetrahedron* **1992**, *48*, 1637. (n) Nagashima, H.; Ozaki, N; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464. (o) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Tatsunori, S.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360.
3. Esch, P. M.; Hiemstra, H.; De Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659.
4. Viehe, H. G.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.*, **1985**, *18*, 148.
5. For a recent paper on the captodative radical stabilization of glycidyl radicals, see: Schulze, R.; Beckhaus, H.-D.; Rüchardt, C. *Chem. Ber.* **1993**, *126*, 1031.
6. Part of this work was published as a communication: Udding, J. H.; Hiemstra, H.; Van Zanden, M. N.

A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 3123.

7. See for a detailed discussion on the synthetic significance of captodatively stabilized glycine radicals in copper(I)-catalyzed chlorine transfer cyclizations: Udding, J. H.; Tuijp, C. J. M.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Perkin 2* **1992**, 857.
8. Esch, P. M.; Boska, I. M.; Hiemstra, H.; De Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**,*47*, 4039.
9. a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. b) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.
10. A similar abstraction of hydrogen atoms from the solvent is described by Weinreb and coworkers in the Ru(II)-catalyzed radical cyclization of ethyl 2,2-dichloro-6-heptynoate with toluene or cumene as a solvent, see: Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am Chem. Soc.* **1988**, *110*, 5533.
11. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
12. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
13. (a) Lolkema, L. D. M.; Hiemstra, H.; Al Ghouch, A. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 1491. (b) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
14. Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270.
15. Udding, J. H.; Fraanje, J.; Goubitz, K.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 425
16. Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.
17. Experimental details of the X-ray structure determination of **12b1**, ORTEP representation of **12b1**, and tables of fractional atomic coordinates, thermal parameters, and interatomic distances and angles for **12b1** were deposited by the Editor at the Cambridge Crystallographic Data Centre.

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