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# Chirality Multiplication and Efficient Chirality Transfer in *exo*- and *endo*-Radical Cyclization Reactions of 4-(4′-Iodobutyl)quinolones

**Martina Dressel and Thorsten Bach***

*Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany*

*thorsten.bach@ch.tum.de*

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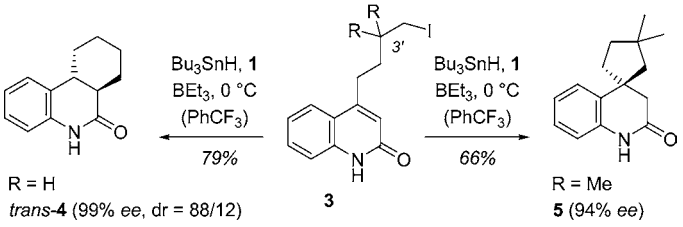
## ABSTRACT




**Enantioselective radical cyclization reactions were performed in the presence of chiral complexing agent 1. The title compounds 3 yielded, depending on the 3′-substitution (R = H, Me), the corresponding *endo*- (4) or *exo*-product (5). The highest enantioselectivities (99% and 94% ee) were achieved with 2.5 equiv of complexing agent. The cyclization product *trans*-4 was obtained in 55% ee in the presence of only 0.1 equiv of complexing agent.**

In recent years, enantioselective radical reactions have emerged as a powerful tool for the construction of stereogenic carbon atoms by C−C or C−H bond formation.[1] Reagent-controlled enantioselectivity has been achieved by the use of chiral hydrogen donor reagents.[2] Alternatively, the radical trapping agent[3] or the radical itself[4] can be embedded in a chiral environment by appropriate complexation. Chiral Lewis acids have been the complexing agents of choice for the latter strategy.[5] Catalytic processes (chirality multiplication) are possible as a result of Lewis acid induced substrate activation. Enantioselective radical cyclization reactions have been rarely reported.[6]

Our approach to enantioselective radical reactions aims at an association of the radical or its precursor to the chiral complexing agent **1** by *hydrogen bonding*.[7] Previously, we have shown that hydrogen atom transfer reactions to pro-

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stereogenic radicals can occur in up to 88% ee at −78 °C.[8] In preliminary experiments, we have now studied radical cyclization reactions of prochiral substrates and found these reactions to be highly enantioselective even at 0 °C (up to 99% ee) or at ambient temperature (up to 96% ee). These experiments open a conceptually new route to highly enantioselective radical cyclization reactions. The results surpass by far the enantioselectivities we have previously achieved using complexing agent **1**. Moreover, an unexpected chirality multiplication was observed. Complexing agent **1**

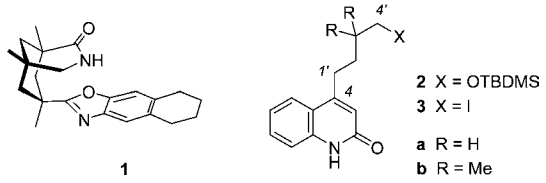
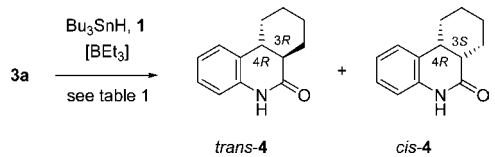



**Figure 1.** Structure of the enantiomerically pure complexing agent **1**, of the synthetic intermediates **2**, and of the prochiral radical precursors **3**.

is obtained in either enantiomeric form from Kemp's triacid.[9,10] The synthesis includes five steps (61% yield) and a conventional resolution with menthyl chloroformate. Compound **1** features a hydrogen bond donor (NH) and a hydrogen bond acceptor (C═O) site. In nonpolar solvents it binds lactams efficiently and facilitates a differentiation of their enantiotopic faces due to the bulky tetrahydronaphthalene backbone.[11] For the present study, the 4-(4′-iodobutyl)-quinolones **3** were prepared from 4-methylquinolone. Deprotonation and alkylation with the corresponding 3-*tert*-butyldimethylsilyl(TBDMS)oxy-1-iodopropane gave the silyl ethers **2**, which were converted into the iodides **3** by deprotection and iodo-dehydroxylation (see Supporting Information for further details). Radical reactions of the unsubstituted iodide **3a** were initially attempted at low temperature in toluene with $BEt_3$ as initiator and $Bu_3SnH$ as reducing agent. Because there was no conversion, the reaction was conducted at 25 °C. Under these conditions the racemic 6-*endo*-cyclization products **4** were formed with the *cis*-diastereoisomer prevailing (Scheme 1, Table 1, entry 1).

**Scheme 1**




Reactions in the presence of superstoichiometric (2.5 equiv) amounts of complexing agent **1** resulted in high ee's

**Table 1.** Reaction Conditions, Yields, and Diastereo- and Enantioselectivities in the Radical Cyclization of Substrate **3a** (Scheme 1)

| entry | **1**[a] [equiv] | temp [°C] | solvent | yield[b] [%] | dr[c] | ee[d] (*trans*-**4**) |
|---|---|---|---|---|---|---|
| 1 | | 25 | $PhCH_3$ | 99 | 47/53 | |
| 2 | 2.5 | 25 | $PhCH_3$ | 99 | 63/37 | 80 |
| 3 | 2.5 | 25 | $PhCF_3$ | 84 | 77/23 | 96 |
| 4 | 2.5 | 0 | $PhCH_3$ | 82 | 87/13 | 96 |
| **5** | **2.5** | **0** | **$PhCF_3$** | **79** | **88/12** | **99** |
| 6 | 1.0 | 0 | $PhCH_3$ | 86 | 70/30 | 86 |
| 7 | 1.0 | 0 | $PhCF_3$ | 88 | 73/26 | 91 |
| 8 | 0.5 | 0 | $PhCH_3$ | 91 | 63/37 | 70 |
| 9 | 0.5 | 0 | $PhCF_3$ | 86 | 67/33 | 82 |
| 10 | 0.25 | 0 | $PhCH_3$ | 85 | 54/46 | 46 |
| 11 | 0.25 | 0 | $PhCF_3$ | 87 | 53/47 | 62 |
| 12 | 0.1 | 0 | $PhCF_3$ | 82 | 54/46 | 55 |

[a] The reaction was conducted at a substrate concentration of 15 mM with 2.0 equiv of $Bu_3SnH$ and 0.5 equiv of $BEt_3$ (see Supporting Information). [b] Yield of isolated product. [c] The diastereomeric ratio (dr) *trans*-**4**/*cis*-**4** was determined by $^1H$ NMR spectroscopy and GLC analysis. [d] The enantiomeric excess (ee) was determined by chiral GLC (2,3-di-*O*-methyl-6-*O*-TBDMS-$\beta$-cyclodextrin).

both at 25 °C (entry 2) and at 0 °C (entry 4) for the predominant *trans*-diastereoisomer *trans*-**4**. Even with stoichiometric (entry 6) and substoichiometric amounts (entries 8 and 10) of the complexing agent the ee's remained moderate to good. A major improvement was achieved upon replacing the solvent toluene with trifluorotoluene. Selectivities significantly increased under all conditions (entries 3, 5, 7, 9), and catalytic reactions could be conducted with 25 and 10 mol % of **1** (entries 11, 12).

Proof for the absolute configuration of compounds **4** was obtained from their specific rotation.[12] In addition, the GLC retention times for all stereoisomers of compound **4** are known.[12b] Recovery yields of the complexing agent were in all cases higher than 90%. In this respect, entry 5 describes the synthetically most useful conditions combining high yield, high diastereoselectivity, and high enantioselectivity.

The effective chirality transfer and the chirality multiplication in the reaction **3a** → *trans*-**4** is presumably linked to the low solubility of the substrate **3a** in trifluorotoluene. The reaction mixture remained heterogeneous throughout the reaction. It is likely that complexing agent **1** dissolves the substrate and allows the radical reaction to occur under homogeneous conditions. A model explaining the outcome of the reaction both with regard to enantioselectivity and diastereoselectivity is suggested in Figure 2. The stereogenic

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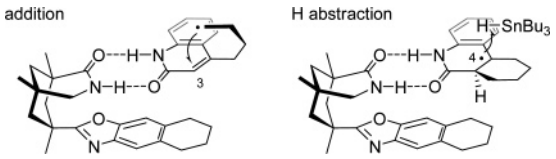
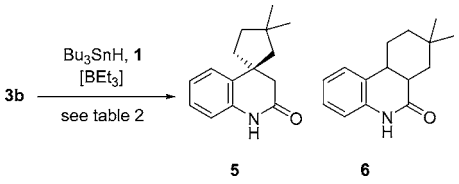



**Figure 2.** Model to explain the enantioselectivity and the diastereoselectivity of the radical cyclization to compound *trans*-**4**.

center at C-3 is formed in the radical addition step, the stereogenic center at C-4 in the hydrogen abstraction step. Both steps occur from the face opposite to the tetrahydronaphthalene of the complexing agent.

The radical cyclization of precursor **3b** occurred with regioselectivity different from that of **3a**. The 5-*exo*-product was formed predominantly. In the absence of any complexing agent the regioisomeric ratio **5**/**6** was 65/35. In the presence of the complexing agent the 6-*endo*-product **6** was not detected (Scheme 2, Table 2) and the 5-*exo*-product **5** was the exclusive product.

**Scheme 2**




The radical cyclization to **5** allowed us to access directly the enantioselectivity of the cyclization (addition) step. Best results were obtained in trifluorotoluene as the solvent with 2.5 equiv of **1** at 0 °C (entry 5). Both yields and enantioselectivities decreased upon reducing the amount of complexing agent (entries 6, 7). In comparison to the reaction **3a** → *trans*-**4** the product ee's were generally inferior under otherwise identical conditions (cf. Tables 1 and 2).

The lower enantioselectivity achieved with **3b** as compared to that of **3a** can be accounted for by the two selection steps involved in the formation of *trans*-**4** from **3a**. A cyclization of **3a** to the minor enantiomeric (3*S*)-radical does not necessarily lead to the formation of the enantiomer of *trans*-**4** but rather leads to the formation of *cis*-**4**. In addition, reactions **3a** → **4**, which do not occur on the template, show a slight preference for *cis*-**4** (Table 1, entry 1). The enantioselectivity for the formation of *cis*-**4** was consequently lower in all experiments than for *trans*-**4**.

The *endo*-regioselectivity observed in the cyclization of substrate **3a** is likely due to the formation of a stabilized benzylic radical.[13] Stereoelectronic factors,[14] which favor the chair-type transition state of the *exo*-cyclization, become more important in the cyclization of substrate **3b**. The rate constant for 5-*exo*-ring closure of the 2,2-dimethyl-5-hexenyl radical is (at 80 °C) higher by a factor of 10 than for the 5-hexenyl radical.[15] It is not fully clear at present why the complexing agent further increases the 5-*exo*-selectivity in the reaction **3b** → **5**/**6**. Inspection of molecular models suggests that the interaction of a 1′-H atom and the tetrahydronaphthalene part of the complexing agent is more severe in the transition state of the 6-*endo*-cyclization of **3b** than in the chairlike transition state of the 5-*exo*-cyclization. Further studies are underway to further elucidate the selectivity issues and to extend the described method to other radical reactions.

**Table 2.** Reaction Conditions, Yields, and Regio- and Enantioselectivities in the Radical Cyclization of Substrate **3b** (Scheme 2)

| entry | **1**[a] [equiv] | temp [°C] | solvent | yield[b] [%] | rr[c] | ee[d] (**5**) |
|---|---|---|---|---|---|---|
| 1 | | 25 | $PhCH_3$ | 76 | 65/35 | |
| 2 | 2.5 | 25 | $PhCH_3$ | 64 | >95/5 | 55 |
| 3 | 2.5 | 25 | $PhCF_3$ | 62 | >95/5 | 69 |
| 4 | 2.5 | 0 | $PhCH_3$ | 66 | >95/5 | 90 |
| **5** | **2.5** | **0** | **$PhCF_3$** | **66** | **>95/5** | **94** |
| 6 | 1.0 | 0 | $PhCF_3$ | 59 | >95/5 | 75 |
| 7 | 0.5 | 0 | $PhCF_3$ | 43 | >95/5 | 62 |

[a] The reaction was conducted at a substrate concentration of 15 mM with 2.0 equiv of $Bu_3SnH$ and 0.5 equiv of $BEt_3$ (see Supporting Information). [b] Yield of isolated product. [c] The regioisomeric ratio (rr) **5**/**6** was determined by $^1H$ NMR spectroscopy and GLC analysis. [d] The enantiomeric excess (ee) was determined by chiral GLC (2,3-di-*O*-methyl-6-*O*-TBDMS-$\beta$-cyclodextrin).

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**Supporting Information Available:** Experimental procedures for the preparation of compounds **2** and **3**, experimental details for the radical cyclization reactions, analytical data for all new compounds, and NMR spectra of **3a**, **3b**, *trans*-**4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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