Communication

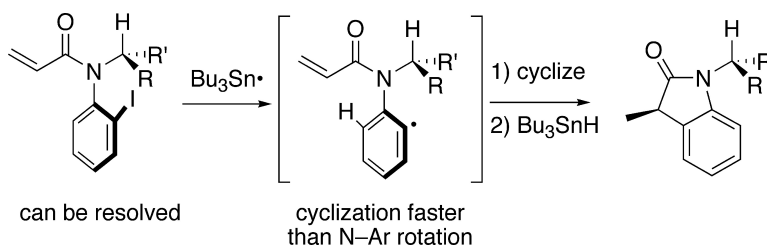# Relaying Asymmetry of Transient Atropisomers of *o*-Iodoanilides by Radical Cyclizations

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Relaying Asymmetry of Transient Atropisomers of *o*-Iodoanilides by Radical Cyclizations

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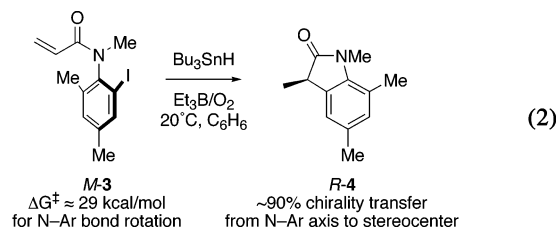
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Unlike most ionic and pericyclic reactions, the rates of radical and diradical reactions are often faster than common conformational changes in organic molecules. A growing number of processes involving memory or transfer of chirality[1] use the lightning speed of radical reactions to translate a transient feature of asymmetry in a precursor into a permanent feature in a product. For example, a ring[2] or chain[3] conformational preference in a precursor can be relayed to a stereocenter in a product. We report herein that simple *o*-iodoacrylanilides can be resolved, and that the asymmetry of the resulting transient atropisomers can be locked into a stereocenter by a subsequent rapid radical cyclization.

In an early attempt to use chiral auxiliaries in radical cyclizations,[4] Jones and McCarthy reported that cyclizations of acrylanilides bearing chiral *N*-substituents formed dihydroindolones with very low levels of asymmetric induction.[5] For example, cyclization of *N*-2-phenylethyl acrylanilide **1** with Bu₃SnH in toluene at 105 °C provided dihydroindolone **2** as a 51/49 mixture of stereoisomers (eq 1). This apparent failure to observe stereoselectivity has been accommodated by a standard model in which a single intermediate aryl radical partitions between two diastereomeric cyclization pathways of about equal energy.
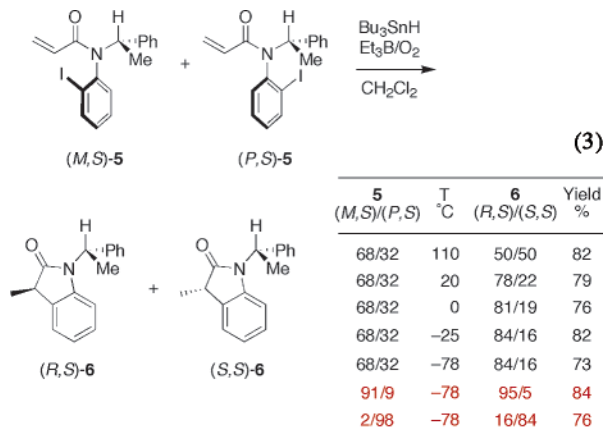

Current model

One aryl radical, two cyclization transition states
of about equal energy ($k_{c\alpha} \approx k_{c\beta}$)

(1)
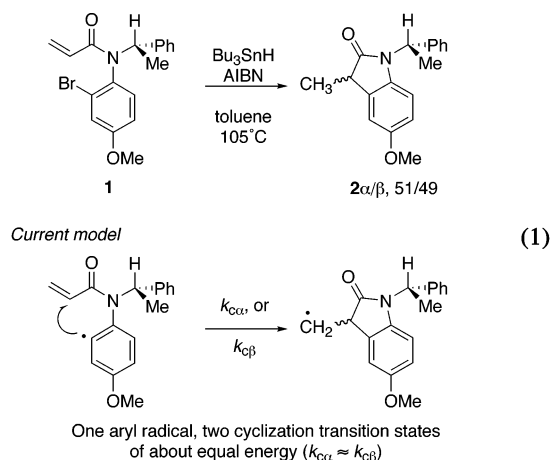
Results on radical cyclizations of iodoanilides like **3** bearing methyl groups at the other ortho position[6] (eq 2) began to suggest to us that, when viewed within the proper mechanistic framework, the Jones/McCarthy experiment could actually be a success. Iodoanilides **3** can be resolved and are relatively stable at room temperature. Radical cyclizations of the individual enantiomers of **3** provide dihydroindoles **4** with levels of chirality transfer of about 90%.

Accordingly, we hypothesized that molecules like **1** lacking a second ortho substituent should also exist in solution as a pair of equilibrating atropisomers. In turn, these atropisomers could produce a pair of diastereomeric radicals that cyclize faster than they interconvert. In other words, perhaps the low selectivity observed by Jones and McCarthy (eq 1) masks two highly selective cyclizations of atropisomeric radicals that are generated in about equal ratio.

(2)

M-**3**
$\Delta G^{\ddagger} \approx 29$ kcal/mol
for N–Ar bond rotation

R-**4**
~90% chirality transfer
from N–Ar axis to stereocenter

To address this question, we prepared iodoacrylanilide **5** from (*S*)-phenethylamine and studied its radical cyclizations in detail (eq 3). NMR spectroscopic studies show that **5** exists as an equilibrium mixture of atropisomers (*M*,*S*)-**5**/(*P*,*S*)-**5** in a ratio of 68/32 at room temperature.[7] Radical cyclization of this mixture provided the expected 50/50 ratio of products (*R*,*S*)-**6** and (*S*,*S*)-**6** at 110 °C,[7] but the ratio increased as the reaction mixture was cooled through 20 °C (78/22) to 0 °C (81/19) down to −20 °C (84/16). There was no further increase on cooling to −78 °C. This unusual temperature dependence is symptomatic of a change in mechanism. Interestingly, however, the level of stereoselectivity observed at the low temperature limit (84/16) actually exceeds the starting rotamer ratio (68/32).

(3)

5 (*M*,*S*)/(*P*,*S*)	T °C	6 (*R*,*S*)/(*S*,*S*)	Yield %
68/32	110	50/50	82
68/32	20	78/22	79
68/32	0	81/19	76
68/32	−25	84/16	82
68/32	−78	84/16	73
91/9	−78	95/5	84
2/98	−78	16/84	76

(*R*,*S*)-**6**   (*S*,*S*)-**6**

To the best of our knowledge, there are no examples of resolution of mono-*ortho*-substituted anilides, except when the ortho-substituent is *tert*-butyl.[8] Nonetheless, we were able to resolve **5** into its atropisomeric components (*M*,*S*)-**5** and (*P*,*S*)-**5** by preparative HPLC experiments. The isolated atropisomers interconvert with a barrier $\Delta G \approx 23$ kcal/mol ($t_{1/2} \approx 2.5$ h at 25 °C, see Supporting Information for measurements). Cyclization at −78 °C of a 91/9 ratio of (*M*,*S*)-**5**/(*P*,*S*)-**5** gave (*R*,*S*)-**6** and (*S*,*S*)-**6** in a 95/5 ratio, while a mixture in a 2/98 ratio gave (*R*,*S*)-**6**/(*S*,*S*)-**6** in 16/84 ratio. Thus, each atropisomer of **5** cyclizes to a different major product **6**. But consistent with the results of cyclization of the equilibrium mixture at low temperature, the cyclization of one of the atropisomers [(*M*,*S*)-**5**] is more selective than that of the other [(*P*,*S*)-**5**].

We interpret these results within the mechanistic framework shown in Figure 1. Tributyltin radical abstracts iodine from
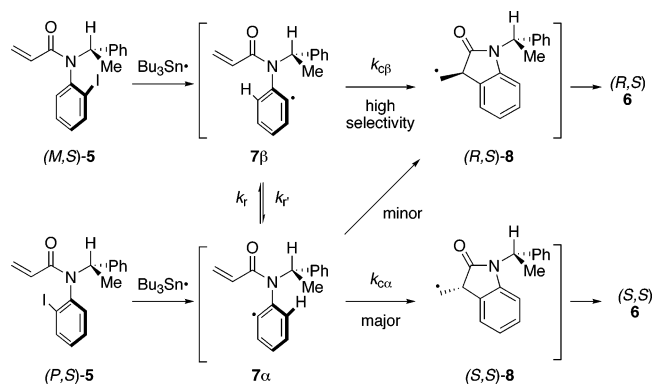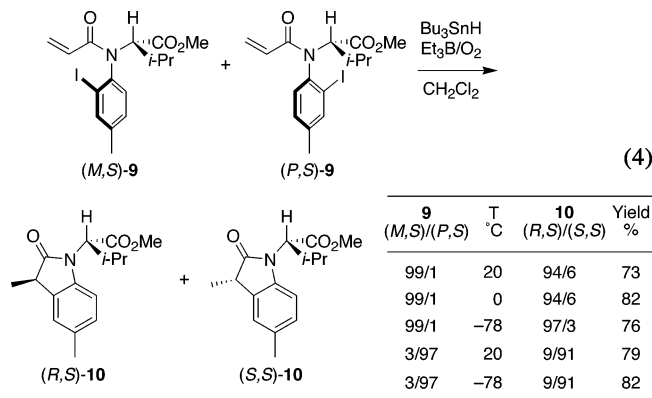
Figure 1. Proposed mechanism for temperature-dependent cyclizations of aryl radicals derived from **5**.

atropisomers (*M*,*S*)-**5** and (*P*,*S*)-**5** with about equal rates to give radicals **7β** and **7α** in a ratio that reflects that starting iodide ratio.[9] These radicals must have a significantly lower barrier to interconversion than **5**, but they now have the competitive option of radical cyclization. The lack of selectivity observed at 110 °C suggests that interconversion of **7β** and **7α** is more rapid than cyclization in the high-temperature regime (k_r, $k_{r'} > k_{c\alpha}$, $k_{c\beta}$). On cooling, cyclization begins to compete with rotation. Somewhere below 0 °C, transition to the low-temperature regime is complete. Here the two radicals **7α,β** no longer interconvert, and each cyclizes with its own selectivity in favor of opposite diastereomers **8**. Radical **7β** cyclizes to (*R*,*S*)-**8** with high fidelity, while **7α** cyclizes predominately to (*S*,*S*)-**8** but with significant (~20%) leakage to (*R*,*S*)-**8**. This leakage accounts for the observation that the product ratios differ from the starting atropisomer ratios when (*P*,*S*)-**5** is present in significant amounts.

We next prepared iodoanilide **9** from L-valine (eq 4). At ambient temperature, this exists as a 58/42 equilibrium mixture of (*M*,*S*) and (*P*,*S*) rotamers, which were again separable by preparative HPLC. Also, slow crystallization of the equilibrium mixture from hexanes deposited exclusively (*M*,*S*)-**9** in a crystallization-induced asymmetric transformation.

9 (*M*,*S*)/(*P*,*S*)	T °C	**10** (*R*,*S*)/(*S*,*S*)	Yield %
99/1	20	94/6	73
99/1	0	94/6	82
99/1	−78	97/3	76
3/97	20	9/91	79
3/97	−78	9/91	82

The interconversion barrier between the rotamers of **9** is 24.3 kcal/mol. Cyclization of a 99/1 mixture of rotamers (*M*,*S*)-**9**/(*P*,*S*)-**9** faithfully provided (*R*,*S*)-**10** (94/6−97/3), while cyclization of a 97/3 mixture enriched in (*P*,*S*)-**9** faithfully provided (*S*,*S*)-**10** (91/9).

The successful resolution and selective cyclization of diastereomeric atropisomers in eqs 3 and 4 suggests that analogous enantioselective transformations are possible. Indeed, despite the low rotation barriers (23 kcal/mol, see Supporting Information), we succeeded in obtaining significantly enantioenriched samples

of iodoanilides **11a,b** (eq 5) by rapid preparative chromatography over a Whelk-O chiral column. Cyclizations of these enantioenriched samples indeed occurred with good levels of chirality transfer to produce enantioenriched samples of dihydroindolones (*R*)- or (*S*)-**12a,b**.
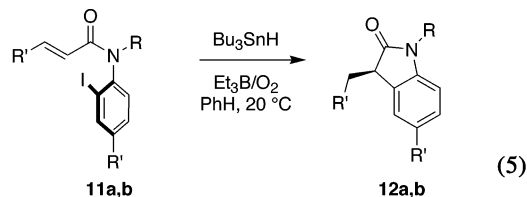
Precursor	R	R'	(*M*)/(*P*)	Product	(*R*)/(*S*)	Yield %
M-**11a**	*i*Pr	H	83/17	*R*-**12a**	76/24	85
P-**11a**	*i*Pr	H	14/86	*S*-**12a**	25/75	78
M-**11b**	*c*-C$_6$H$_{11}$	Me	91/9	*R*-**12b**	71/29	81
P-**11b**	*c*-C$_6$H$_{11}$	Me	14/86	*S*-**12b**	25/75	85

These results show that the atropisomeric *o*-iodoanilides bearing only a hydrogen atom at the other *ortho*-position can be resolved and handled rapidly under ambient laboratory conditions. The asymmetry present in these transient atropisomers can then be locked into a stereocenter by a subsequent radical cyclization, which occurs with good to excellent levels of chirality transfer. Among other implications, the results suggest that a chiral auxiliary that provides a high equilibrium bias for one of the diastereomeric atropisomeric iodides will provide a single product stereoselectivity without the need to resolve the precursors. Likewise, the diastereoselective formation of a complex between a chiral Lewis acid and a racemate like **11** could provide a single product enantioselectively.

Supporting Information Available: Full experimental details, crystal structure data, and copies of key spectra (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Assignments of configuration are presented in the Supporting Information.

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(9) Control experiments at partial conversion showed that (*M*,*S*)-**5** and (*P*,*S*)-**5** were consumed at about equal rates, so diastereoselective iodine abstraction seems unlikely.

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