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Asymmetric Radical and Anionic Cyclizations of Axially Chiral Carbamates†

David B. Guthrie and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

curran@pitt.edu

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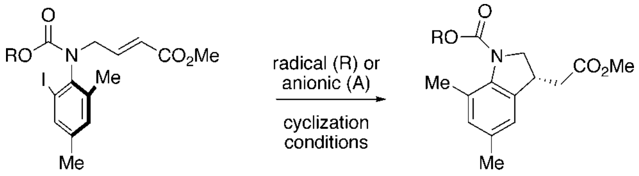
ABSTRACT



axial chirality of the precursor is erased, yet configuration is preserved in the new stereocenter of the product

Standard Boc, Alloc, and Cbz derivatives of *N*-2,4-dimethyl-6-iodophenyl-*N*-allyl anilines are axially chiral and can be readily resolved into atropisomers whose racemization barriers exceed 30 kcal/mol. The resolved axially chiral carbamates undergo radical and anionic cyclizations with high levels of chirality transfer from the N−Ar axis to the new stereocenter in the substituted dihydroindole products. The carbamate groups of the products are readily removed.

Axially chiral amides have emerged as valuable substrates for diverse classes of stereocontrolled reactions.[1] In particular, axially chiral anilides like **1** and **3** are accessible in highly enantioenriched form and often show very high levels of chirality transfer in radical cyclizations to provide products **2** and **4** (Figure 1).[2] In each of these cyclizations, the chiral axis in the precursor is erased, yet its configuration is preserved in the new stereocenter of the product. High chirality transfer has also been recorded in Heck reactions of axially chiral anilides related to **1**.[3] Recently, axially chiral diarylureas and diarylethers have also been synthesized and studied.[4]

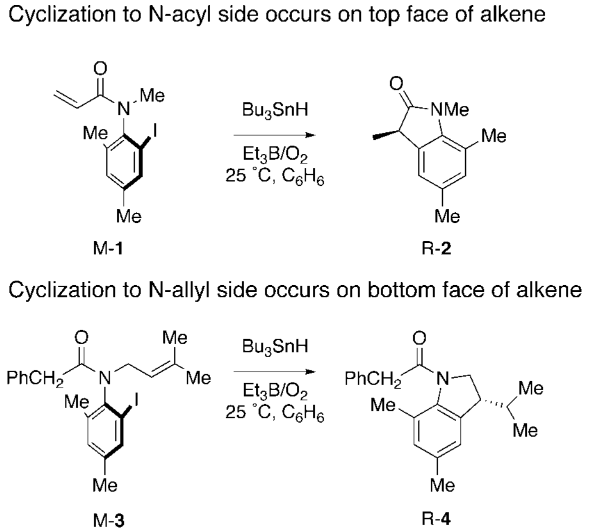


Figure 1. Radical cyclizations of axially chiral amides occur more rapidly than racemization by N−Ar bond rotation.

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† We dedicate this paper to Professor Larry Overman on the occasion of his 65th birthday.

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Cyclizations of substrates like **3** might have value in synthesis of chiral dihydroindoles (indolines) and related molecules, but the flexibility of the downstream chemistry is limited because the amide substituent of products like **4** can be difficult to remove. Herein we report that attractive intermediates bearing standard carbamate protecting groups on nitrogen can be accessed with high stereoselectivity through radical and anionic reactions of axially chiral carbamates.

Although rotation barriers for several *o*-substituted *N*-aryl carbamates have been measured[5a,b] and a stable carbamate atropisomer has recently been reported,[5c] to the best of our knowledge, these are the first asymmetric reactions of axially chiral carbamates. They are also the first examples of chirality transfer from an N−Ar axis to a stereocenter in an anionic cyclization.

Racemic substrates **5a**−**c** bearing *N*-allyloxycarbonyl (Alloc), *N*-*tert*-butyloxycarbonyl (Boc), and *N*-benzyloxy−carbonyl (Cbz) groups were readily prepared and resolved into their enantiomeric components by preparative chiral HPLC (see Supporting Information).[6] We expected that the carbamates might have lower rotation barriers than analogous amides because alkoxy groups are smaller than alkyl groups by most measures of size, including a measure based on biaryl rotation.[7] However, the resolved enantiomers of **5** were quite stable at room temperature during extended storage. Convenient racemization rates were accessed by heating samples in 90/10 hexane/isopropanol in sealed tubes at 115 °C. Rotation barriers were measured in the usual way and are shown in Figure 2.

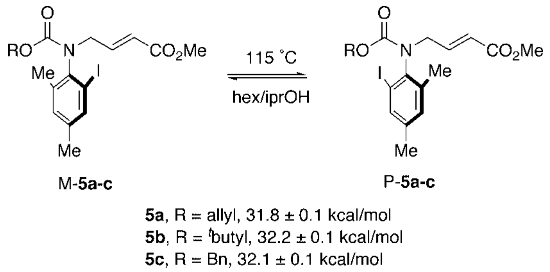


Figure 2. Structures and rotation barriers of axially chiral carbamates **5**.

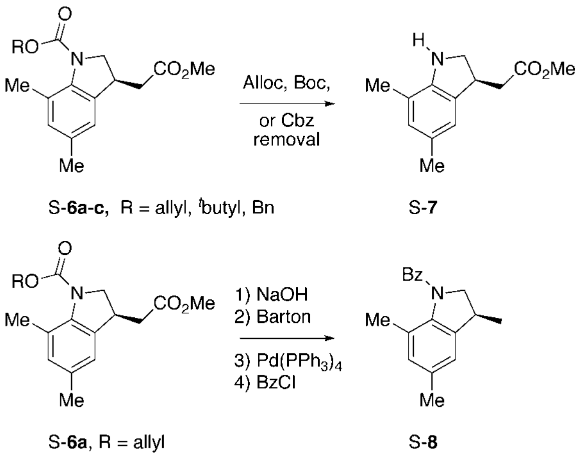
These barriers (~32 kcal/mol) are comparable to axially chiral amides bearing alkyl groups on the carbonyl carbon atom and larger than amides bearing aryl groups.[2] The surprisingly high barriers are convenient for handling ($t_{1/2}$ for racemization at 25 °C is several centuries) and for onward axial chirality transfer applications. For comparison, carbamates related to **5** but lacking the *ortho*-methyl group have a rotation barrier of about 19 kcal/mol ($t_{1/2}$ for racemization at 25 °C is a few seconds).[4a,b]

The yields and levels of chirality transfer in the radical and anionic cyclizations of substrates **5a**−**c** are summarized in Table 1. The radical cyclizations were conducted in benzene at ambient temperature by a standard procedure with tributyltin hydride (0.01 M) as the reductant and triethylborane as the initiator (conditions "R"). The yields of isolated, purified products **6a**−**c** were generally excellent (86−97%). The enantiomeric ratios of both the precursors and the products were assessed by chiral HPLC analysis to provide the level of chirality transfer of about 90%. This is comparable to the levels of chirality transfer typically observed in radical cyclizations of axially chiral amides like **3**.[2c,d]

Anionic cyclizations of **5** were conducted at −98 °C with *n*-BuLi and TMSCl in THF/ether/hexane (conditions "A")[8] without compromising either the carbamate or the ester functionalities. After standard workup and purification, the isolated yields of the products **6** were somewhat lower than in the radical reactions (68−74%); however, the levels of chirality transfer were even higher (>90%). In each case, a given enantiomer of the precursor **5** produced the same major enantiomer of the product **6** in both the radical and organolithium cyclizations. The anionic cyclization conditions proved quite general, and seven other cyclizations of racemic or achiral carbamates are described in the Supporting Information.

Removal of the carbamate groups from *S*-**6a**−**c** under standard conditions (see Supporting Information) yielded the same enantiomer *S*-**7** as assessed by chiral HPLC (Scheme 1). These experiments demonstrate the facile removal of the nitrogen substituent and show that the sense of chirality transfer is the same for all three different

Scheme 1. Assignments of Product Configurations By Correlation



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(6) In addition to N−Ar rotation, precursors **5** existed as rotamers about the carbamate N−CO bond in ratios 2.5−5.0/1 according to NMR spectroscopic analysis. The NMR spectra of the products did not show evidence for carbamate rotamers.

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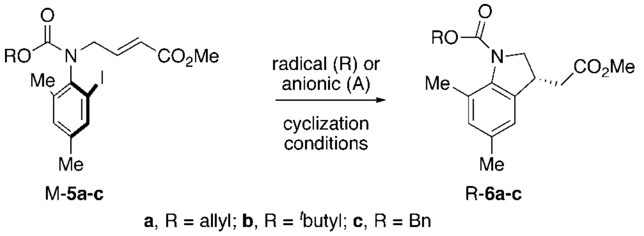
Table 1. Radical and Anionic Cyclizations of Axially Chiral Carbamates



entry	sm	er **5**	cond[a]	prod	yield[b]	er **6**	ct[c]
1	*P*-**5a**	99/1	R	*S*-**6a**	97%	92/8	93
2	*P*-**5a**	99/1	A	*S*-**6a**	67%	98/2	99
3	*M*-**5a**	87/13	R	*R*-**6a**	100%	75/25	86
4	*M*-**5a**	87/13	A	*R*-**6a**	70%	82/18	94
5	*P*-**5b**	99/1	R	*S*-**6b**	87%	86/14	87
6	*P*-**5b**	99/1	A	*S*-**6b**	72%	90/10	91
7	*M*-**5b**	90/10	R	*R*-**6b**	91%	82/18	91
8	*M*-**5b**	87/13	A	*R*-**6b**	72%	81/19	93
9	*P*-**5c**	99/1	R	*S*-**6c**	93%	91/9	92
10	*P*-**5c**	99/1	A	*S*-**6c**	74%	97/3	98
11	*M*-**5c**	89/11	R	*R*-**6c**	97%	77/23	87
12	*M*-**5c**	89/11	A	*R*-**6c**	71%	82/18	92

[a] R = radical: Bu_3SnH, Et_3B, C_6H_6, rt; A = anionic: *n*-BuLi, TMSCl, THF/ether/hexane, −98 °C. [b] Isolated yield after flash chromatography. [c] ct = chirality transfer, the percentage of major enantiomer of the product expected from an enantiopure sample of the precursor.

carbamate precursors. To assign the absolute configuration of the products, the ester of *S*-**6a** was hydrolyzed, and the resulting acid was subjected to Barton decarboxylation.[9] Palladium-catalyzed removal of the Alloc group followed by benzoylation provided a sample of *S*-**8** whose configuration was assigned by comparison (rotation, chiral HPLC retention time) with an authentic sample.[2c,2d]

To assign the configuration ofl the precursors **5**, we rely on the similarities between the new carbamate and prior anilide radical cyclizations. The radical cyclization of *M*-**3** is known to give *R*-**4** (Figure 1).[2c,2d] Assuming the same sense of radical cyclization with **5**, it follows that the precursor to *R*-**6** must be *M*-**5** while *S*-**6** comes from *P*-**5**.

The high levels of transfer of axial chirality of **5** to the new stereocenter of **6** show that the cyclizations are faster than rotation of an intermediate radical or anion around the N−Ar bond axis. This lack of rotation is necessary but not sufficient for chirality transfer because the alkene has two diastereotopic faces in the transition state that lead to enantiomeric products after the chiral axis is erased. Thus, the results also require a face-selective cyclization. Figure 3 shows the proposed favored and disfavored transition states for the radical and anionic cyclizations.[2c]

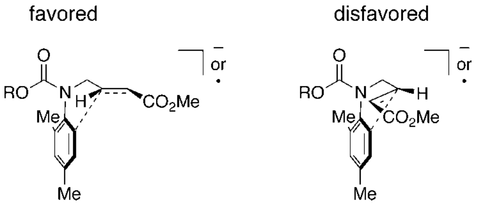


Figure 3. Transition state models for chirality transfer in radical and anionic cyclizations. The anionic TS is simplified by omitting lithium.

The synthetic value of the products **6** in Table 1 is somewhat limited since they all bear an *ortho*-Me group that is used to lock out rotation in the atropisomers **5**. However, by analogy to anilide radical cyclizations, it should be possible to conduct cyclizations with substrates bearing other ortho substituents, including removable ones,[10] or even with no ortho substituents.[11] Thus, the method has good potential for extension to make diverse chiral dihydroindoles. The features of high rotation barrier, high chirality transfer, and ease of removal of the N-substituent unite to make axially chira carbamates valuable precursors for radical, anionic, and presumably other types of transformations.

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Supporting Information Available: Contains experimental procedures, complete compound characterization, and additional examples of anionic cyclizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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