Protecting/Radical Translocating Chiral Auxiliaries: A New Concept in Radical-Mediated Asymmetric Synthesis

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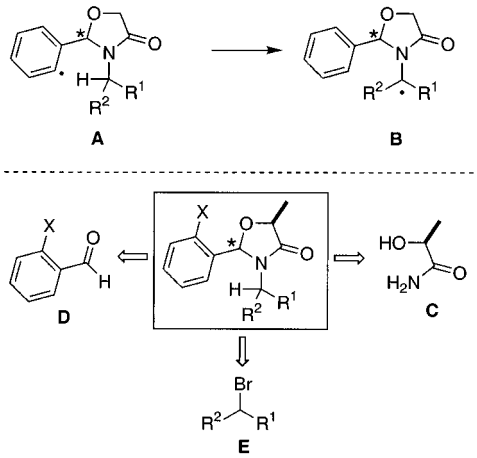
1-Amidoalkyl radicals are highly interesting intermediates for the synthesis of biologically active compounds such as alkaloids, unusual amino acids, and other nitrogen-containing molecules.[1,2] However, the generation of these radicals is often problematic due to the instability of the radical precursors. Excellent results have been obtained by using translocation of hydrogen atoms.[3] The development of protecting/radical translocating (PRT) groups[4,5] represents an efficient and attractive method for the generation of 1-amidoalkyl radicals.[6−17] We present here the first examples where the PRT group also plays the role of a chiral auxiliary.[18−21] This approach has been applied to the preparation of α-alkylated amino acid and 1-substituted primary amine derivatives. The general strategy is outlined in Scheme 1; the amido-substituted radical **B** is generated from the initial aryl radical **A** via a 1,5-hydrogen atom transfer. This approach involves three components: lactic acid **C** (more precisely lactamide) as primary source of chirality, 2-halobenzaldehyde **D** as radical precursor/secondary source of chirality,[22] and finally an alkyl halide **E** as carbon skeleton for the final amine.

Table 1. Radical Deuteration of 2, 3, 5, and 6 with Bu_3SnD According to Eq 1

entry	precursor	R	R$^\alpha$	*T* (°C)	product	H-transfer[a] (%)	yield[b] (%)	dr[c]
1	**2**	H	H	80	**7**	96	81	60:40
2	**2**	H	H	10	**7**	41	83	73:27
3	**3**	H	Me	80	**8**	44	76	89:11
4	**3**	H	Me	10	**8**	28	78	96:4
5	**5**	Me	H	80	**9**	95	80	64:36
6	**5**	Me	H	10	**9**	64	83	80:20
7	**5**	Me	H	10	**9**	95	53	86:14[d]
8	**6**[e]	Me	Me	80	**10**	97	88	84:16[f]
9	**6**[e]	Me	Me	10	**10**	77	79	98:2[f]

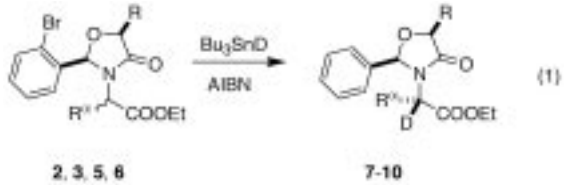
[a] Percentage of translocated product, the rest to 100% being the product of direct reduction. [b] Isolated yields of reduced product (translocation and direct reduction). [c] Determined by ^{1}H and ^{2}H NMR. [d] In trifluoroethanol instead of benzene. [e] Starting from **6**-*cis*/**6**-*trans* 65:35. [f] Identical ratios of diastereomers were obtained for the cis and trans isomers.

Scheme 1



It was anticipated that the stereochemical outcome of the radical reactions would be controlled by the stereogenic acetal center and not by the α-center of lactic acid. Therefore, and for the sake of simplicity, the first experiments were run with a simple model system derived from glycolic acid. The radical precursors **2** and **3** were prepared by acetalization of glycolamide with 2-bromobenzaldehyde followed by N-alkylation of the oxazolidinone **1** with ethyl bromoacetate and ethyl 2-bromopropionate, respectively (Scheme 2). Similarly, the racemic and the enantiopure radical precursors **5** and **6** were prepared from racemic and (*S*)-lactamide. The oxazolidinone **4** was isolated as a cis/trans 66:34 mixture of isomers, which were N-alkylated. The cis and trans diastereomers of **5** were separated by column chromatography, and the reactions were run with the major cis isomer. The radical precursor **6** was used as a 65:35 cis/trans mixture.

The reduction of the radical precursors **2**, **3**, **5**, and **6** with tributyltin deuteride was first examined (eq 1), results are summarized in Table 1. The diastereoselectivities were



(1)

measured by ^{1}H and ^{2}H NMR. The experiments with the

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Scheme 2

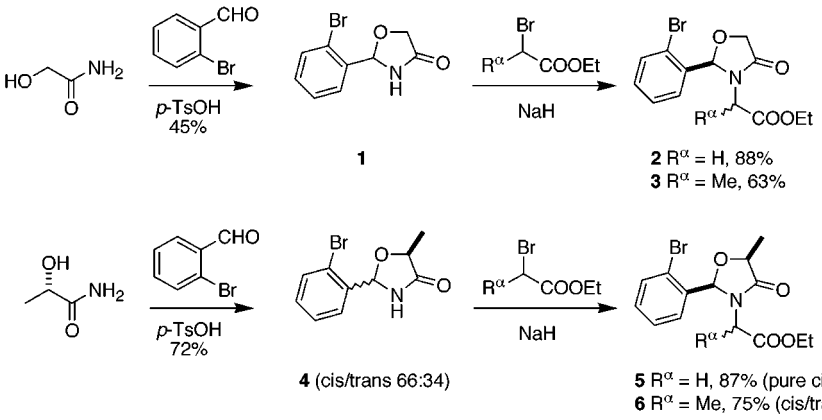


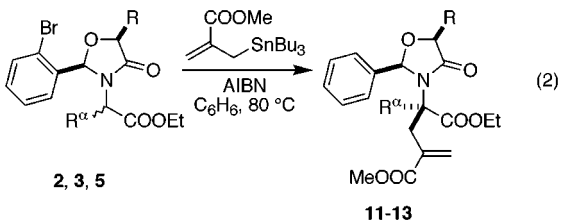
Table 2. Radical Allylation of 2, 3, 5, and 6 with Methyl 2-[(Tributylstannyl)methyl]propenoate at 80 °C According to Eq 2

entry	pre-cursor	R	R^α	prod-uct	yield[a] (%)	dr[b]
1	**2**	H	H	**11**	59	66:34
2	**2**	H	H	**11**	61	84.16[c]
3	**3**	H	Me	**12**	74	98:2
4	**5**	Me	H	**13**	85	72:28

[a] Isolated yields. [b] Determined by ^{1}H and ^{2}H NMR. [c] At 10 °C.

glycolamide derivatives (Table 1, entries 1−4) showed that 1,5-hydrogen transfers were occurring with a satisfactory efficiency at 80 °C (Table 1, entries 1 and 3). The transfer was less efficient at 10 °C (Table 1, entries 2 and 4), but the diastereoselectivity was enhanced (entries 1 vs 2 and 3 vs 4). The only detected side products were the products of direct reduction. Interestingly, the alanine derivative **3** (R^α = Me) gave much higher diastereoselectivities (up to 96:4 at 10 °C) than the glycine derivative **2** (R^α = H). This trend was confirmed with the lactamide-derived radical precursors **5** and **6** (Table 1, entries 5−9). With these two compounds, the ratio of hydrogen transfer was in all cases superior to 64%. The glycine derivative **5** gave moderate stereoselectivities at 80 °C (Table 1, entry 5, dr 64:36). However, a much better stereocontrol was achieved at 10 °C (Table 1, entry 6, dr 80:20). The reaction in trifluoroethanol was even slightly more stereoselective (Table 1, entry 7, dr 86:14). The reaction of the alanine derivative **6** (cis/trans 65:35) gave an excellent diastereoselectivity at 10 °C (Table 1, entry 9, cis dr 98:2, trans dr 98:2). The major cis and trans products have the opposite configuration at the newly formed stereogenic center (α center) (see the Supporting Information). This confirms the hypothesis that the stereoselectivtiy is fully controlled by the acetal center.

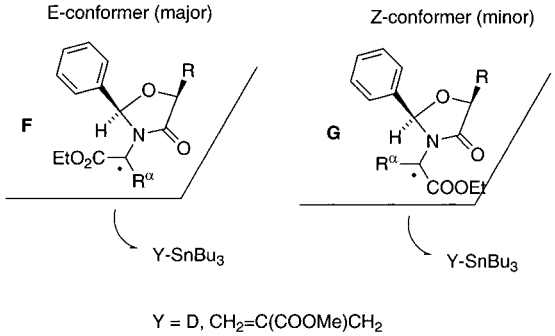
A series of allylation reactions was conducted with methyl 2-[(tributylstannyl)methyl]propenoate (eq 2). The results are



(2)

shown in Table 2. The desired products **11**−**13** are formed in satisfactory yields (59−85%). The diastereoselectivities are higher than the corresponding deuteration, but the same trends can be observed: (a) moderate diastereocontrol with the glycine derivative **2** and **5** at 80 °C (Table 2, entries 1 and 4) which is noticeably enhanced at 10 °C (Table 2, entry 2, dr 84:16) and (b) high selectivity with the alanine derivative **3** (Table 2, entry 3, dr 98:2).

Scheme 3



Y = D, CH_2=C(COOMe)CH_2

The relative configuration of **10** was established by comparison with an authentic sample prepared by an alternative synthesis starting from ethyl L-(−)-lactate and ethyl L-(+)-alanine hydrochloride (see the Supporting Information). The relative stereochemistry of the other products has not been proved but attributed by analogy (same reaction topicity). A possible rationalization of the stereochemical outcome is given in Scheme 3. The radical intermediate exists preferentially in the E conformation (model **F**). We assume that the radical lies in this conformation because it minimizes dipole−dipole interactions between the ester and the amide moiety.[23] Moreover, the minor Z conformer (model **G**) is further destabilized when R^α is a methyl group by steric repulsion with the phenyl group. This explains the observed enhancement of stereoselectivity when R^α is a methyl group relative to a hydrogen atom.

In conclusion, we have demonstrated that oxazolidinones prepared from lactic acid and 2-bromobenzaldehyde are suitable for the generation of glycinyl and alaninyl radicals and for the control of the stereochemistry of the subsequent reactions. Relative to classical methods of alkylation of amino acids, this approach offers promising opportunities for the synthesis of cyclic amino acids by taking advantage of unique radical cyclizations. Further work in this direction is currently underway.

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Supporting Information Available: Detailed experimental procedures and spectral data (^{1}H NMR, ^{13}C NMR, IR, MS, and elemental analyses) for compounds **1**−**13** and assessment of the relative configuration of **10** by chemical correlation (13 pages).

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