J|A|C|S
ARTICLES

Synthesis of Highly Enantioenriched 3,4-Dihydroquinolin-2-ones by 6-*Exo-trig* Radical Cyclizations of Axially Chiral α-Halo-*ortho*-alkenyl Anilides

David B. Guthrie, Steven J. Geib, and Dennis P. Curran*

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

Received August 5, 2009; E-mail: curran@pitt.edu

Abstract: Radical cyclizations (Bu$_3$SnH, Et$_3$B/air, rt) of racemic α-halo-*ortho*-alkenyl anilides provide 3,4-dihydroquinolin-2-ones in high yield. Cyclizations of enantioenriched precursors occur in similarly high yields and with transfer of axial chirality to the new stereocenter of the products with exceptionally high fidelity (often >95%). Single and tandem cyclizations of α-halo-*ortho*-alkenyl anilides bearing an additional substituent on the α-carbon occur with high chirality transfer and high diastereoselectivity. Straightforward models are proposed to interpret both the chirality transfer and diastereoselectivity aspects. These first examples of an approach for axial chiral transfer from a reactive species in the amide to an acceptor suggest broad potential for extension both within and beyond radical reactions.

Introduction

The dihydroquinolin-2-one ring is an important heterocycle that is featured in both natural products and medicinally active compounds.[1] Dihydroquinolin-2-ones can exist as isolated ring systems, as in the penigquinolones,[2] pinolinone,[3] α$_2$β$_3$ integrin antagonists[4] (see **1**, Figure 1), and a class of HIV reverse transcriptase inhibitors.[5] Or, they can be conjoined with other rings, as in scandine and the related meloscine alkaloids (see **2**, Figure 1).[6,7] Many methods exist to make racemic dihydroquinolin-2-ones, but only a few routes toward single enantiomers have been reported.[8] These methods suffer from various drawbacks (low ee, limited generality), so new methods are needed.

Many of the most important dihydroquinolin-2-ones have alkyl or other substituents at the C-4 position, and convenient
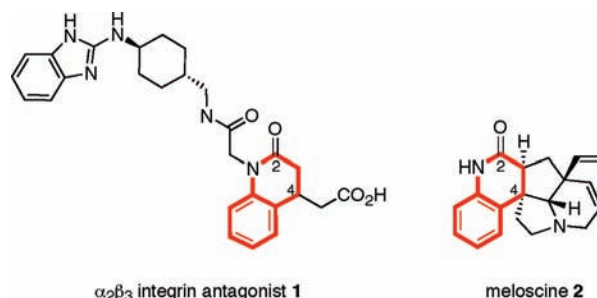

Figure 1. Representative 3,4-dihydroquinolin-2-ones with ring system highlighted in red.

ways to access such compounds in racemic form involve 6-*exo-trig* cyclizations. Figure 2 shows examples of both radical[9] and ionic approaches. Jones reported that reduction of **3** with Bu$_3$SnH provided target dihydroquinolin-2-one **4** along with comparable amounts of the product of 1,5-hydrogen transfer **5** in 51% combined yield.[10] In this method (Approach 1), a radical generated on the aryl ring cyclizes to an acceptor on the anilide carbonyl group. Ikeda[11] and Parsons[12] took the reverse strategy (Approach 2), generating a radical adjacent to the amide

(1) For a more complete collection of references to biologically active 3,4-dihydroquinolin-2-ones and methods of synthesis, see: Zhou, W.; Zhang, L.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982–1987.

(2) Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1344–1348.

(3) Kimura, Y.; Kusano, M.; Koshino, H.; Uzawa, J.; Fujioka, S.; Tani, K. *Tetrahedron Lett.* **1996**, *37*, 4961–4964.

(4) (a) Ellis, D.; Kuhen, K. L.; Anaclerio, B.; Wu, B.; Wolff, K.; Yin, H.; Bursulaya, B.; Caldwell, J.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4246–4251. (b) Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943–1945.

(5) Seitz, W.; Geneste, H.; Backfisch, G.; Delzer, J.; Graef, C.; Hornberger, W.; Kling, A.; Subkowskic, T.; Norbert, Z. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 527–531.

(6) Isolation: (a) Bernauer, K.; Englert, G.; Vetter, W. *Experientia* **1965**, *21*, 374–375. (b) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886–1905. (c) Oberhänsli, W. E. *Helv. Chim. Acta* **1969**, *52*, 1905–1911. (d) Plat, M.; Hachem-Mehri, M.; Koch, M.; Scheidegger, U.; Potier, P. *Tetrahedron Lett.* **1970**, *39*, 3395–3398.

(7) Synthesis: (a) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610. (b) Denmark, S. E.; Cottell, J. J. *Adv. Synth. Catal.* **2006**, *348*, 2397–2042. (c) Selig, P.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082–5084. (d) Selig, P.; Herdtweck, E.; Bach, T. *Chem.—Eur. J.* **2009**, *15*, 3509–3525.

(8) (a) El Ali, B.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264–4270. (b) Dong, C.; Alper, H. *Tetrahedron: Asymmetry* **2004**, *15*, 35–40. (c) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307–2309. (d) Blay, G.; Cardona, L.; Torres, L.; Pedro, J. R. *Synthesis* **2007**, 108–112. (e) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731–5734.

(9) Other radical approaches include bimolecular additions, see ref 1, and cyclizations to isocyanates, see: Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960–2963.

(10) (a) Clark, A. J.; Jones, K.; McCarthy, C.; Storey, J. M. D. *Tetrahedron Lett.* **1991**, *32*, 2829–2832. (b) Clark, A. J.; Jones, K. *Tetrahedron* **1992**, *48*, 6875–6882. Related additions to aryl rings: (c) Lopez de Turiso, F. G.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151–154.

(11) (a) Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perk. Trans. 1* **1991**, 353–359. (b) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, *6*, 695–713.

(12) Allan, G. M.; Parsons, A. F.; Pons, J.-F. *Synlett* **2002**, 1431–1434.

Approach 1: radical on aryl ring cyclizes to acceptor on
N-acyl group

3 → **4** 51%, ~1/1 + **5**
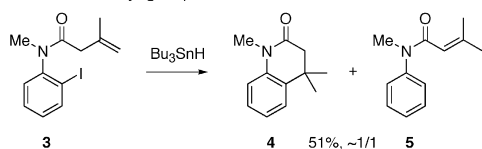
Approach 2: radical or anion on N-acyl group cyclizes to
acceptor on aryl ring

6 → **7**, 79%

8 → 1) K₂CO₃ 2) SmI₂ → **9**, 57%
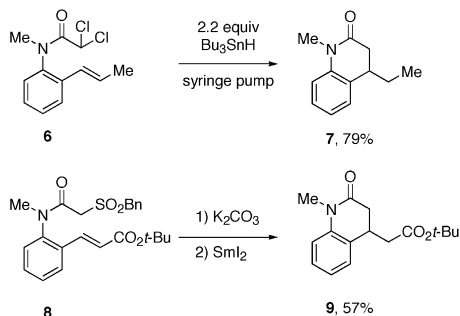
Figure 2. Two 6-*exo-trig* cyclization approaches to racemic dihydroquinolin-2-ones.

carbonyl group and allowing it to cyclize onto an alkene at the *ortho* position of the aryl ring. For example, cyclization of **6** under syringe pump conditions provided **7** in 79% isolated yield.

Cyclization strategies toward these targets are not limited to radical approaches. Procter and co-workers have developed a general approach to racemic dihydroquinolin-2-ones by using intramolecular conjugation addition of α-arene sulfonyl anilides.[13] For example, base-promoted cyclization of **8** followed by reductive desulfonylation with samarium diiodide provided **9** in 57% yield. α-Alkylation can be conducted between the cyclization and the desulfonylation steps to provide products with substitution at C-3. The sulfone can also be grafted to a polymer bead for solid phase synthesis.

It is now widely recognized that *ortho*-substituted anilides like **3**, **6** and **8** are not planar, as implied by the two-dimensional drawings in Figure 2. Instead, the planes of the amide group and the aryl ring are roughly orthogonal, as shown by the structures in Figure 3.[14] Accordingly, the molecules are axially chiral, and stable atropisomers result with suitable substitution patterns.[15] With such molecules, cyclizations (radical or otherwise) might occur with transfer of axial chirality to give a product whose configuration is predetermined by that of the starting material.[16] For example, tin hydride cyclizations of *o*-iodoacrylanilides **10** provide indol-2-ones **11** in high yields with excellent levels of chirality transfer. The scope of this radical reaction is excellent, and anionic[17] and organometallic[18] variants also exist. Because this produces an indol-2-one rather

10 → Bu₃SnH → **11**
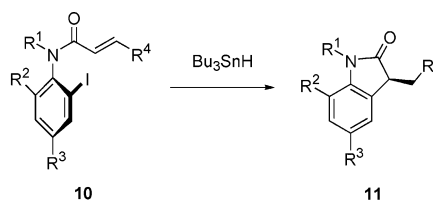
• ≥90% transfer of chirality from the axis of **10** to the stereocenter of **11**
• related anionic cyclizations and Heck reactions

Approach 1: 1,5-hydrogen transfer may be a fatal design flaw; removing an o-substituent reduces the N–Ar rotation barrier of **13**

12 → **13** →
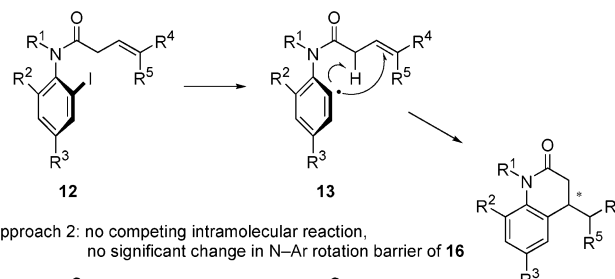
Approach 2: no competing intramolecular reaction, no significant change in N–Ar rotation barrier of **16**

15 → **16** →

14
axial chirality erased, new stereocenter
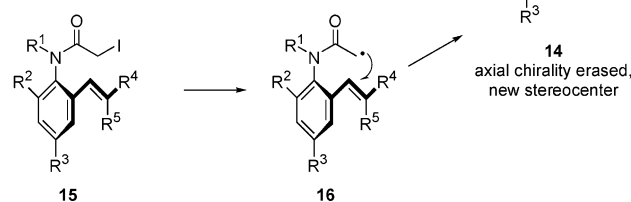
Figure 3. (top) Established approach to indol-2-ones compared to (bottom) two potential approaches to dihydroquinolin-2-ones.

than a dihydroquinolin-2-one, this reaction can be viewed as a lower homologue of Approach 1 in Figure 2.

However, in assessing prospects for making dihydroquinolin-2-ones by axial chirality transfer, we felt that Approach 2 was considerably more interesting than Approach 1 for three reasons. First, the scope and generality of Approach 1 may be limited; *β,γ*-unsaturated amides like **12** are not as easy to make or handle as α,β-unsaturated analogs, and the competing 1,5-hydrogen transfer reaction that these substrates permit (see **13**) could be a fatal design flaw in many cases.[19] Second, Approach 2 represents a potentially new class of chirality transfer reaction for axially chiral anilides. In all previous reactions, a reactive intermediate (radical, anion, metal) on the aryl ring is generated first and reacts in turn with an acceptor in a pendant side chain on the amide. Is it possible to reverse the roles of the two partners without sacrificing the high chirality transfer?

The third reason has to do with N–Ar bond rotation, which must be avoided because it results in racemization. Consider the generation of radical **13** from **12** in Approach 1. This event

(13) McAllister, L. A.; Turner, K. L.; Brand, S.; Stefaniak, M.; Procter, D. J. *J. Org. Chem.* **2006**, *71*, 6497–6507.

(14) (a) Oki, M. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E., Wilen, S. H., Eds.; Wiley InterScience: New York, 1983; Vol. 14, pp 1−81. (b) Oki, M. *The Chemistry of Rotational Isomers*; Springer-Verlag: New York, 1993. (c) Wolf, C. *Dynamic Stereochemistry of Organic Compounds*; RSC Publishing: Cambridge, UK, 2008.
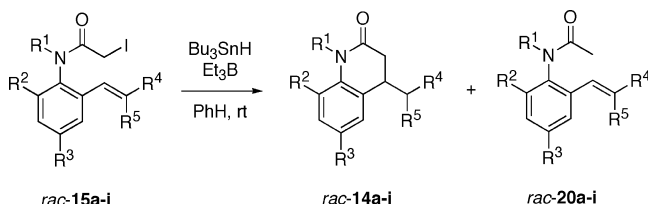
(15) (a) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955–3975. (b) Adler, T.; Bonjoch, J.; Clayden, J.; Font-Bard'a, M.; Pickworth, M.; Solans, X.; Solé, D.; Vallverdú, L. *Org. Biomol. Chem.* **2005**, *3*, 3173–3183. (c) Petit, M.; Lapierre, A. J. B.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 14994–14995.

(16) (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131–3132. (b) Curran, D. P.; Liu, W. D.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012–11013. (c) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131. (d) Curran, D. P.; Chen, C. H. T.; Geib, S. J.; Lapierre, A. J. B. *Tetrahedron* **2004**, *60*, 4413–4424. (e) Petit, M.; Geib, S. J.; Curran, D. P. *Tetrahedron* **2004**, *60*, 7543–7552.

(17) Guthrie, D. B.; Curran, D. P. *Org. Lett.* **2009**, *11*, 249–251.

(18) Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494–495.

(19) Curran, D. P.; Abraham, A. C.; Liu, H. T. *J. Org. Chem.* **1991**, *56*, 4335–4337.

Table 1. Isolated Yields of Radical Cyclization Products **14a−i** from Racemic Precursors **15a−i**[a]

| entry	α-I	R¹	R²	R³	R⁴	R⁵	% yield[b]
1	**15a**	Me	Me	Me	CO₂t-Bu	H	83
2	**15b**	PMB	Me	Me	CO₂t-Bu	H	85
3	**15c**	PMB	OMe	H	CO₂t-Bu	H	97
4	**15d**	Ts	Me	Me	CO₂t-Bu	H	nd[c,d]
5	**15e**	PMB	TMS	Me	CO₂t-Bu	H	93
6	**15f**	PMB	Br	Me	CO₂t-Bu	H	61
7	**15g**	PMB	Me	Me	4-BrC₆H₄	H	nd[c]
8	**15h**	PMB	Me	Me	CN	H	<70[d]
9	**15i**	PMB	Me	Me	CO₂t-Bu	Me	51[e]

[a] Conditions: Bu₃SnH and Et₃B in 20 mL PhH were added over 2 h via syringe to a 10 mM PhH solution of **15**. [b] Yield of racemic **14** after isolation by column chromatography on 10% w/w KF/silica gel. [c] nd = Not determined. [d] Fixed concentration of Bu₃SnH at 5 mM. [e] Directly reduced **20** was detected in crude reaction mixture by TLC or ¹H NMR.

must cause a significant decrease in the N−Ar rotation barrier because one of the *ortho*-substituents is now a radical, which is much smaller than its precursor. In contrast, the N−Ar rotation barriers of precursor **15** and radical **16** in Approach 2 are likely comparable because their substitution patterns are very similar. Even so, strict prevention of N−Ar bond rotation is a necessary but not sufficient condition for axial chirality transfer. Addition to the alkene must also be face selective, as must addition to the radical (rho selectivity) if it has three different substituents (this later selectivity is not illustrated in Figure 3 because the radical has two hydrogen atoms).

Here we report details of an in-depth study of 6-*exo-trig* radical cyclizations of both racemic and enantiopure axially chiral α-halo-*ortho*-alkenyl anilides. Dihydroquinolin-2-ones are formed in good yields and with exceptionally high fidelity in transfer of axial chirality. As a bonus, the reactions of alkyl-substituted amide radicals are also highly diastereoselective. These first results suggest that there is excellent potential to extend Approach 2 for axial chirality transfer both within and beyond radical reactions.

Results and Discussion

Synthesis of Radical Cyclization Precursors. An initial set of nine radical cyclization precursors **15a−i** (Table 1) was prepared in racemic form to assess the efficiency of the radical cyclization as a function of substituent pattern. The synthesis of **15a** is typical and is summarized in Scheme 1. Heck reaction of 2-iodo-*N*,4,6-trimethylaniline **17**[16e] with *t*-butyl acrylate under ligand-free conditions[20] provided **18a** in 92% yield. Acylation of **18a** with chloroacetyl chloride gave α-chloroanilide **19a** in 90% yield. This was converted to the α-iodoanilide **15a** by the Finkelstein reaction in 93% yield. The syntheses of all the precursors **15a−i** are described in detail in the Supporting Information. Most pathways were similar to Scheme 1, with suitable variations for substrate. Other protocols were sometimes

Scheme 1. Typical Synthesis of a Radical Cyclization Precursor Illustrated with **15a**
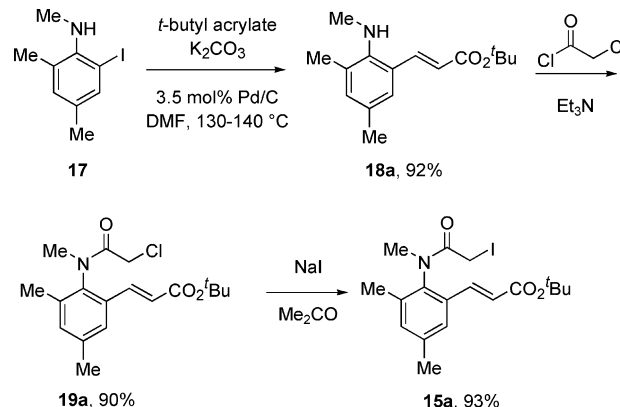
used for the Heck reaction,[21] and the trisubstituted alkene of **15i** was appended by Negishi coupling.[22]

Cyclizations of Racemic Precursors. Table 1 compiles the key results of cyclization experiments conducted under a standard set of conditions. In a typical experiment, Bu₃SnH and Et₃B initiator[23] were dissolved in degassed PhH, and this solution was added dropwise by syringe pump over 2 h to a nondegassed PhH solution of substrate **15a** at room temperature. TLC analysis showed that the reaction was complete at the end of the addition period. The solvent was removed, and the crude mixture was directly chromatographed on 10% w/w KF/silica gel.[24] This removed the tin byproducts and at the same time purified the target product **14a**, which was isolated in 83% yield. A similar experiment at a fixed Bu₃SnH concentration of 10 mM was complete in 5 min, but provided only 55% yield of a sample of **14a** that was not completely separable from the directly reduced product **20a**.

Substrate **15b,** with an *N*-*p*-methoxybenzyl (PMB) substituent, provided product **14b** in 83% purified yield. The *ortho* substituent was also varied in this series to include methoxy (**15c,** lacking the *p*-methyl group), trimethylsilyl (TMS, **15e**) and bromine (**15f**) while holding the *N*-PMB group and the acceptor constant. The corresponding products **14c,e,f** were isolated in 97, 93, and 61% yields. The TMS group of **14e** survived chromatography over KF-doped silica gel.

The substituents on the acceptor were also changed to *p*-bromophenyl (**15g**), cyano (**15h**), and dimethyl (**15i**). Reduction of the *p*-bromophenyl substrate **15g** provided a complex product mixture that did not obviously contain the expected product **14g** or the reduced product **20g**. The aryl bromide of **15g** is probably not the culprit for this failure, because bromide **15f** cyclized smoothly. Instead, we speculate that the benzyl radical resulting from cyclization will not react quickly enough with tin hydride under these conditions (low concentration and temperature)[25] and instead finds other pathways. Reduction of nitrile **15h** under the syringe pump conditions provided product **14h** in about 70% yield but in unsatisfactory purity even after chromatography. A similar experiment conducted at fixed 5 mM

(20) Opatz, T.; Ferenc, D. *Org. Lett.* **2006**, *8*, 4473−4475.

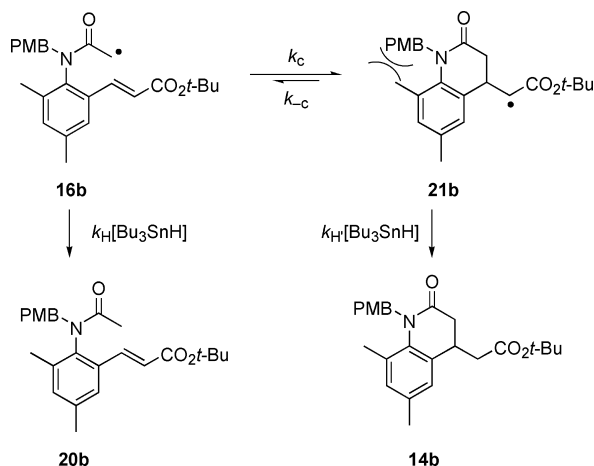(21) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130.

(22) Campbell, J. B., Jr.; Firor, J. W.; Davenport, T. W. *Synth. Commun.* **1989**, *19*, 2265−2272.

(23) Yorimitsu, H.; Oshima, K. In *Radicals in organic synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 11−27.

(24) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968−1969.

(25) Franz, J. A.; Suleman, N. K.; Alnajjar, M. S. *J. Org. Chem.* **1986**, *51*, 19−25.

Figure 4. Mechanistic framework for rate constant measurements.

concentration gave the same product in about the same yield, but now the purity was considerably better (95% estimated). The dimethyl substrate **15i** provided pure **14i** in 51% isolated yield. Small amounts of the directly reduced product were also produced, presumably because the alkene of **15i** is not as good of a radical acceptor as the other alkenes.

Finally, a tosyl group was also probed as the *N*-substituent, but reduction of **15d** gave a mixture of products whose major component (∼80%) was the directly reduced product **20d**. This failure is surprising since *N*-tosyl groups have been used in the past to facilitate cyclizations of α-amidoyl radicals.[26]

Rate Constant Measurements. The necessity of syringe pump conditions to minimize premature reduction in reactions of compounds **15** implies a relatively low rate constant for 6-*exo-trig* cyclization. This is not surprising since 6-heptenyl radicals typically cyclize more slowly than analogous 5-hexenyl ones. All the atoms connecting the radical precursor and radical acceptor are sp^2-hybridized in **15**, so estimating rate constants by analogy to other hexenyl and heptenyl radicals is risky. Therefore, we undertook kinetic competition experiments[27] to determine the cyclization rate constant k_c for the reaction of a representative compound **15b**.

The mechanistic framework for the rate constant analysis is shown in Figure 4. Radical **16b** derived from **15b** can be directly reduced in a bimolecular reaction with tin hydride to give **20b**. Alternatively, it can undergo 6-*exo* cyclization to provide a new radical **21b**, which in turn reacts with tin hydride to give **14b**. Measurement of the ratio of cyclized **14b** to reduced **20b** products as a function of tin hydride concentration provides the rate constant k_c in the usual way.[27]

The competition experiments were performed by mixing stock benzene solutions (nondegassed) of **15b** (0.025 mmol), Bu$_3$SnH (0.030 mmol), and eicosane (internal GC standard) in round-bottom flasks open to air. A hexane solution of Et$_3$B (0.010 mmol) was added all at once. The reaction mixtures were stirred for 10 min and were then subjected to GC analysis without workup to provide standardized yields of **14b** and **20b**. The average results of three trials at each concentration are summarized in Table 2, and the usual kinetic competition plot of this data is shown in Figure 5. Reactions were complete,

(26) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723–727.
(27) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176. (b) Newcomb, M. In *Radicals in Organic Synthesis*, 1st ed.; Renard, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 317–336.

Table 2. Summary of Results of Competition Experiments with **15b**

[Bu$_3$SnH][a]	% yld **14b**[b]	% yld **20b**[b]	total yld	red:cyc[c]
14.9 mM	67	21	89	24:76
19.9 mM	64	25	89	28:72
27.0 mM	59	30	88	33:67
37.0 mM	58	39	97	40:60
49.2 mM	50	46	95	48:52
58.8 mM	45	45	90	50:50
73.2 mM	33	43	76	57:43

[a] Initial concentration. [b] GC yield, using eicosane as an internal standard. Yields are an average of three trials. [c] Ratio of reduced **20b** to cyclized **14b**.
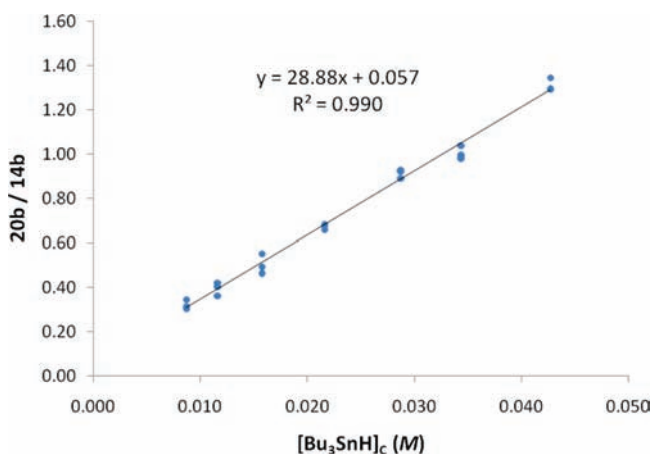
Figure 5. Kinetic competition plot of the data in Table 2 for reactions of radical **16b**.

reproducible, high-yielding (76−95%), and clean (no significant side peaks in GC analysis) in all cases.

By using the estimated value $k_H = 2.3 \times 10^6$ M^{-1} s^{-1} for radical **16b**,[28] we calculated k_c at 25 °C as 8×10^4 s^{-1}. This value is about an order of magnitude higher than that for the 6-*exo* cyclization of the 6-heptenyl radical,[27] presumably due to the activating effect of the ester on the alkene. It is coincidentally close to the rate constant for 5-*exo* cyclization of the 5-hexenyl radical (1×10^5 s^{-1}), a value that synthetic chemists often use as a touchstone for radical cyclizations of intermediate rate.

The intercept of a plot of data for an irreversible cyclization should be zero, but the intercept in Figure 5 appears to be slightly positive. This raises the possibility that the cyclization of **16b** may be reversible. From the value of the intercept, we calculated that the ring-opening rate constant of k_{-c} of **21b** must be at least 25 times slower than cyclization, so the back cyclization can probably be neglected for most practical purposes. Even so, most 6-*exo* cyclizations to activated alkenes are irreversible.[29] We speculate that the unfavorable 1,3-steric interactions between the *N*-substituent and the substituent of C-8 of the cyclized intermediate **21b** (see Figure 4) may both retard the cyclization and promote the reverse reaction.
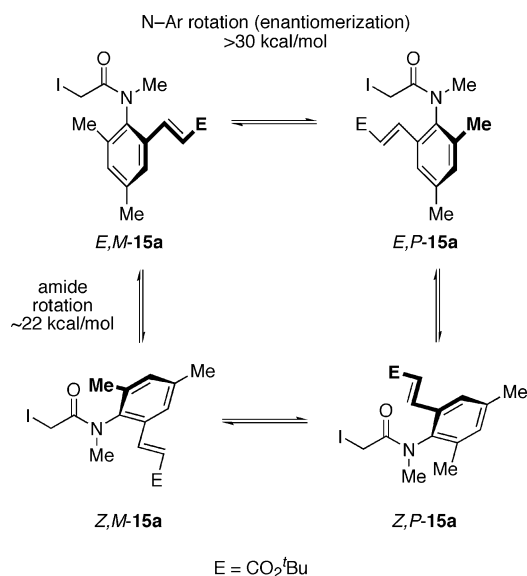
Resolution and Measurements of Rotation Barriers. To perform the chirality transfer experiments, we secured highly enantioenriched samples of seven of the precursors by resolution

(28) (a) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399–6403. (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.
(29) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.
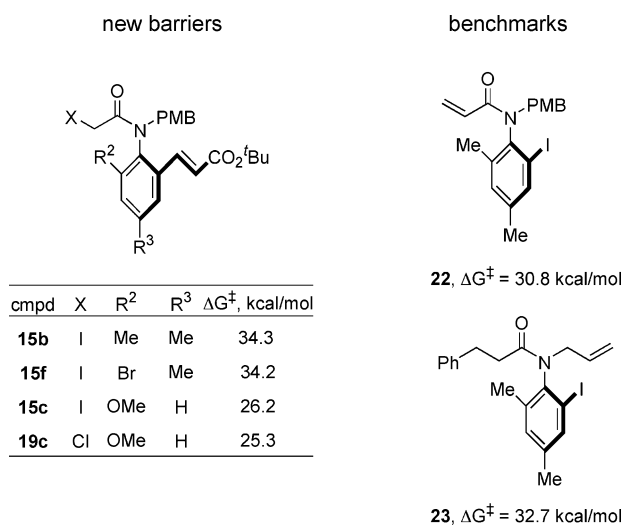
Figure 6. Rotational dynamics of *N*-methyl anilide **15a**.

Figure 7. Measured rotation barriers for amides **15** and **19** along with literature benchmarks **22** and **23**.

on semipreparative chiral HPLC. Typically, samples of **15** were dissolved in *i*-PrOH and injected onto either a Chiralcel OD or (*S,S*)-Whelk-O 1 column (25.0 cm × 21.1 mm ID) and eluted with a hexane:*i*-PrOH solvent mixture. Depending on the ease of separation, samples ranging in size from 40−120 mg were resolved per injection. After fraction collection and solvent removal, the enantiomeric ratios of the resolved compounds were measured by analytical chiral HPLC. Six of the compounds exhibited the expected two peaks for the individual enantiomers, which were isolated in >98% ee.

The HPLC behavior of *N*-methyl congener **15a** was an interesting exception. This exists as a 94/6 ratio E/Z of amide rotamers as assessed by ^{1}H NMR analysis (see Figure 6). The amide rotamers are visible by silica TLC analysis but not isolable under ambient laboratory conditions. Analytical HPLC (Whelk, 80:20 hexanes:*i*-PrOH) of the sample showed a small peak at 10.5 min, followed by two large peaks at 14.5 and 18.5 min. Analysis of the resolved fractions allowed interpretation of this chromatogram. The peak at 10.5 min is the minor Z-amide rotamer of (−)-**15a**, while the major E amide rotamer of (+)-**15a** elutes at 14.5 min. The minor Z amide rotamer of (+)-**15a** and the major E amide rotamer of (−)-**15a** overlap at 18.1 min. A plateau between the minor and major amide rotamer peaks of each enantiomer shows partial interconversion on the time scale of the HPLC separation. Based on this behavior, we estimate that the barrier for E/Z rotation is in the vicinity of $\Delta G^{\ddagger}_{E/Z} \approx 22$ kcal/mol. This barrier is considerably higher than that for typical amides;[30] however, E/Z rotamers of anilides with even larger ortho substituents have even higher barriers and can be separated and handled at ambient temperature.[31] This effect complicates the measurement of the enantiomer ratio (er) of resolved **15a**, but the relatively small proportion of the minor Z rotamer (6%) minimizes any error.

The other samples with *N*-PMB groups instead of the *N*-Me group did not have significant amounts of the Z rotamer at equilibrium according to analysis of their ^{1}H NMR spectra (E/Z

>98/2), and their resolutions were straightforward. Like **15a**, these samples probably have a substantial barrier to E/Z rotation, but the population of the Z rotamer is so low at equilibrium that it can be neglected entirely.

Small samples of four substrates bearing *N*-PMB groups were then racemized to measure their respective barriers to *N*-aryl bond rotation. The samples were dissolved in 90:10 hexane/*i*-PrOH and heated in a sealed tube at an appropriate temperature. Racemization was monitored by periodically measuring the er of aliquots of the solution by analytical chiral HPLC. The experimental data and details of the standard analysis are in the Supporting Information.

The newly measured rotation barriers are summarized in Figure 7 along with benchmarks **22** and **23** from previous work in our group.[16d,e] The barrier to rotation of *o*-methyl substrate **15b** was $\Delta G^{\ddagger}_{rot}$ = 34.3 kcal/mol, while the *o*-Br substrate **15f** had a similar barrier of 34.2 kcal/mol. The magnitudes of these barriers are surprisingly high when contrasted against compounds like **22**, which has the alkenyl group on the amide rather than the aryl ring; its barrier to rotation is about 3 kcal/mol lower. Even **23**, which contains a primary group on nitrogen (allyl) rather than Me, has a barrier 1.5 kcal/mol lower than that for **15b**. With estimated half-lives >20 000 years, atropisomers like **15b,f** are essentially indefinitely stable at ambient temperature.
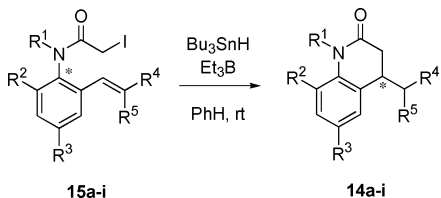
The barrier to rotation of *o*-methoxy substrate **15c** was much lower, $\Delta G^{\ddagger}_{rot}$ = 26.3 kcal/mol, and the α-chloro analog **19c** was a little lower still at 25.3 kcal/mol. The 8.1 kcal/mol barrier difference between **15c** and **15b** is significantly larger than expected from related axially chiral systems. For example, Sternhell's model for effects of *ortho*-substituents in biphenyl rotation[32] predicts only a 2−4 kcal/mol difference. The half-lives of the *o*-methoxy analogs are on the order of days at ambient temperature. So rapid room temperature reactions can be conducted with these substrates, but the resolved samples must be stored in the cold.

Chirality Transfer in 6-*Exo-trig* Cyclizations. Enantioenriched samples of **15a−c,e−f,h−i** were subjected to optimized reaction conditions for reductive cyclization. The cyclized products were

(30) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517−551.
(31) (a) Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297−2303. (b) Ototake, N.; Taguchi, T.; Kitagawa, O. *Tetrahedron Lett.* **2008**, *49*, 5458−5460. (c) Nobutaka, O.; Masashi, N.; Yasuo, D.; Haruhiko, F.; Osamu, K. *Chem.−Eur. J.* **2009**, *15*, 5090−5095.

(32) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618−5626.

Table 3. Yields and Chirality Transfer Levels in Cyclizations of Enantiomeric Precursors **15** to Give **14**[a]


entry	precursor	R¹	R²	R³	R⁴	R⁵	er	% yield 14[b]	er	% ct[e]
1	(+)-**15a**	Me	Me	Me	CO₂t-Bu	H	98.5/1.5	79	91/9	92
2	(−)-**15a**	Me	Me	Me	CO₂t-Bu	H	85/15	81	84/16	99
3	(+)-**15b**	PMB	Me	Me	CO₂t-Bu	H	100/0	87	95/5	95
4	(−)-**15b**	PMB	Me	Me	CO₂t-Bu	H	100/0	85	96/4	96
5	(+)-**15c**	PMB	OMe	H	CO₂t-Bu	H	99/1	94	93/7	94
6	(−)-**15c**	PMB	OMe	H	CO₂t-Bu	H	99/1	96	93/7	94
7	(+)-**15e**	PMB	TMS	Me	CO₂t-Bu	H	100/0	95	95/5	95
8	(−)-**15e**	PMB	TMS	Me	CO₂t-Bu	H	100/0	93	94/6	96
9	(P)-**15f**	PMB	Br	Me	CO₂t-Bu	H	99/1	63	95/5	96
10	(M)-**15f**	PMB	Br	Me	CO₂t-Bu	H	0/100	66	94/6	94
11	(+)-**15h**	PMB	Me	Me	CN	H	99.5/0.5	71	93/7	93[e]
12	(−)-**15h**	PMB	Me	Me	CN	H	99/1	68	96/4	97[e]
13	(+)-**15i**	PMB	Me	Me	Me	Me	99/1	57	80/20	81
14	(−)-**15i**	PMB	Me	Me	Me	Me	0/100	55	80/20	80

[a] Conditions: Bu₃SnH and Et₃B in 20 mL PhH were added over 2 h via syringe pump to a stirred 10 mM PhH solution of **15**. [b] Yield of **14** after isolation by column chromatography on 10% w/w KF/silica gel. [c] Absolute configuration determined by X-ray crystallography. [d] Percent chirality transfer. [e] Neat Bu₃SnH and Et₃B were added sequentially in one portion to a stirred PhH solution of iodide with [Bu₃SnH]ᵢ = 5 mM.

isolated by column chromatography over KF-doped silica, and enantiopurities were determined by chiral HPLC with reference to racemic standards of the product 3,4-dihydroquinolin-2-ones. The results of this series of experiments are shown in Table 3. Both enantiomers of each substrate were tested, and provided identical results within experimental error. Isolated yields of each product were comparable to yields of reactions with racemic substrate (Table 1). The precursor and product enantiomers are correlated in Table 3 by sign of optical rotation, except for **15f/14f**, whose absolute configurations are known (see below). Correlation by elution order in the chiral HPLC is provided in the Supporting Information. Unfortunately, there was no obvious correlation between the optical rotation or HPLC elution order of substrates and the respective products of cyclization, so assigning absolute configurations by analogy is not straightforward.

Briefly, the levels of chirality transfer were outstanding in almost all cases, ranging from 92 up to 99%. These high levels were not changed by altering the *N*-substituent (Me or PMB) or the ortho substituent (Me, Br, TMS). Even the samples of **15c** with the *o*-methoxy group cyclized with excellent chirality transfer (94%). The only exception was **15i**, which gave **14i** with a chirality transfer of 80−81% (Entries 13−14). This substrate differs from the others because it lacks an activating group on the alkene and because its R⁴ group is Me, not H. Either difference could be responsible for the erosion, as discussed below. These values of chirality transfer in the first examples of "Approach 2" cyclizations are comparable to and usually better than those observed in "Approach 1" room temperature cyclizations of *N*-allyl-*o*-iodoacetamides (74−97%) and *N*-acryloyl-*o*-iodoanilides (49−94%).

The substrate/product pair **15f/14f** incorporating an *ortho*-bromine atom was designed to allow assignment of absolute configuration by X-ray crystallography. Unfortunately **15f** did not cooperate. With the goal of making crystalline salts, a sample of (+)-**15f** (99/1 er) was treated with TFA in CH₂Cl₂ producing α,β-unsaturated acid **24** in 71% yield (Figure 8). Salt formation
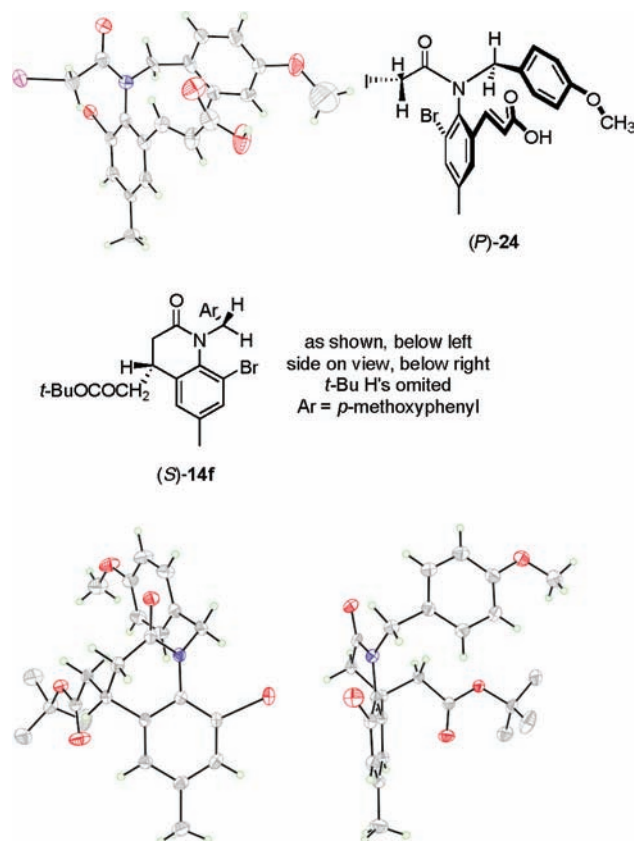
Figure 8. X-ray crystal structures of (P)-**24** (top) and (S)-**14f** (bottom, with front and side views).

became unnecessary when that acid itself crystallized by slow vapor diffusion method.

Acid **24** crystallized with four unique molecules in the unit cell, as two pairs of dimers displaying hydrogen bonding between the carboxylic acid groups. The differences in geom-
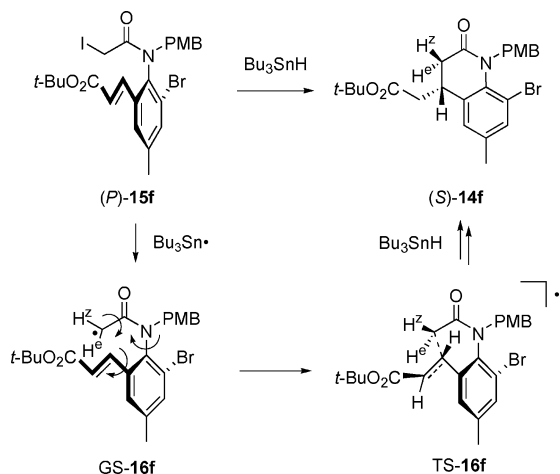
Figure 9. Model for chirality transfer illustrated with **15f**.

Scheme 2. Synthesis and Separation of Two Diastereomers of Precursor **25**

minor, **25a**, 33% yield; major, **25b**, 65% yield
relative configuration unassigned

etries between the four structures are small, so only one is shown in Figure 8. In this structure, the plane of the aromatic ring is almost completely orthogonal to the plane of the amide, with a torsion angle of 83°. The alkene acceptor exists in the *s*-trans conformation (an *s*-cis conformation would have significant A-strain) and is twisted slightly out of planarity with the aromatic ring (torsion angle = 156°). Interestingly, the *N*-PMB group is twisted to the same side of the molecule as the α,β-unsaturated carboxylic acid, with their planes nearly parallel. The 3.32−3.86 Å distance range between the two quasi-parallel planes is close to ideal for $\pi-\pi$ stacking.[33] Notice that the PMB group shields one face of the alkene. However, this shielding cannot be important in the radical cyclization because the PMB substituent is not essential for high chirality transfer. The absolute configurations of all four molecules in the unit cell were the same and were assigned by the anomalous scattering method;[34] **24** and accordingly its precursor (+)-**15f** have the (*P*) configuration.

The product **14f** was more cooperative; both the racemate and the pure enantiomers spontaneously solidified on standing. A crystal of (+)-**14f**—the product of cyclization of (+)-**15f**—was grown by vapor phase diffusion and the structure was solved as above; (+)-**14f** has the (*S*) configuration. Two views of this structure are shown in Figure 8. The view on the left is oriented to facilitate comparison with the structure of **15f**. The view on the right, looking into the side of the 3,4-dihydroquinolin-2-one ring, shows how the serious 1,3-interaction between the *N*-PMB group and the *o*-bromine atom is minimized. The angle between these two groups cannot be 90° as in the precursor, and it cannot be 0° as normally preferred for sp^2 hybridized atoms. Instead, a compromise of about 40° is reached because the lactam ring adopts a boat-like conformation that twists the N-Aryl bond. This twisting occurs without appreciable pyramidalization at N, and the $CH_2CO_2{}^t Bu$ substituent adopts the less-crowded axial-like orientation.

These results validate a working model that is shown in Figure 9. Iodine abstraction by a tributyltin radical from (*P*)-**15f** produces a ground state α-amidoyl radical GS-**16f** that has roughly orthogonal amide and aryl planes as in the precursor.
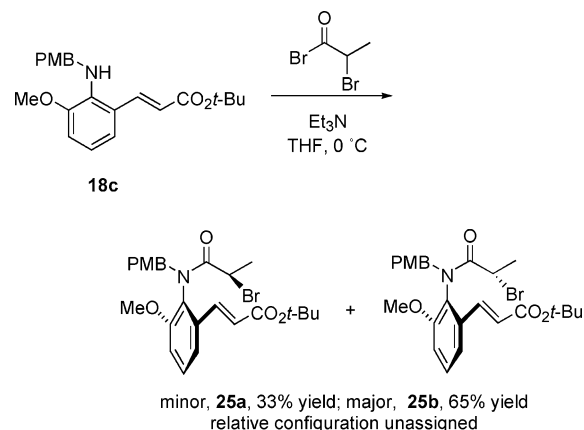
Likewise, the key radical SOMO and the alkene LUMO orbitals are also nearly orthogonal in this ground state of the radical. Coordinated rotation of the *N*-aryl bond, the aryl-alkenyl bond and the $CO-CH_2\bullet$ bond brings the radical to a twisted transition state TS-**16f**. This in turn progresses to the cyclized radical (not shown), and then the cyclized product (*S*)-**14f** after Bu_3SnH reduction.

Production of the enantiomeric product (*R*)-**14f** from radical GS-**16f** requires either that the N−Ar or Ar-alkenyl bond rotates the other way (or alternatively, rotates on past the TS). The former rotation seems unlikely due to the very high barrier. The latter is disfavored because the alkene C=C bond begins to eclipse the N−Ar bond.

In the model shown in Figure 9, the twisting about the NC(O)-$CH_2\bullet$ bond has no stereochemical consequence because a new stereocenter is not formed at the radical carbon atom. That changes if one of the two hydrogen atoms, labeled H^e and H^z in Figure 9, is another group. α-Amidoyl radicals of the general structure NC(O)-CHR• prefer the *s*-cis orientation rather than *s*-trans.[35] In other words, an R group that is appended to radical GS-**16f** alpha to the carbonyl group will take the position of H^e, not H^z. The model TS-**16f** then predicts that a diastereoselective cyclization should occur to give a *trans*-3,4-disubstituted-3,4-dihydroquinolin-2-one.
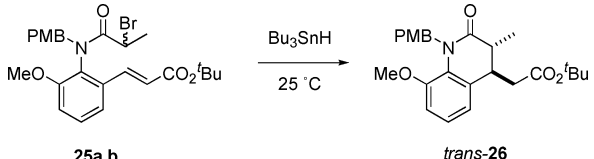
Single and Tandem Cyclizations of 2-Substituted-α-Amidoyl Radicals. To test the prediction of diastereoselectivity, we prepared precursor **25** by acylation of PMB-aniline **18c** with racemic 2-bromopropanoyl bromide, as shown in Scheme 2. Precursors **25** have both a chiral axis and a stereocenter, so two racemic diastereomers were produced. These proved to be easily separable by column chromatography and were isolated in yields of 33 and 65%. Each diastereomer was fully characterized, but we could not unambiguously assign relative configurations. Since both diastereomers gave the same products (see below), this ambiguity did not prove to be important in the reaction analysis.

Data for the reductive cyclizations of various isomers of **25** are summarized in Table 4. Racemic samples of **25** were reacted with Bu_3SnH and Et_3B at room temperature according to the usual syringe pump procedure. Both diastereomers gave the single product *trans*-**26** in excellent yield (95−97%). The trans relative configuration was initially assigned based on analysis

(33) (a) Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793−802. (b) Roesky, H. W.; Andruh, M. *Coord. Chem. Rev.* **2003**, *236*, 91−119.

(34) Dunitz, J. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4167−4173.

(35) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296−304.

Table 4. Cyclizations of Secondary Radical Precursor **25** to **26**

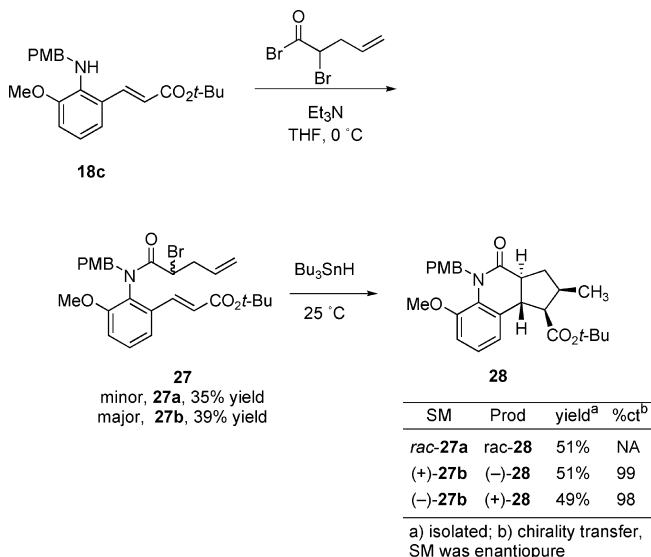| entry	substrate	er	product	% yield[a]	er	% chirality transfer
1	*rac*-**25a**	50/50	*rac*-**26**	95	50/50	N/A
2	*rac*-**25b**	50/50	*rac*-**26**	97	50/50	N/A
3	(+)-**25a**	98/2	(+)-**26**	98	98/2	100
4	(−)-**25a**	99/1	(−)-**26**	96	98/2	99
5	(+)-**25b**	100/0	(−)-**26**	98	99/1	99
6	(−)-**25b**	100/0	(+)-**26**	97	99.5/0.5	99.5

[a] Yield after isolation by column chromatography on 10% w/w KF/silica gel.

of coupling constants ($J_{3,4} = 14$ Hz), and this assignment was later confirmed by crystallography (see below). The cis isomer was not detected.

Next, both samples **25a,b** were resolved by chiral HPLC to high enantiopurity, and the four pure stereoisomers were cyclized as usual (entries 3−6). Yields were reproducibly high (96−98%), and chirality transfers were nearly perfect. The values (99−100%) are even higher than those observed for the primary α-amide radical precursor series. Each enantiomer in a given diastereomeric pair gives a different enantiomer of the product. Across the diastereomeric pairs, (+)-**25a** and (−)-**25b** give the same enantiomer of the product (+)-**26**, so these compounds must have the same configuration in the chiral axis and opposite configurations at the stereocenter. Likewise for the (−)-**25a** and (+)-**25b** pair; each gives (−)-**26**. These results show that the stereoselectivity is dictated by the chiral axis and not the stereocenter. In other words, the diastereomeric pairs of bromides with the same chiral axis configuration provide the same radical. This is sensible since the initially produced radical has sp^2 geometry.[35,36]

Radical cyclizations often proceed with high levels of diastereoselectivity when the radical and alkene acceptor are connected by a preformed ring, so we extended the design to incorporate a second cyclization that incorporated new elements of stereoselectivity.[37] The synthesis and cyclizations of tandem precursor **27a−b** are shown in Scheme 3. Racemic 2-bromo-4-pentenoic acid was converted to the acid chloride, which was used to acylate **18c**. This produced diastereomers **27a** (35% yield) and **27b** (39% yield) that were separated by column chromatography. Again, the relative configurations of **27a,b** were not assigned.

Tandem cyclization of a single enantiomer of **27** can give as many as 16 stereoisomers of **28**; however, we already know that racemization will not occur and that the first cyclization should be highly diastereoselective for the *trans* isomer. This reduces to four the number of likely product isomers. Since we already understood the effect of the relative stereochemistry from

(36) Interestingly, however, the rate of rotation about the NC(O)−CHMe(•) may be similar to or possibly even slower than the rate of radical cyclization. If that is the case, then both diastereomers of precursor must produce the same s-cis radical. For rotation rate information, see: (a) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379–4383. (b) Musa, O. M.; Choi, S. Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 786–793.

(37) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH Publishers, Inc.: New York, 1996; see especially pp 30−82.

Scheme 3. Synthesis and Cyclization of Tandem Precursor **27**

SM	Prod	yield[a]	%ct[b]
rac-**27a**	*rac*-**28**	51%	NA
(+)-**27b**	(−)-**28**	51%	99
(−)-**27b**	(+)-**28**	49%	98

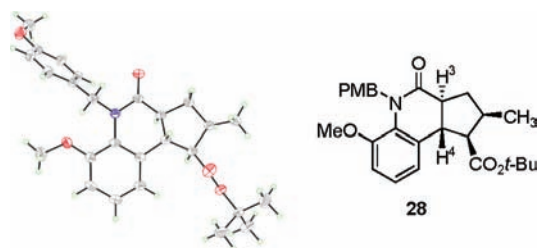a) isolated; b) chirality transfer, SM was enantiopure

the experiments in Table 3, we cyclized one of the diastereomers of **27** as a racemate, and resolved the other prior to cyclization.

Racemic **27a** was treated with Bu$_3$SnH under syringe pump conditions at room temperature (Scheme 3). After column chromatography, tricyclic product *rac*-**28** was isolated in 51% yield as a single diastereomer. Other fractions of side products contained, among other unidentified compounds, two minor diastereomers of the 6-*endo-trig*/5-*exo-trig* sequence, as evidenced by two distinct doublets in the upfield region denoting the respective methyl signals of the diastereomers. Enantiopure samples of **27b** were accessed by resolution with chiral HPLC, and were also subjected to the reaction conditions. These reactions provided the same diastereomer but opposite enantiomers of **28** in similar yields and excellent chirality transfer (98−99%).

Because the minor products and various impurities were inseparable from each other, it was not possible to characterize any of the secondary products or to provide an accurate measure of the diastereoselectivity in the second cyclization. However, we conservatively estimate that none of the minor products exceeded 10% of the mixture, so the second cyclization must also be reasonably diastereoselective (≥4/1).

The structure of *rac*-**28** was established by X-ray crystallography, and a diagram is shown in Figure 10. The ring fusion is *trans*,[38] and $J_{3,4}$ is again 14.1 Hz with a dihedral angle H^3-C^3-C^4-H^4 of 176° in the crystal. This confirms the assignment of *trans* relative configuration of **26** above.
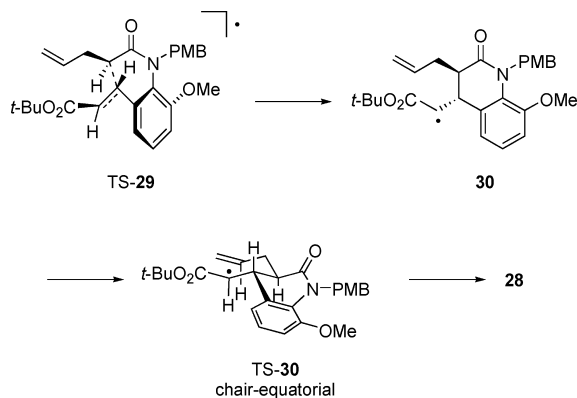
Models for the first and second cyclizations of the radicals generated from **27** are shown in Figure 11. The model for the first cyclization, which also serves for the radical derived from **25**, follows directly from the model for the primary radical

Figure 10. X-ray crystal structure of tricycle **28**.

Figure 11. Models of first and second cyclizations of radicals derived from **27**.

(Figure 9). The alkyl group on the radical center (R = Me or CH$_2$CH=CH$_2$) orients itself *s-cis* to the anilide carbonyl group. Then, twisting as indicated in **TS-29** directs the first cyclization with control of both relative and absolute configuration. The structure of the major isomer **28** formed in the second cyclization follows directly from the Beckwith–Houk model[39] of a chairlike transition state **TS-30** with equatorial-like substituents on the forming ring. The minor products can arise from a chairlike transition state with the radical substituent in a quasi-axial orientation, or boat-like transition states with either axial or equatorial orientations. In flexible systems, the chair and boat can flip to provide additional possible geometries, but the rigidity of the ring fusion to the 3,4-dihydroquinolone ring prevents that flip in this case.

Conclusions

Radical cyclizations (Bu$_3$SnH, Et$_3$B/air, rt) of an assortment of α-halo-*ortho*-alkenyl anilides provide 3,4-dihydroquinolin-2-ones in high yield. The precursors are axially chiral (stable atropisomers) but the products are not. Cyclizations of enantioenriched precursors occur with transfer of axial chirality to the new stereocenter of the products with exceptionally high fidelity (often >95%). Single and tandem cyclizations of α-halo-*ortho*-alkenyl anilides bearing an additional substituent on the α-carbon occur with both high chirality transfer and high diastereoselectivity. Overall, the new method is an attractive route for stereoselective synthesis of diverse 3,4-dihydroquinolin-2-ones.

Crystal structures have been used to rigorously assign configurations of one precursor and two products. Straightforward models interpret both the chirality transfer and diastereoselectivity aspects, reinforcing the notion that predictions of stereochemical outcomes of reactions of axially chiral amides are both easy and reliable.

Prior reactions with axial chirality transfer in the anilide series have featured reactive intermediates (radicals, anions, transition metals) on the aryl ring of the anilide and acceptors in the amide. This first-in-class example of the reverse approach suggests broad potential for axial chirality transfer from assorted reactive intermediates in the amide to acceptors on the aryl ring.

Supporting Information Available: Contains procedures of synthesis and characterization data of all new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(38) Akritopoulou-Zanze, I.; Whitehead, A.; Waters, J. E.; Henry, R. F.; Djuric, S. W. *Tetrahedron Lett.* **2007**, *48*, 3549–3552.

(39) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376.