Transfer of Chirality in Radical Cyclizations. Cyclization of *o*-Haloacrylanilides to Oxindoles with Transfer of Axial Chirality to a Newly Formed Stereocenter

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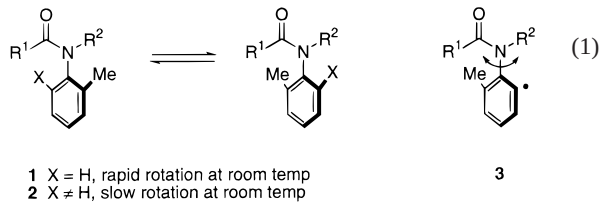
Control of stereoselectivity has become an increasingly important concern as the use of radical reactions in organic synthesis has continued to mature.[1] Because the development of asymmetric radical reactions lagged well behind asymmetric reactions of other types, it is logical that ionic, transition metal, and pericyclic reactions have often served both as inspirations for designing asymmetric radical reactions and as touchstones for comparison of results.[1d] However, several asymmetric reactions have recently emerged that capitalize on the transient nature of radicals and are therefore not so easily related back to traditional models in other areas.[2] For example, stereoselection at the steady state is a fundamental new strategy to control stereochemistry that has only been executed to date with radicals.[3]

Transfer of chirality is another area where the speed of radical reactions offers unique options. Rychnovsky has recently shown that stereocontrol in reactions of certain tetrahydropyranyl radicals depends on the configuration of the radical precursor.[4] And Giese has shown that photocyclizations of certain amino acids involving diradicals can be stereoselective even though the key stereocenter is destroyed in the process.[5] In this communication, we report examples of a new class of transfer of chirality. Axially chiral *o*-haloacrylamides cyclize to alkyl-substituted lactams with a high level of stereoinduction. Even though the chirality axis is destroyed in the process, the products faithfully "remember"[6] the configuration of their precursors. An analysis of the results suggests that it may be possible to extend this type of transfer of chirality beyond radical chemistry.

Equation 1 summarizes several key observations culled from the literature that underlie the design of the experiments reported herein. Despite resonance considerations, *N*-alkyl-*N*-*o*-tolylamides

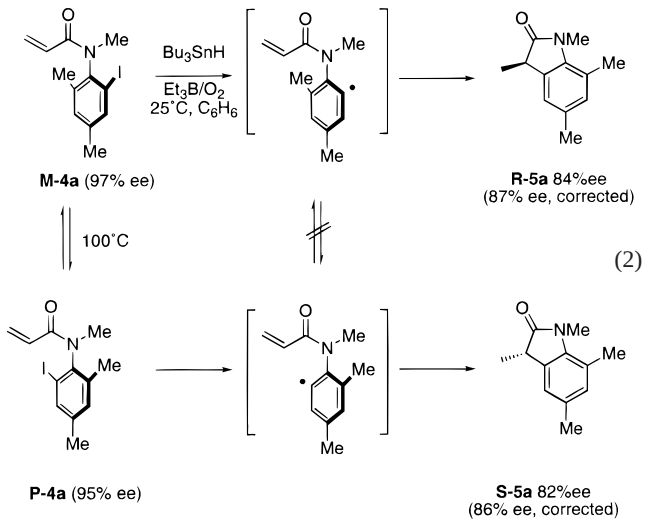


(1)

such as **1** are not planar, and indeed the two planes of the amide and the aryl ring are nearly orthogonal.[7] Barriers for rotation (enantiomerization) of the *N*-aryl bond are in the neighborhood of 19 kcal/mol, so the enantiomers interconvert readily at room temperature. In contrast, doubly ortho-substituted anilides such as **2** have barriers well over 25 kcal/mol, so they can be resolved (provided that X ≠ CH_3).[8] If X is a radical precursor, then radical **3** can be generated. The rotation barrier of **3** is unclear but it is likely somewhat less than that of **1**. Nonetheless, there could still be a very significant barrier, and we hypothesized that cyclization reactions of radicals **3** would show a memory effect of their precursors **2**.

To test this hypothesis, we initially prepared acrylanilide derivatives **M-4a** and **P-4a**, measured their rotation barrier, and then studied the cyclizations of the derived radicals. If C−NAr bond rotation is faster than cyclization, then racemic products must result from enantiopure starting materials. But if cyclization is faster, then chirality transfer is possible. Iodide **M-4a** was synthesized by a chiral pool route starting from lactic acid[9] with chromatographic separation of the diastereomers.[10] The absolute configuration of **M-4a** was assigned through a crystal structure on one of the synthetic intermediates.[10] Highly enantioenriched samples (≥95% ee) of **M-4a** and **P-4a** were racemized by heating at 100−110 °C. The rotation barrier was measured to be 30.8 kcal/mol. This high rotation barrier results in stable enantiomers at room temperature, as anticipated in eq 1.

Cyclizations of **M-4a** and **P-4a** were then conducted at room temperature with Bu_3SnH as the radical chain reagent and Et_3B/O_2 for initiation.[11] The concentration of **4a** was 0.01 M in benzene, and reactions took less than 1 h. The oxindole product **5** is no longer axially chiral due to the lactam ring, but there is a new stereocenter formed during the course of the reaction. The ee's of the products were measured by HPLC with an analytical (*S,S*)-Whelk-O1 column.[12] The data for these experiments are summarized in eq 2. Precursors **M-4a**/**P-4a** cyclize to give **R-5**/**S-5a**



(2)

in about 65% isolated yield (80−87% NMR yield) with about 86−87% ee. These results prove that radical cyclization is faster

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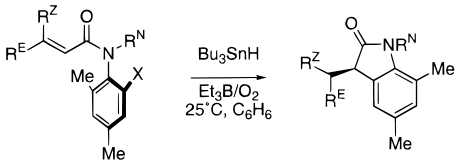
Table 1. Cyclizations with Transfer of Axial Chirality



M- 4b-e **R-5b-e**

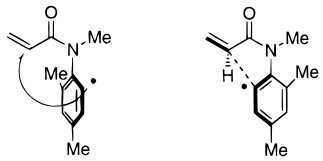
entry	precursor	R^N	R^E	R^Z	X	product	yield,[a] %	ee,[b] %
1	**M-4b-I**	Me	Me	H	I	**R-5b**	73	89
2	**P-4b-I**	Me	Me	H	I	**S-5b**	70	85
3	**M-4b-Br**	Me	Me	H	Br	**R-5b**	60	92
4	**P-4b-Br**	Me	Me	H	Br	**S-5b**	60	87
5	**M-4c**	Me	Ph	H	I	**R-5c**	75	94
6	**P-4c**	Me	Ph	H	I	**S-5c**	73	92
7	**M-4d**	Me	Me	Me	I	**R-5d**	91	49
8	**P-4d**	Me	Me	Me	I	**S-5d**	88	50
9	**M-4e**	Et	Me	H	I	**R-5e**	93	90
10	**P-4e**	Et	Me	H	I	**S-5e**	86	90

[a] Determined by NMR against an internal standard. [b] Corrected for ee of **4**, which was 95−98%.

than C−NAr bond rotation. The absolute configuration of the products is readily predicted from a model (see below, eq 3), and this was tentatively confirmed by calculation of the sign and magnitude of rotation of **5** by the method of Kondru, Wipf, and Beratan.[13]

The generality of the method was probed by synthesizing a number of related substrates **4b**−**e** and studying their cyclizations. The data for this series of experiments are summarized in Table 1. These substrates were all synthesized in racemic form and then resolved by semipreparative chiral HPLC. All the cyclizations occurred in good yield, and ee's tended to be slightly better than those in the parent system. Traces of directly reduced, noncyclized products (<10%) were detected in some experiments. These products were identified by comparison to authentic samples, but were not isolated. As expected, bromide and iodide precursors of the same radical produced the same products in about the same ee (compare entries 1,3 and 2,4). The dimethylacrylate substrate (entries 7,8) is the only substrate studied with a *Z*-alkene substituent, and this gave a reduced ee of about 50%. The absolute configurations of the products were all assigned by analogy to the results in eq 2. The validity of this analogy is supported by a reliable trend in the chiral HPLC separation; the first eluting enantiomer of the precursor always provides the second eluting enantiomer of the product.

Prior to the experiments, we had predicted the sense of chirality transfer from the crude model shown in eq 3. These acrylanilides



6 **7**

radical in front attacks alkene front face (3)

are known to exist with an *s-cis* acryloyl group and an E amide (oxygen trans to the Ar ring).[7,8] Inspection of this conformation suggests that the cyclization of the radical must occur to the front face of the alkene, as shown in **6**. Clearly **6** is a ground-state model not a transition-state model, and the alkene and the aryl radical must rotate toward each other for cyclization to occur, as illustrated by **7**. The origin of the minor product is not clear at this point. It could result from rotation of the alkene away from the aryl radical to expose its other face, or it could result from rotation of the N−Ar bond (that is, racemization of the radical competes with cyclization).

The results clearly show that transfer of chirality occurs in these radical cyclizations. The products "remember" the absolute configuration of the precursors even though a cursory analysis would suggest that both enantiomeric precursors would pass through the same achiral intermediate. The cursory analysis misleads because the radical cyclization is faster than the process leading to racemization. Since there are already quite a number of related radical cyclizations in the racemic series,[14] this type of reaction has immediate synthetic utility. However, this utility is somewhat limited since the enantiopure precursors have to date only been made by chemical or chromatographic resolution. Extensions to other types of radical reactions in both the anilide and the benzamide[15] series should also be possible. Finally, given the relatively high bond rotation barriers involved in this series, it is probable that transfer of chirality can also be observed in nonradical reactions.[16]

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Supporting Information Available: Details of the separation, cyclization, and characterization for the reactions in Table 1 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For example, Overman and co-workers have reported catalytic asymmetric Heck reactions of related *o*-iodoanilides lacking the second *ortho* substituent. One possible origin (among several others) for the stereoselection in these reactions is that stereoselective insertion of the chiral catalyst into one of the (equilibrating) enantiomeric iodides (dynamic kinetic resolution) is followed by an insertion into the nearby C═C bond that is faster than N−Ar bond rotation. See: Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.