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Asymmetric radical cyclization reactions of axially chiral *N*-allyl-*o*-iodoanilides to form enantioenriched *N*-acyl dihydroindoles☆,☆☆

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We dedicate this paper to Professor Leo Paquette on the occasion of his 70th birthday

Abstract—Radical cyclizations of enantiomerically enriched *N*-allyl-*o*-iodoanilides provide *N*-acyl-3-alkyl-2,3-dihydroindoles in good yields and with good to excellent levels of chirality transfer from the *N*–Ar axis to the new stereocenter. In competitive cyclizations of *N*-acryloyl-*N*-allyl-*o*-iodoanilides, the addition of an *o*-methyl group reverses the regioselectivity of the radical cyclization from the acryloyl group to the allyl group. Approximate rate constants for representative radical cyclizations have been measured to provide insight into the origin of these observations.

1. Introduction

Axially chiral benzamides, anilides and related imides have been known for several decades,[1] and work over the last 10 years has focused on asymmetric reactions of these species.[2–6] A recurring theme is the occurrence of an inter- or intramolecular reaction more rapidly than rotation of a C–N or C–C bond of an amide. Intermolecular reactions usually result in formation of a new stereocenter with retention of the chiral axis (asymmetric induction), while intramolecular reactions often result in formation of a new stereocenter with loss of the chiral axis (chirality transfer). Representative examples of intermolecular reactions are shown in Figure 1 and include the nitrile oxide cycloaddition reaction to *o-tert*-butylacrylanilide **1** (asymmetric induction by a C–N axis) to give **2**[2] and the addition of PhMgBr to *o*-formylnaphthamide **3** (asymmetric induction by a C–C axis) to give alcohol **4**.[7]

The radical cyclization of *N*-acryloyl anilide **5** to provide **6** (Fig. 2) is an example of an intramolecular reaction that occurs with faithful chirality transfer (enantiomer ratios >90/10).[2c] In this reaction, the intermediate aryl radical **7** must have a much lower barrier of rotation than its precursor **5**, but its barrier to cyclization to give **8** is even lower yet, so racemization of the intermediate radical is not a significant reaction.

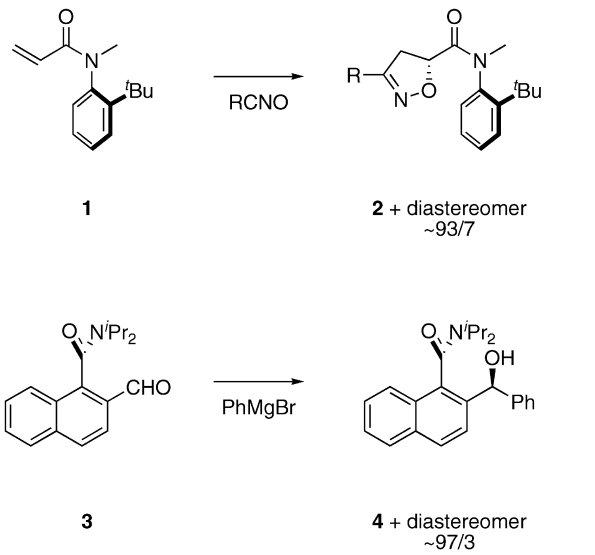

Figure 1. Examples of asymmetric induction with axially chiral anilides (top) and naphthamides (bottom).

Radical cyclizations of *o*-haloanilides lacking another *ortho* substituent to provide racemic products predate the above asymmetric cyclizations,[8–11] and these cyclizations occur whether the radical acceptor is present in the *N*-acyl group

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† Direct questions regarding the X-ray crystal structures to this author

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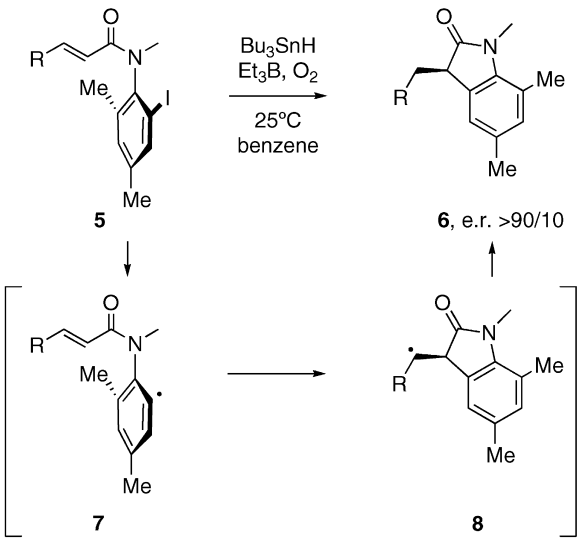


Figure 2. Chirality transfer in radical cyclizations of *o*-iodoacryanilides.

or the *N*-alkyl group (Fig. 3). For example, Bowman and coworkers[11a] have reported that cyclization of *N*-crotonoyl derivative **9** provided **10**, while Dittami[8a] and Toga[8b] observed that cyclization of *N*-allyl derivative **11** provided **12**. When the two types of cyclizations were pitted against each other by Jones and Storey in substrate **13**, then closure to the crotonoyl group dominated and **14** was the only observed product.[9a,12] Jones and McCarthy also reported attempted asymmetric cyclizations of chiral anilides like **15**, but the diastereomeric ratios of **16** were very poor.[13] These poor selectivities were interpreted in terms of a traditional chiral auxiliary model where a single radical passes through two diastereomeric transition states that are close in energy. However, our results[2c,d] suggest that an equally plausible model is that there are two diastereomeric iodides **15**, which in turn are precursors of two diastereomeric radicals, each of which cyclizes predominantly to a different isomer of **16**.

Following up on our previous studies on asymmetric cyclization reactions of enantioenriched *N*-acryloyl-*o*-iodoanilides,[2c] we now describe a complementary study of cyclization reactions of axially chiral *N*-allyl-*o*-iodoanilides **17** (Eq. 1). These reactions are general and good levels of chirality transfer to **18** are observed. The absolute configurations of the precursors and products are assigned, and a model is put forth to explain the observed chirality transfer. Finally, we have discovered that the presence of the

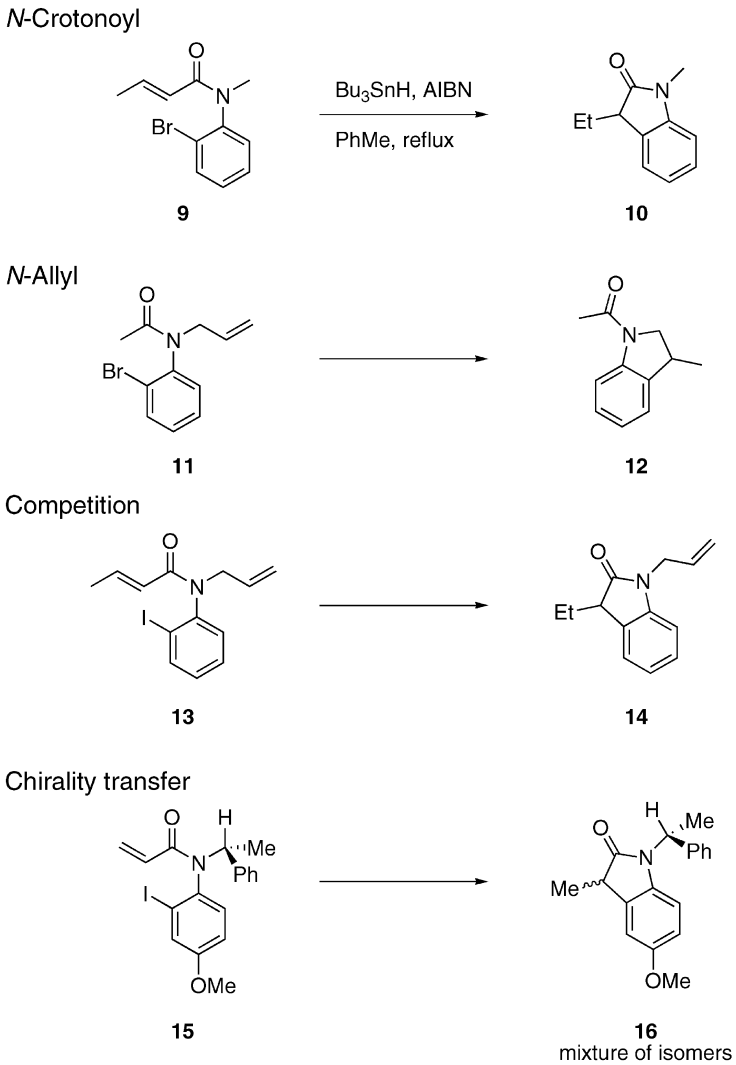
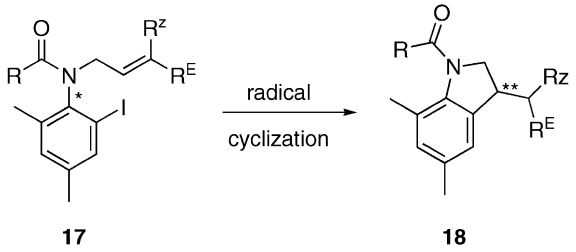


Figure 3. Radical cyclizations of iodo/bromoanilides lacking *ortho* substituents.

o-methyl group in these substrates reverses the regioselectivity in competitive cyclizations like that described by Jones (**13→14**), and we have measured approximate rate constants for representative cyclizations to help provide insight into the origin of this surprising observation.

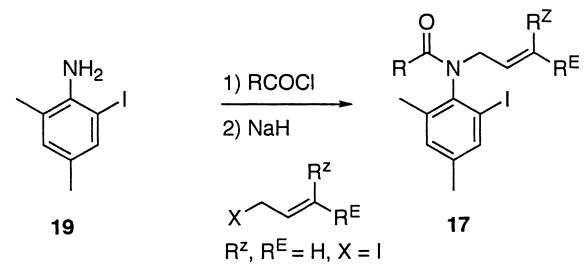


axial chirality (*) in **17** transfered to new stereocenter (**) in **18** (1)

2. Results and discussion

2.1. Precursor and product preparation, resolution and rotation barriers

All of the cyclization precursors **17a-i** used in this study were prepared as racemates from 2-iodo-4,6-dimethylaniline **19**[14] by a straightforward sequence of N-acylation followed by N-allylation, as shown in Eq. 2. Racemic standards of all the cyclization products **18** (see Eq. 1) were readily prepared from all these precursors by standard tin hydride mediated cyclizations. Section 4 contains representative procedures along with complete characterization data for the racemates.



	R	R^Z	R^E	% yield[a]
17a	Ph	H	H	35
17b	*p*-BrC_6H_4	Me	Me	54
17c	$PhCH_2$	H	H	50
17d	$PhCH_2$	H	Ph	47
17e	$PhCH_2$	H	Me	20
17f	$PhCH_2$	Me	Me	37
17g	$PhCH_2CH_2$	H	H	74
17h	*E*-CH_3CH=CH	H	H	20
17i	Me	H	H	69

a Overall isolated yield

(2)

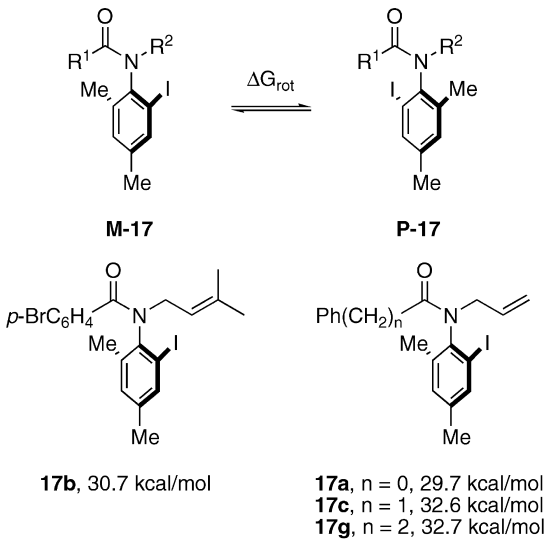


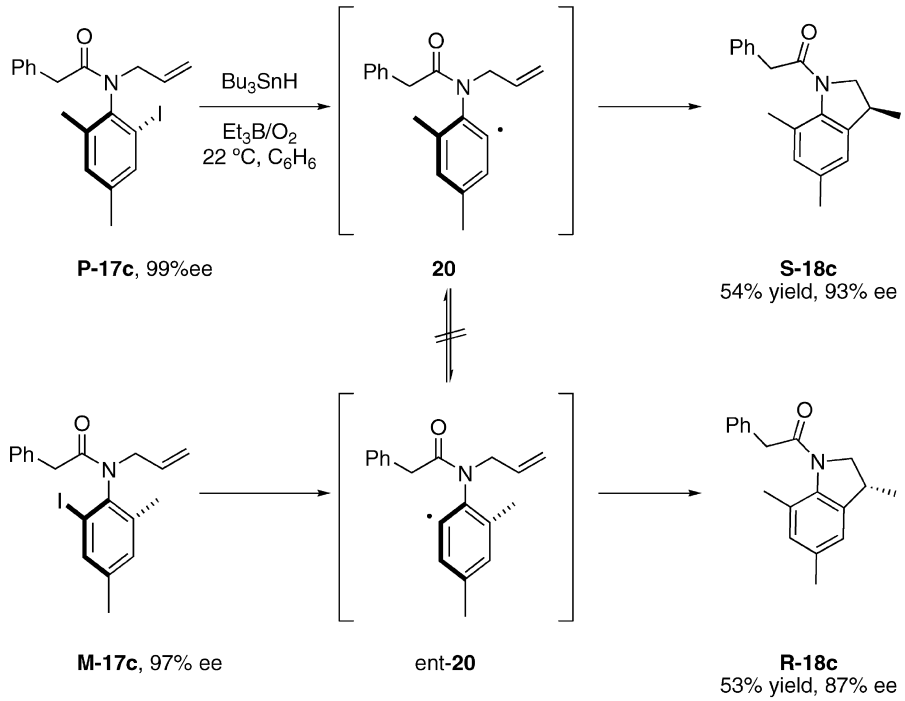
Figure 4. Rotation barriers for four axially chiral anilides.

Racemic precursors **17a-g** were resolved on a semi-preparative column ((*S*,*S*)-Whelk-O1, 25 cm×10.0 mm I.D., 10–40% *i*PrOH in hexanes, 8–10 mL/min).[15] Preparative injections ranged from 40 to 80 mg, depending on the effectiveness of the separation, and several hundred milligrams of most of the precursors were obtained in ees ranging from 96 to 99%. All the racemic products **18a-g** were injected into an analytical (*S*,*S*)-Whelk-O1 column and each pair of enantiomers was well resolved, thereby paving the way for a convenient quantitative analysis of chirality transfer experiments by chiral hplc.

Rotation barriers for four of the precursors were also measured (Fig. 4). In a typical experiment, phenmethyl-substituted anilide **17c** (>99% ee) was heated at 140 °C in 9:1 hexane:*i*PrOH, and the decrease in ee was measured as a function of time by chiral hplc analysis. A standard plot of this data (see Supplementary information) showed the expected first order racemization, and provided a rotation barrier of 32.6 kcal/mol. Phenethyl-substituted amide **17g** exhibited a similar rotation barrier of 32.7 kcal/mol, while benzamides **17a** and **17b** exhibited slightly lower rotation barriers of 30.7 and 29.7 kcal/mol, respectively. All of these barriers are well within the range to permit convenient handling of these compounds at room temperature. The lower barriers of benzamides have been observed previously,[14b] and presumably result because the phenyl ring of the benzamide group can twist out of plane with respect to the amide carbonyl group and thereby present a smaller substituent for the iodine or methyl group of the anilide to rotate past in the transition state.

2.2. Chirality transfer in radical cyclizations

With the enantioenriched radical precursors in hand, tin hydride cyclizations were conducted to measure the level of chirality transfer. The radical cyclization of substrate **17a** is typical of all the cyclizations and is summarized in Eq. 3. Triethylborane[16] (1.0 equiv.) was added to an aerated benzene solution of **17c** and Bu_3SnH (1.5 equiv., 0.01 M) to initiate the reaction, and progress was monitored by tlc. After about 30 min, the reaction was worked up and the

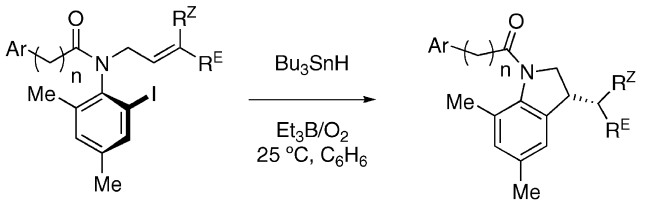


(3)

product was purified by flash chromatography and then analyzed by chiral hplc. Oxindole **S-18c** was produced in 54% yield and 93% ee starting from **P-17c** of 99% ee while **R-18c** was produced in 53% yield and 87% ee starting from **M-17c** of 97% ee. The levels of chirality transfer are 97 and 95%, and these levels are within experimental error, as expected for enantiomers. These results prove that the cyclization of intermediate radicals **20** and *ent*-**20** is much more rapid than their interconversion by *N*-aryl bond rotation.

Cyclizations of the other resolved precursors were conducted by similar procedures, and the data for this set of reactions are summarized in Table 1. These data reveal a number of trends. In all cases, the dextrorotatory (+) enantiomer of the precursor gave the dextrorotatory enantiomer of the product, and vice versa. In six of the

Table 1. Summary of radical cyclizations of **17a-g**



Entry	Precursor[a]	Ar	*n*	R^Z	R^E	Product	Yield[b]	%ee_{SM}[c]	%ee_P[d]	Chirality transfer[e] (%)
1	**P-17a**	Ph	0	H	H	**S-18a**	95	99	86	93
2	**M-17a**	Ph	0	H	H	**R-18a**	92	>99	87	93
3	**P-17b**	4-BrC_6H_4	0	Me	Me	**S-18b**	72	99	48	72
4	**M-17b**	4-BrC_6H_4	0	Me	Me	**R-18b**	95	98	47	72
5	**P-17c**	Ph	1	H	H	**S-18c**	54	>99	93	97
6	**M-17c**	Ph	1	H	H	**R-18c**	53	97	87	95
7	**P-17d**	Ph	1	H	Ph	**S-18d**	40	>99	74	87
8	**M-17d**	Ph	1	H	Ph	**R-18d**	50	98	76	88
9	**P-17e**	Ph	1	H	Me	**S-18e**	77	>99	79	89
10	**M-17e**	Ph	1	H	Me	**R-18e**	71	>99	83	91
11	**P-17f**	Ph	1	Me	Me	**S-18f**	79	>99	63	81
12	**M-17f**	Ph	1	Me	Me	**R-18f**	81	>99	57	78
13	**P-17g**	Ph	2	H	H	**S-18g**	67	96	85	94
14	**M-17g**	Ph	2	H	H	**R-18g**	74	>99	90	95

[a] The P configuration is assigned to the dextrorotatory enantiomers and M to levorotatory.
[b] Isolated yield after chromatography.
[c] ee of precursor.
[d] ee of product **18**.
[e] Yield (not excess) of the major enantiomer of **18** expected from an enantiopure sample of **17**.

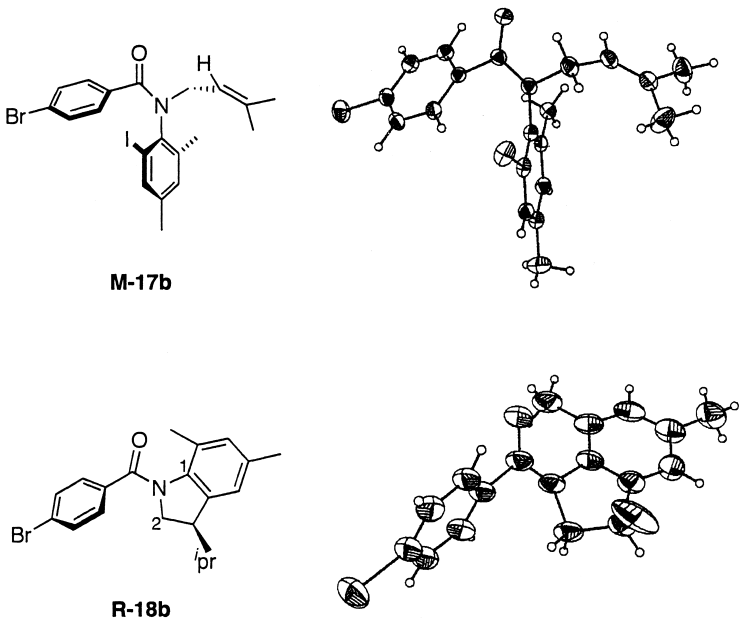


Figure 5. ORTEP representations of crystal structures of precursor **M-17b** (top) and product **R-18b** (bottom, the *iso*-propyl methyl groups are disordered and removed for clarity).

seven enantiomeric pairs, the first eluting enantiomer of the precursor gave the second eluting enantiomer of the product, and vice versa. The exception to this trend was **17a/18a**.

The last column of Table 1 records the level of chirality transfer, which corresponds to the yield of the major enantiomer of **18** expected from an enantiopure sample of **17**. This is an enantiomer ratio, not an enantiomeric excess. Levels of chirality transfer exhibited by enantiomeric pairs were comparable. All substrates with terminal or *E*-disubstituted acceptors cyclized with good to excellent levels of chirality transfer (87–97%, see entries 1/2, 5/6, 7/8, 9/10, 13/14), while acceptors with terminal *Z*-substituents exhibited somewhat lower selectivities (72–81%, entries 3/4, 11/12). These trends with the *N*-allyl acceptors are remarkably similar to those exhibited by the previously studied *N*-acryloyl class.[2c]

The absolute configurations of precursor **17b** (second eluting enantiomer) and its derived product **18b** (first eluting enantiomer) were determined by X-ray crystallography using the anomalous dispersion method, and the crystal structures of these compounds are shown in Figure 5.[17] The amide plane of precursor **17b** is nearly perpendicular to the N-Ar plane (117°), and the benzamide aryl plane is also significantly twisted (36°). The amide group is planar and the *N*-aryl group and the amide oxygen are trans, as expected. Product **18b** is strikingly different—the amide nitrogen is pyramidalized towards the viewer (sum of angles is 349°), with larger (O=C)NC^1 and (O=C)NC^2 angles (123 and 122°) not compensating for the small C^{1}NC^2 angle (104°). The *N*–Ar group is now more nearly cis to the carbonyl oxygen (angle 10°) while the N–CH$_2$ group is more nearly trans (angle 150°). This unusual geometry is a reflection of the severe strain that is imposed by the *o*-methyl group in standard planar geometries. Based on the trends observed in chirality transfer and rotation sign, we assigned the absolute configurations of all of the other compounds by analogy, and these assignments are shown in Table 1.

A model for chirality transfer that follows from these results is shown in Figure 6. To obtain a favorable geometry for cyclization, the aryl ring of perpendicular radical **21/22** must twist towards the allyl group. The alkene can twist its terminal CH$_2$ group either away from the radical to expose the back side of the alkene (as in **21→23**) or towards the radical to expose the front side (as in **22→24**). The formation of the product is consistent with twisting away from the radical (**21→23→25**). In striking contrast, the current model for cyclization of radicals derived from *N*-acryloyl anilides like **26** involves twisting of the acryloyl group towards the aryl radical as in **27** to give **28**.[2c] The only difference between the two classes of substrates is the location of the amide carbonyl group, which is either outside of (*N*-allyl) or within (*N*-acryloyl) the forming ring.

2.3. Regioselectivity, competitive cyclizations and rate constants

As a comparison to the Jones internal competition experiment in Figure 3, we also studied the cyclization of *rac*-**17h** (Eq. 4). This substrate has the same *N*-crotonoyl and *N*-allyl groups as Jones's compound **13**,[9a] but the aryl ring now has an *o*-methyl group in place of hydrogen. (There is also a *p*-methyl group in place of H, but this is presumably inconsequential) To our surprise, cyclization of *rac*-**17h** occurred to produce not the expected **30h** resulting from cyclization to the crotonoyl group, but instead produced exclusively **18h** resulting from cyclization to the *N*-allyl group. Dihydroindole **18h** was isolated in 65% yield by flash chromatography, and a careful analysis of the ^{1}H NMR spectrum of the crude product did not reveal any resonances attributable to the expected product **30h**. To ensure that the Jones structure assignment was correct, we

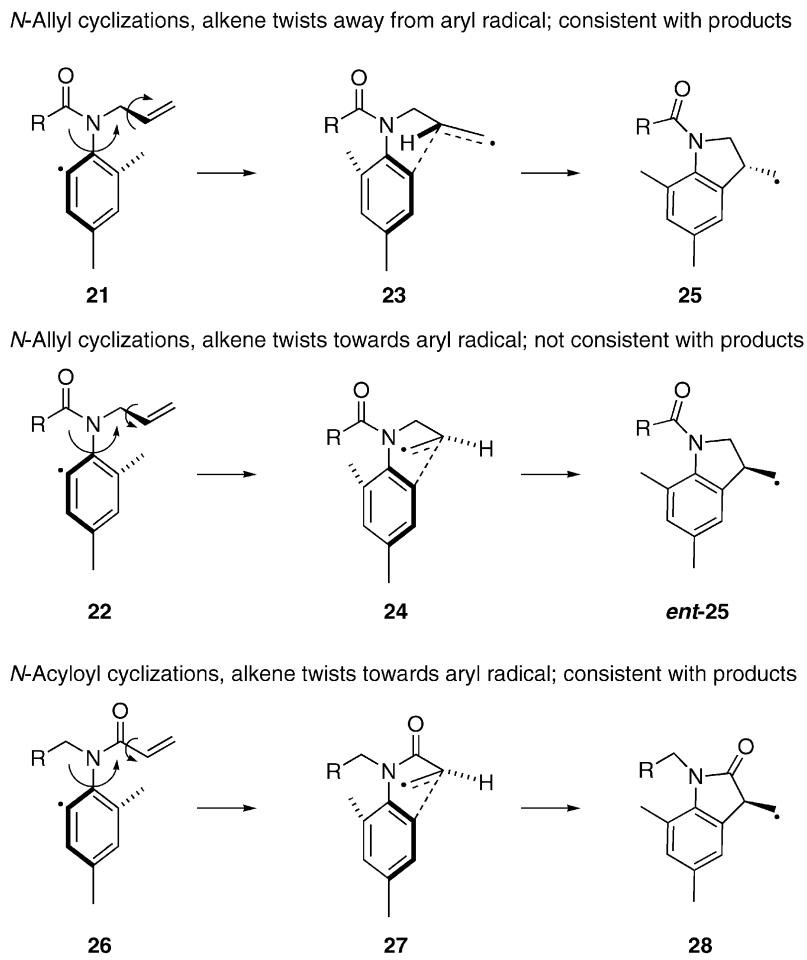
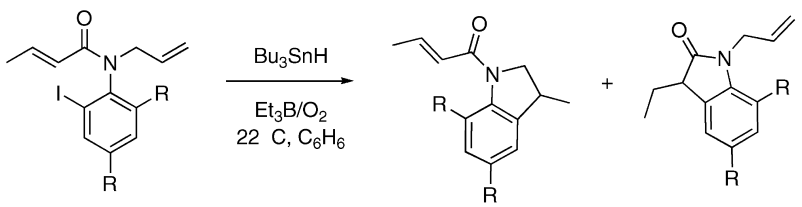


Figure 6. Transition state models for chiralitry transfer.

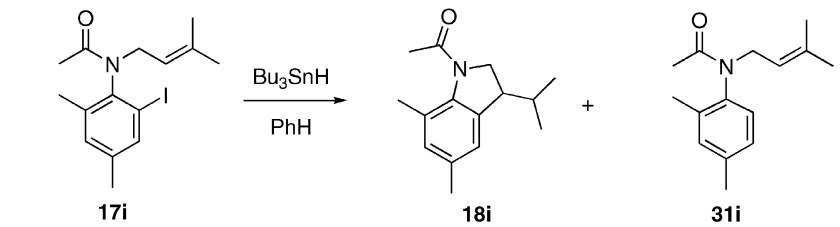
remade precursor **13** and, as billed,[9a] this provided exclusively **14**, and **29** was not detected. Accordingly, the regioselectivity in the cyclization of these anilide radicals is completely controlled by the presence or absence of an *ortho* methyl group.



(4)

To help understand the reversal in regioselectivity, we prepared racemic substrates *rac*-**17i** and **32** and measured their cyclization rate constants by standard competition kinetics with Bu_3SnH at 80 °C. Data for these experiments are summarized in Figure 7, and the calculated rate constants are summarized in Figure 8.[18] Consistent with the observed regioselectivity of **17h** (Eq. 4), the rate constant for cyclization of **35** (3.0×10^9 s^{-1}) was found to be about 40 times larger than the rate constant for cyclization of **39** (7.8×10^7 s^{-1}). We also attempted to measure the rate constant for cyclization of radical **37** derived from Jones substrate **13** at 80 °C; however, the cyclization of this radical was so fast that only traces of reduced product (<5%) were detected at the highest tin hydride concentrations (1–2 M). From this result, we can estimate a lower limit for cyclization of radical **37** at about 10^{10} s^{-1}.

These results show that cyclization to the *N*-acryloyl group (**37→38**) is inherently extremely fast, but is retarded by at least two orders of magnitude by introduction of an *o*-methyl group (**37→38**). This dramatic retardation allows the inherently less favorable cyclization to the *N*-allyl group (**35→36**) to intervene in the cyclization of **17h**. Figure 9 speculates on why cyclization to the acryloyl group is dramatically retarded by an *o*-methyl group while



[Bu_3SnH]	**18i/31i**	[Bu_3SnH]	**33/34**
0.01 M	29/1	0.02 M	5.2/1
0.37 M	6.6/1	0.03 M	3.5/1
1.0 M	2.7/1	0.05 M	2.2/1
3.6 M	0.8/1	0.1 M	1.1/1

Figure 7. Data from competition experiments with **17i** and **32**.

cyclization to the allyl group is not. Cyclization to the acryloyl group probably requires considerable twisting of the aryl radical and the alkene towards each other. When R°=Me, this results in a considerable steric interaction between this Me group and the CH_2 of the *N*-allyl group. In contrast, the *N*-allyl group is not constrained by amide resonance. The alkene can reach out to meet the aryl radical better (by rotation of the $N-CH_2$ bond) and less twisting of the aryl ring is required. This cyclization of the aryl radical to the *N*-allyl group does not result in a comparable steric interaction between the *o*-methyl group and the C=O on the other side. From the preparative standpoint, this analysis suggests that the regioselectivity of these reactions can be reversed by any medium or large *ortho*-substituent.

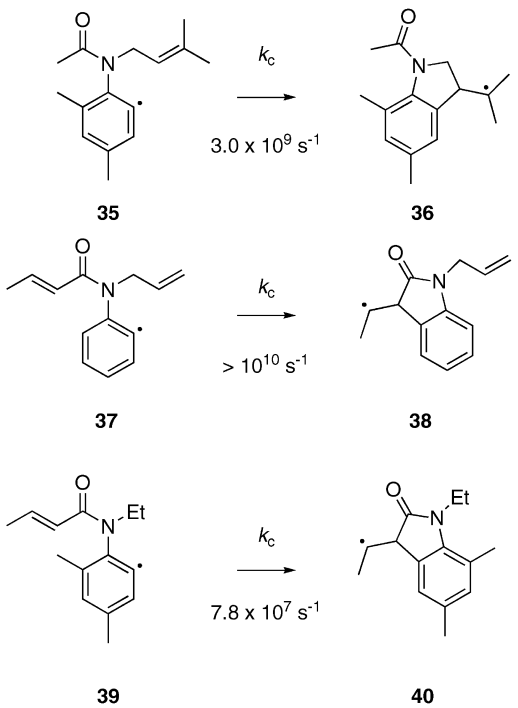


Figure 8. Competition experiments and rate constants.

3. Conclusions

In summary, radical cyclizations of axially chiral *N*-allyl-*o*-iodoanilides mirror their predecessor *N*-acryloyl-*o*-iodoanilides in both selectivity and trends, but give opposite enantiomeric products. Useful levels of chirality transfer are observed in many cases, and a straightforward model can be applied to predict the configuration of the major stereoisomer.

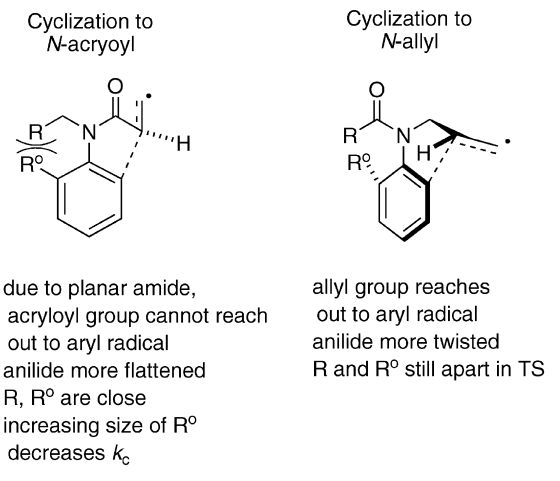


Figure 9. Twisting and effects of the *o*-methyl group on *N*-acryloyl (left) and *N*-allyl (right) cyclizations.

In all these reactions, the removal of the large iodine atom to generate a tiny radical is expected to dramatically reduce the barrier to rotation with attendant racemization, but the speed of the radical cyclization is so high that rotation cannot compete. Speed alone is not sufficient to ensure chirality transfer, yet one of two possible transition states is lower in energy, thereby ensuring selectivity. The presence of the *o*-substituent dictates not only stereoselectivity but also regioselectivity, in a surprising reversal from *N*-acryloyl cyclization to *N*-allyl cyclization. The detailed understanding of rotation barriers, regio- and stereoselectivity in this class of molecules sets the stage for future synthetic applications in asymmetric synthesis of oxindoles, dihydroindoles and related molecules.

4. Experimental

4.1. General procedure for acylation of 2-iodo-4,6-dimethylaniline (I)

To a CH_2Cl_2 (0.3 M) solution of 2-iodo-4,6-dimethylaniline (1.0 equiv.) was added triethylamine (1.1 equiv.). The reaction mixture was cooled to 0 °C and the respective acid chloride (1.1 equiv.) was added dropwise. The solution was warmed to room temperature. The reaction mixture was monitored by TLC and quenched accordingly with water upon completion. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×) and dried with $MgSO_4$. Filtration and solvent evaporation in vacuo followed by purification by using flash chromatography on silica gel eluting with hexanes/ethyl acetate or recrystallization from hexanes provided the corresponding *o*-iodoanilide.

4.2. General procedure for N-allylation of anilides (II)

To a THF slurry of NaH (1.1 equiv.) at 0 °C was added the respective *o*-iodoanilide (1.0 equiv.) dissolved in THF (2 mL/mmol iodoanilide). The reaction mixture was stirred until the solution became clear and then the appropriate allyl bromide/iodide (1.3 equiv.) was added dropwise. The solution was warmed to room temperature. The reaction mixture was monitored by TLC and quenched with water upon completion. The resulting mixture was extracted with diethyl ether (3×, 25 mL/mmol of anilide). The combined organic layers were washed with brine (1×) and dried with $MgSO_4$. Filtration and solvent evaporation in vacuo followed by purification by flash chromatography on silica gel eluting with hexanes/diethyl ether (typically 9:1→7:3) provided the respective anilide.

4.3. General procedure for thermally initiated radical cyclization of anilides to make racemic cyclization products (III)

To a benzene solution of the respective *o*-iodoanilide (1.0 equiv.) was added Bu_3SnH (1.5 equiv., 0.01 M) and AIBN (0.2 equiv.). The reaction mixture was refluxed until the starting material was consumed by TLC (typically less than 1 h). The solvents were removed in vacuo and the crude was submitted to the DBU workup.[19] Purification of the remaining crude by flash column chromatography on silica gel eluting with hexanes/diethyl ether (9:1) provided the respective dihydroindole.

4.4. General procedure for Et_3B initiated radical cyclization of anilides (IV)

To a benzene solution of the respective *o*-iodoanilide (1.0 equiv. and Bu_3SnH (1.5 equiv., 0.01 M) was added a hexane solution (1.0 M) of Et_3B (1.0 equiv.). The reaction mixture was sealed and stirred at room temperature until the starting material was deemed consumed by TLC. The solvents were removed in vacuo and the crude was submitted the DBU workup.[18] Purification of the crude product by flash column chromatography on silica gel eluting with hexanes/diethyl ether (typically 100% hexanes→8:2) provided the respective dihydroindole.

4.4.1. *N*-(2-Iodo-4,6-dimethylphenyl)benzamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 175–176 °C) was obtained in quantitative yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1679, 1500, 1480, 1265, 1257; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 6H), 7.06 (s, 1H), 7.45–7.60 (m, 3H), 7.55 (s, 1H), 7.65 (s, 1H), 7.97 (d, J=7.1 Hz, 2H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.5, 99.3, 127.4, 128.7, 131.8, 131.9, 134.2, 134.4, 137.2, 137.3, 139.1, 165.6; HRMS (EI) calcd for $C_{15}H_{14}INO$ 351.0120, found 351.0107; LRMS (EI) *m*/*z* 351 (M^+, 50), 259 (29), 246 (51), 224 (49), 105 (100), 77 (50).

4.4.2. *N*-(2-Iodo-4,6-dimethylphenyl)-2-phenylacetamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 161–162 °C) was obtained in 47% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3388, 3015, 2923, 1680, 1601, 1558, 1490, 1283, 1236, 852; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.24 (s, 3H), 3.80 (s, 2H), 6.70 (s, 1H), 6.99 (s, 1H), 7.45 (m, 5H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.4, 44.1, 99.0, 127.6, 129.2, 129.9, 131.7, 134.2, 134.6, 136.9, 137.0, 139.1, 169.1; HRMS (EI) calcd for $C_{16}H_{16}INO$ 365.0277, found 365.0289; LRMS (EI) *m*/*z* 365 (M^+, 3), 274 (3), 27 3 (4), 247 (66), 238 (100), 91 (71).

4.4.3. *N*-(2-Iodo-4,6-dimethylphenyl)-3-phenylpropionamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 156–157 °C) was obtained in 76% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1689, 1482, 1421, 1265; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.25 (s, 3H), 2.74 (t, J=8.1 Hz, 2H), 3.10 (t, J=8.1 Hz, 2H), 6.93 (s, 1H), 6.98 (s, 1H), 7.15–7.45 (m, 5H), 7.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 31.5, 38.3, 99.4, 126.3, 128.5, 128.6, 131.7, 134.4, 137.0, 137.1, 139.0, 140.7, 170.5; HRMS (EI) calcd for $C_{17}H_{18}INO$ 379.0433, found 379.0439; LRMS (EI) *m*/*z* 379 (M^+, 37), 351 (88), 252 (68), 247 (53), 224 (99), 111 (80), 105 (100).

4.4.4. *N*-(2-Iodo-4,6-dimethylphenyl)-4-bromobenzamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 242–244 °C) was obtained in 82% yield. IR (thin film, $CH-_2Cl_2$, NaCl, cm^{-1}) 1681, 1477, 1421, 1271, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 6H), 7.09 (s, 1H), 7.45 (bs, 1H), 7.57 (s, 1H), 7.65 (d, J=6.8 Hz, 2H), 7.68 (d, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.5, 99.1, 126.8, 129.0,

132.0, 132.1, 133.0, 134.1, 137.1, 137.3, 139.4; HRMS (EI) calcd for $C_{15}H_{13}NOBrI$ 428.9225, found 428.9225; LRMS (EI) *m/z* 429 (M^+,23), 302 (87), 183 (100).

4.4.5. *N*-(2-Iodo-4,6-dimethylphenyl)acetamide. This compound was prepared according to general procedure I. A tan, crystalline solid (169–170 °C) was obtained in 82% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3416, 3377, 2924, 1687, 1486, 1369, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 6.95 (s, 1H), 7.01 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 23.4, 99.5, 131.8, 134.5, 137.0, 137.8, 139.2, 168.6; HRMS (EI) calcd for $C_{10}H_{12}INO$ 288.9964, found 288.9974; LRMS (EI) *m/z* 289 (M^++H, 7), 247 (61), 224 (16), 162 (100), 120 (48), 91 (30).

4.4.6. *N*-(2-Iodo-4,6-dimethylphenyl)-*trans*-crotonamide. This compound was prepared according to general procedure I. A white, crystalline solid was obtained in 31% yield. IR 3396, 2913, 1620, 1478, 1286; ^1H NMR (300 MHz, $CDCl_3$) 1.95 (d, *J*=5.6 Hz, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 6.06 (d, *J*=13.9 Hz, 1H), 6.89 (dq, *J*=13.9, 5.6 Hz, 1H), 6.94 (s,1H), 7.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 19.4, 20.4, 41.6, 99.3, 120.3, 131.2, 131.6, 134.2, 138.7, 138.9, 141.4, 169.2; HRMS (EI) calcd for $C_{12}H_{14}INO$ 315.0120, found 315.0127; LRMS (EI) *m/z* 315 (M^+, 33), 247 (62), 188 (100), 69 (73).

4.4.7. 3,5,7-Trimethyl-2,3-dihydroindole. This compound was prepared according to general procedure III. A clear, orange oil was obtained in 72% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2964, 2927, 2872, 2857, 1660, 1605, 1486, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J*=6.8 Hz, 3H), 2.22 (s, 3H), 2.37 (s, 3H), 3.19 (t, *J*=8.6 Hz, 1H), 3.38–3.50 (m, 1H), 3.78 (t, *J*=8.6 Hz, 1H), 6.82 (s, 1H), 6.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 18.6, 20.7, 36.9, 55.4, 118.8, 121.4, 128.1, 128.7, 133.9, 147.2; HRMS (EI) calcd for $C_{11}H_{15}N$– 161.1204, found 161.1211; LRMS (EI) *m/z* 161 (M^+, 67), 146 (100), 131 (67).

4.4.8. *rac*-*N*-Allyl-*N*-(2-iodophenyl)-*trans*-crotonamide (13).[9a] This compound was prepared according to general procedure I. A clear, yellow oil was obtained in 59% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1666, 1630, 1470, 1422, 1386, 1271; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, *J*= 7.0 Hz, 3H), 3.62 (dd, *J*=14.6, 7.6 Hz, 1H), 4.83 (dd, *J*= 14.6, 5.2 Hz, 1H), 4.98–5.11 (m, 2H), 5.44 (d, *J*=15.0 Hz, 1H), 5.80–5.98 (m, 1H), 6.94 (dq, *J*=14.6, 7.0 Hz, 1H), 7.06 (t, *J*=7.6 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.91 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 51.1, 100.7, 118.4, 122.3, 129.1, 129.6, 130.9, 132.6, 139.6, 142.1, 143.8, 165.2; HRMS (EI) calcd for $C_{13}H_{14}INO$ 327.0120, found 327.0123; LRMS (EI) *m/z* 327 (M^+, 3), 259 (21), 200 (99), 130 (33), 69 (100).

4.4.9. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)benzamide (17a). This compound was prepared according to general procedure II. A clear, colorless oil was obtained in 35% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1641, 1380, 1258; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.18 (s, 3H), 4.04 (dd, *J*=14.2, 7.9 Hz, 1H), 4.80 (dd, *J*= 14.2, 6.1 Hz, 1H), 5.05–5.20 (m, 2H), 6.08 (dddd, *J*=14.0, 9.9, 7.8, 6.2 Hz, 1H), 6.82 (s, 1H), 7.13 (t, *J*=7.6 Hz, 2H), 7.21 (d, *J*=7.6 Hz, 1H), 7.39 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.3, 53.1, 101.4, 119.0, 127.3, 127.9, 129.8, 132.0, 132.5, 135.8, 137.6, 138.3, 139.3, 140.7; HRMS (EI) calcd for $C_{18}H_{18}INO$ 391.0433, found 391.0432; LRMS (EI) *m/z* 391 (M^+, 27), 264 (70), 223 (31), 144 (32), 105 (100), 77 (58). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes: *i*PrOH; first eluting enantiomer (P) α_D^{23} +140, 87% ee (*c* 5.4 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} −191, 97% ee (*c* 2.4 mg/mL, $CHCl_3$).

4.4.10. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2-enyl)-4-bromobenzamide (17b). This compound was prepared according to general procedure II. A white, crystalline solid was obtained in 66% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1642, 1442, 1399, 1264, 1012; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.66 (s, 3H), 2.08 (s, 3H), 2.23 (s, 3H), 4.11 (dd, *J*=14.5, 8.6 Hz, 1H), 4.71 (dd, *J*=14.5, 6.8 Hz, 1H), 5.42 (app t, *J*=7.0 Hz, 1H), 6.85 (s, 1H), 7.28 (m, 4H), 7.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.6, 20.3, 25.7, 47.5, 101.2, 118.4, 124.3, 129.7, 130.6, 132.1, 134.9, 136.9, 137.7, 138.5, 139.5, 140.6, 168.8; HRMS (EI) calcd for $C_{20}H_{23}IBrNO$ 496.9851, found 496.9859; LRMS (EI) *m/z* 497 (M^+, 37), 454 (13), 429 (28), 302 (32), 191 (100). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes: *i*PrOH; first eluting enantiomer (M) α_D^{23} +156, 99% ee (*c* 1.4 mg/mL, $CHCl_3$); second eluting enantiomer (P) α_D^{23} −146, 98% ee (*c* 1.5 mg/mL, $CHCl_3$).

4.4.11. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-2-phenylacetamide (17c). This compound was prepared according to general procedure II. A clear, colorless oil was obtained in 93% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3066, 3024, 3013, 2961, 2926, 2858, 1652, 1466, 1456, 1389, 1261, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.33 (s, 3H), 3.22 (d, *J*=15.0 Hz, 1H), 3.40 (d, *J*= 15.0 Hz, 1H), 4.00 (dd, *J*=14.3, 7.5 Hz, 1H), 4.45 (dd, *J*= 14.3, 6.3 Hz, 1H), 5.05 (dd, *J*=10.0, 1.4 Hz, 1H), 5.09 (dd, *J*=17.3, 1.4 Hz, 1H), 5.96 (dddd, J=17.3, 10.0, 7.5, 6.3 Hz, 1H), 7.04 (s, 1H), 7.09 (d, *J*=6.2 Hz, 2H), 7.26 (m, 3H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.8, 41.8, 52.3, 102.3, 119.1, 119.2, 127.0, 128.5, 130.0, 132.5, 133.2, 134.9, 138.7, 140.4, 140.7, 171.0; HRMS (EI) calcd for $C_{19}H_{20}INO$ 405.0590, found 405.0601; LRMS (EI) *m/z* 405 (M^+, 43), 314 (19), 287 (26), 278 (100), 187 (58), 158 (52), 91 (97). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −55, 97% ee (*c* 3.5 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +59, >99% ee (*c* 1.4 mg/mL, $CHCl_3$).

4.4.12. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-phenylallyl)-2-phenylacetamide (17d). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 100% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3008, 2925, 1652, 1495, 1465, 1455, 1393, 1351, 1310, 1247, 968; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.32 (s, 3H), 3.23 (d, *J*=15.0 Hz, 1H), 3.43 (d, *J*=15.0 Hz, 1H), 4.19 (m, 1H), 4.57 (m, 1H), 6.37–6.40 (m,

2H), 7.02 (s, 1H), 7.07–7.12 (m, 2H), 7.18–7.30 (m, 8H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.4, 41.3, 51.3, 101.3, 124.1, 126.3, 126.6, 127.5, 128.1, 128.4, 129.5, 132.2, 133.4, 134.4, 136.5, 138.1, 138.3, 140.0, 140.1, 170.6; HRMS (EI) calcd for $C_{25}H_{24}INO$ 481.0903, found 481.0927; LRMS (EI) *m/z* 481 (M^+, 58), 390 (44), 363 (8), 236 (27), 158 (21), 117 (100), 91 (84). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −17, 94% ee (*c* 6.3 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +11, 98% ee (*c* 9.9 mg/mL, $CHCl_3$).

4.4.13. *rac*-*N*-But-2*E*-enyl-*N*-(2-iodo-4,6-dimethylphenyl)-2-phenylacetamide (17e). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 41% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3012, 2921, 2856, 1650, 1496, 1465, 1455, 1393, 1313, 1262, 1247, 1165, 970; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J*=5.9 Hz, 3H), 2.04 (s, 3H), 2.33 (s, 3H), 3.20 (d, *J*=15.0 Hz, 1H), 3.39 (d, *J*=15.0 Hz, 1H), 3.94 (dd, *J*=14.0, 7.1 Hz, 1H), 4.38 (dd, *J*=14.0, 6.3 Hz, 1H), 5.53 (m, 2H), 7.03 (s, 1H), 7.08 (m, 2H), 7.22 (m, 3H), 7.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.2, 20.3, 41.4, 50.9, 101.9, 125.5, 126.5, 128.0, 129.1, 129.5, 129.9, 132.0, 134.6, 138.2, 139.8, 140.3, 170.4; HRMS (EI) calcd for $C_{20}H_{22}INO$ 419.0746, found 419.0737; LRMS (EI) *m/z* 419 (M^+, 55), 292 (44), 238 (37), 174 (30), 158 (33), 91 (98), 55(100). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −46, 99% ee (*c* 4.7 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +41, 99% ee (*c* 11.4 mg/mL, $CHCl_3$).

4.4.14. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2-enyl)-2-phenylacetamide (17f). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 79% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3026, 3014, 2925, 2861, 1650, 1495, 1455, 1383, 1236, 1186, 1162, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.62 (s, 3H), 2.03 (s, 3H), 2.43 (s, 3H), 3.21 (d, *J*=15.0 Hz, 1H), 3.39 (d, *J*=15.0 Hz, 1H), 4.04 (dd, *J*=14.3, 8.0 Hz, 1H), 4.45 (dd, *J*=14.3, 7.1 Hz, 1H), 5.03 (dd, *J*=7.0, 7.0 Hz, 1H), 7.03 (s, 1H), 7.18 (m, 5H), 7.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 19.0, 20.3, 25.5, 41.1, 45.9, 53.8, 101.7, 118.7, 126.4, 127.9, 129.4, 131.9, 134.5, 136.2, 138.1, 139.7, 140.0, 170.4; HRMS (EI) calcd for $C_{21}H_{24}INO$ 433.0903, found 433.0901; LRMS (EI) *m/z* 433 (M^+, 100), 390 (9), 365 (27), 300 (21), 273 (14), 247 (17), 238 (41), 91 (93), 69 (66). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −49, 99% ee (*c* 2.2 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +43, 99% ee (*c* 4.5 mg/mL, $CHCl_3$).

4.4.15. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-3-phenylpropionamide (17g). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 97% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2926, 1649, 1395; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.28 (s, 3H), 2.95–3.05 (m, 2H), 3.96 (dd, *J*=14.3, 7.6 Hz, 1H), 4.54 (dd, *J*=14.3, 6.5 Hz, 1H), 5.04–5.15 (m, 2H), 5.97 (dddd, *J*=6.5, 7.5, 9.8, 13.7 Hz, 1H), 7.02 (s, 1H), 7.10–7.20 (m, 3H), 7.23 (d, *J*=6.7 Hz, 2H), 7.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.4, 31.2, 36.3, 51.6, 101.4, 118.7, 125.9, 128.3, 128.5, 132.1, 132.9, 137.7, 138.3, 139.9, 140.1, 141.4, 171.8; HRMS (EI) calcd for $C_{20}H_{22}INO$ 419.0746, found 419.0743; LRMS (EI) *m/z* 419 (M^+, 32), 292 (100), 160 (37), 158 (32), 155 (25), 131 (34), 105 (59). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −60, 99% ee (*c* 3.8 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +58, 99% ee (*c* 4.3 mg/mL, $CHCl_3$).

4.4.16. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-*trans*-crotonamide (17h). This compound was prepared according to general procedure I. A white, crystalline solid was obtained in 64% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2984, 2854, 1666, 1629, 1445, 1384, 1273; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (dd, *J*=6.9, 1.5 Hz, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 3.94 (ddd, *J*=14.3, 7.1, 0.6 Hz, 1H), 4.58 (dd, *J*=14.3, 6.4 Hz, 1H), 5.02–5.11 (m, 2H), 5.48 (dd, *J*=15.0, 1.7 Hz, 1H), 5.97 (dddd, *J*=17.0, 10.0, 7.7, 6.5 Hz, 1H), 7.00 (dq, *J*=15.0, 6.9 Hz, 1H), 7.04 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.7, 20.5 51.6, 101.6, 118.7, 121.9, 125.4, 132.0, 133.1, 138.2, 138.8, 139.9, 140.0, 142.4, 165.8; HRMS (EI) calcd for $C_{15}H_{18}INO$ 355.0433, found 355.0445; LRMS (EI) *m/z* 355 (M^+, 25), 340 (20), 313 (13), 287 (16), 228 (100), 18 (39), 158 (32), 69 (68).

4.4.17. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2*E*-enyl)acetamide (17i). This compound was prepared according to general procedure I. An orange-yellow oil was obtained in 84% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3005, 2926, 2858, 1643, 1553, 1467, 1440, 1396, 1289, 1034, 908; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.62 (s, 3H), 1.74 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 3.94 (dd, *J*=14.5, 8.2 Hz, 1H), 4.50 (dd, *J*=14.5, 7.1 Hz, 1H), 5.26 (m, 1H), 7.03 (s, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.4, 20.5, 22.4, 25.7, 45.6, 101.2, 118.9, 132.0, 136.4, 137.9, 138.3, 139.8, 140.9, 170.3; HRMS (EI) calcd for $C_{15}H_{20}INO$ 357.0590, found 357.0603; LRMS (EI) *m/z* 357 (M^+, 95), 314 (37), 300 (46), 289 (83), 247 (56), 232 (46), 162 (87), 69 (100).

4.4.18. Phenyl-(3,5,7-trimethyl-2,3-dihydroindol-1-yl)methanone (18a). This compound was prepared according to general procedure IV. The atropisomer **M-17a** (>99% ee, second eluting enantiomer) yielded a white, crystalline solid in 92% yield (87% ee, −3, second eluting enantiomer). The atropisomer **P-17a** (99% ee, first eluting enantioimer) yielded a white, crystalline solid in 95% yield (86% ee, +3, first eluting enantiomer). A racemic standard of the title compound was prepared in 98% yield by radical cyclization of *rac*-**17a** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2966, 1649, 1371, 1264; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*=7.0 Hz, 3H), 2.20 (s, 3H), 2.34 (s, 3H), 3.33 (sex, *J*=7.3 Hz, 1H), 3.65 (dd, *J*=10.4, 7.6 Hz, 1H), 4.22 (dd, *J*=10.4, 7.7 Hz, 1H), 6.88 (s, 1H), 6.91 (s, 1H), 7.40–7.55 (m, 3H), 7.74 (d, *J*=6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.9, 21.1, 36.9,

61.6, 121.2, 128.4, 128.5, 128.6, 130.3, 131.1, 135.2, 136.2, 139.2, 139.5, 169.6; HRMS (EI) calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1462; LRMS (EI) *m/z* 265 (M^+, 39), 105 (100), 77 (35).

4.4.19. (4-Bromophenyl)-(3-isopropyl-5,7-dimethyl-2,3-dihydroinol-1-yl)methanone (18b). This compound was prepared according to general procedure IV. The atropisomer **P-17b** (99% ee, first eluting enantiomer) yielded a white, crystalline solid in 72% yield (48% ee, +16, second eluting enantiomer). The atropisomer **M-17b** (98% ee, second eluting enantiomer) yielded a white, crystalline solid in 95% yield (47% ee, −15, first eluting enantiomer). IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1649, 1421, 1267, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=7.2 Hz, 3), 1.92 (sex, *J*=6.7 Hz, 1H), 2.16 (s, 3H), 2.33 (s, 3H), 2.99 (m, 1H), 3.86 (dd, *J*=10.8, 3.3 Hz, 1H), 4.08 (dd, *J*=10.8, 8.1 Hz, 1H), 6.89 (s, 1H), 6.91 (s, 1H), 7.60 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 20.0, 20.3, 21.1, 30.8, 48.2, 56.2, 122.8, 125.7, 128.4, 130.2, 130.6, 131.7, 135.1, 134.2, 136.8, 139.6, 168.6; HRMS (EI) calcd for $C_{20}H_{22}N-OBr$ 371.0885, found 371.0870; LRMS (EI) *m/z* 371 (M^+, 33), 183 (87), 91 (100).

4.4.20. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18c). This compound was prepared according to general procedure IV. The atropisomer **M-17c** (97% ee, first eluting enantiomer) yielded a clear oil in 53% yield (87% ee, −32, second eluting enantiomer). The atropisomer **P-17c** (>99% ee, second eluting enantiomer) yielded a clear oil in 54% yield (93% ee, +27, first eluting enantiomer). A racemic standard of the title compound was prepared in 74% yield by radical cyclization of *rac*-**17c** according to general procedure III. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2965, 2928, 1649, 1388; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=6.8 Hz, 3H), 2.26 (s, 3H), 2.30 (s, 3H), 3.21 (sex, *J*=6.9 Hz, 1H), 3.52 (dd, *J*=10.3, 7.3 Hz, 1H), 3.88 (s, 2H), 4.17 (app t, *J*=8.5 Hz, 1H), 6.81 (s, 1H), 6.87 (s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.5, 20.9, 36.5, 43.4, 58.4, 121.0, 126.8, 127.1, 128.6, 128.7, 129.6, 130.4, 135.0, 135.1, 136.0, no carbonyl signal observed; IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1679, 1500, 1480, 1265, 1257; HRMS (EI) calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1627; LRMS (EI) *m/z* 279 (M^+, 64), 188 (7), 161 (100), 146 (69), 91 (52).

4.4.21. 1-(3-Benzyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18d). This compound was prepared according to general procedure IV. The atropisomer **M-17d** (94% ee, first eluting eluting enantiomer) yielded a clear oil in 72% yield (75% ee, −29, second eluting enantiomer). The atropisomer **P-17d** (>99% ee, second eluting enantiomer) yielded a clear oil in 95% yield (75% ee, +24, first eluting enantiomer). A racemic standard of the title compound was prepared in 79% yield by radical cyclization of *rac*-**17d** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1660, 1377, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.29 (s, 3H), 2.53 (dd, *J*=13.9. 9.9 Hz, 1H), 2.96 (dd, *J*=13.9, 5.3 Hz, 1H), 3.35 (m, 1H), 3.76 (m, 1H), 3.82 (d, *J*=3.2 Hz, 2H), 3.94 (dd, *J*=10.6, 7.4 Hz, 1H), 6.75 (s, 1H), 6.91 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.0, 29.7, 39.6, 43.6, 55.9, 121.8, 126.4, 126.9, 128.6 (2C), 128.8 (6C), 130.9, 135.0, 135.1, 127.7, 137.7, 139.2; HRMS (EI) calcd for $C_{25}H_{25}NO$ 355.1936, found 355.1938; LRMS (EI) *m/z* 355 (M^+, 37), 146 (100), 131 (20), 105 (18), 91 (62).

4.4.22. 1-(3-Ethyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18e). This compound was prepared according to general procedure IV. The atropisomer **M-17e** (>99% ee, first eluting enantiomer) yielded a clear oil in 71% yield (83% ee, −38, second eluting enantiomer). The atropisomer **P-17e** (>99% ee, second eluting enantiomer) yielded a clear oil in 77% yield (79% ee, +34, first eluting enantiomer). A racemic standard of the title compound was prepared in 97% yield by radical cyclization of *rac*-**17e** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 2876, 1656, 1598, 1379, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.4 Hz, 3H), 1.25–1.35 (m, 1H), 1.61–1.70 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.95 (m, 1H), 3.69 (dd, *J*=10.3, 5.4 Hz, 1H), 3.88 (s, 2H), 4.09 (app t, *J*=8.8 Hz, 1H), 6.82 (s, 1H), 6.87 (s, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 20.5, 20.9, 26.2, 56.2, 64.7, 121.7, 126.8, 128.7, 128.8, 130.0, 130.6, 134.9, 135.2, 138.4, 139.1; HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1780, found 293.1779; LRMS (EI) *m/z* 293 (M^+, 64), 175 (86), 146 (100), 91 (56).

4.4.23. 1-(3-Isopropyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18f). This compound was prepared according to general procedure IV. The atropisomer **P-17f** (>99% ee, first eluting enantiomer) yielded a white, waxy solid in 79% yield (60% ee, +12, second eluting enantiomer). The atropisomer **M-17f** (>99% ee, second eluting enantiomer) yielded a white, waxy solid in 81% yield (58% ee, −11, first eluting enantiomer). A racemic standard of the title compound was prepared in 63% yield by radical cyclization of *rac*-**17f** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1656, 1602, 1378; ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H), 1.77 (o, *J*=6.7 Hz, 1H), 2.24 (s, 3H), 2.29 (s, 3H), 2.83 (q, *J*=5.9 Hz, 1H), 3.86 (m, 2H), 3.92 (m, 2H), 6.81 (s, 1H), 6.87 (s, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 20.3, 20.7, 21.0, 30.5, 43.7, 48.1, 54.5, 122.8, 126.9, 128.7, 128.9, 130.7, 134.6, 135.0, 136.9, 136.9, 139.4, 168.9; LRMS (EI) *m/z* 307 (M^+, 22), 189 (19), 146 (100), 91 (47), 69 (16); HRMS (EI) calcd for $C_{19}H_{20}INO$ 307.1936, found 307.1931; LRMS (EI) *m/z* 307 (M^+, 27), 189 (22), 146 (100), 91 (37).

4.4.24. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-3-phenylpropanone (18g). This compound was prepared according to general procedure IV. The atropisomer **M-17g** (>99% ee, first eluting enantiomer) yielded a clear oil in 74% yield (90% ee, −25, second eluting enantiomer). The atropisomer **P-17g** (96% ee, second eluting enantiomer) yielded a clear oil in 67% yield (85% ee, +24, first eluting enantiomer). A racemic standard of the title compound was prepared in 68% yield by radical cyclization of *rac*-**17g** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1641, 1421, 1264; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J*=6.8 Hz, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.8 (t, *J*=7.5 Hz, 2H), 3.09 (t, *J*=7.5 Hz, 2H), 3.08–3.20 (m, 1H), 3.46 (dd, *J*=10.1, 7.7 Hz, 1H), 4.10 (m, 1H), 6.81 (s, 1H), 6.86 (s, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.0, 29.7, 31.8, 35.9, 41.4, 58.4,

118.1, 121.1, 126.0, 126.2, 127.6, 128.5, 129.0, 130.4, 132.0, 133.0, 134.9, 138.2, 138.9, 141.1, 172.1; HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1780, found 279.1792; LRMS (EI) *m/z* 293 (M^+, 34), 205 (9), 161 (100), 146 (38), 105 (25), 91 (44).

4.4.25. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-but-2-enone (18h). IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1666, 1630, 1470, 1423; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=6.7 Hz, 3H), 1.92 (dd, J=6.9, 1.5 Hz, 3H), 2.22 (s, 3H), 2.31 (s, 3H), 3.32 (sex, J=7.1 Hz, 1H), 3.61 (dd, J=10.2, 7.6 Hz, 1H), 4.33 (app t, J=8.2 Hz, 1H), 6.17 (d, J=15.0 Hz, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 7.00 (dt, J=15.0, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 18.2, 20.2, 21.0, 21.1, 36.5, 58.9, 121.3, 124.6, 130.4, 134.9, 138.9, 140.2, 141.7, 165.4; HRMS (EI) calcd for $C_{11}H_{15}N-$ 161.1204, found 161.1211; LRMS (EI) *m/z* 161 (M^+, 67), 146 (100), 131 (67).

4.4.26. 1-(3-Isopropyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-methanone (18i). This compound was prepared according to general procedure III in 80% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2957, 2925, 2872, 1667, 1477, 1386; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.9 Hz, 3H), 1.89–2.03 (m, 1H), 2.22 (s, 6H), 2.30 (s, 3H), 2.85–3.00 (m, 1H), 3.80–4.05 (m, 2H), 6.85 (s, 1H0, 6.86 (s, 1H); HRMS (EI) calcd mass for $C_{15}H_{15}NO$ 231.1623, found 231.1619; LRMS (EI) *m/z* 231 (M^+, 19), 189 (8), 146 (100), 130 (22), 115 (6).

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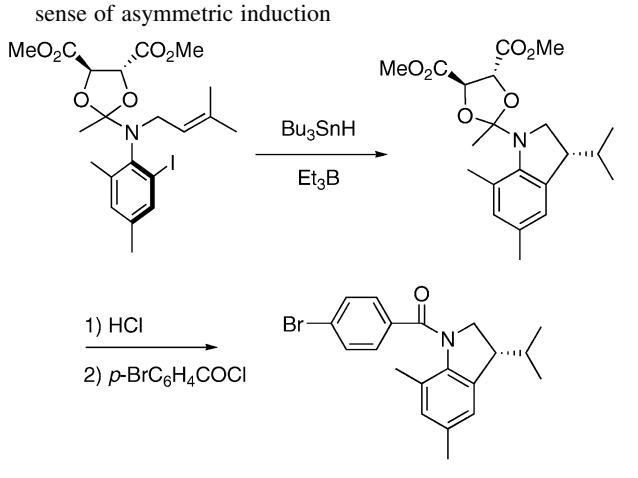

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