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Catalytic Asymmetric Synthesis of Axially Chiral *o*-Iodoanilides by Phase-Transfer Catalyzed Alkylations

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Supporting Information

ABSTRACT: Catalytic asymmetric synthesis of axially chiral *o*-iodoacrylanilides and *N*-allyl-*o*-iodoanilides as useful chiral building blocks was achieved via chiral quaternary ammonium salt-catalyzed *N*-alkylations under phase-transfer conditions. The transition-state structure for the present reaction is discussed on the basis of the X-ray crystal structure of ammonium anilide.

Axially chiral anilides have received much attention in recent years as attractive atropisomeric compounds possessing an N−Ar chiral axis.[1] Many interesting properties of axially chiral anilides have been reported not only in the field of organic chemistry[2,3] but also in peptoid chemistry.[4] Furthermore, the structure of axially chiral anilides is observed in biologically active compounds such as metolachlor[5] and methaqualone;[6] hence, the development of methods for enantioselective synthesis of these axially chiral anilides is an important task for organic chemistry. Although several examples of catalytic asymmetric synthesis of axially chiral anilides have been reported,[7,8] the structure of the products is mainly limited to *o*-*tert*-butylanilides **1** possessing a bulky *tert*-butyl group to obtain high enantioselectivities (Figure 1).[7]

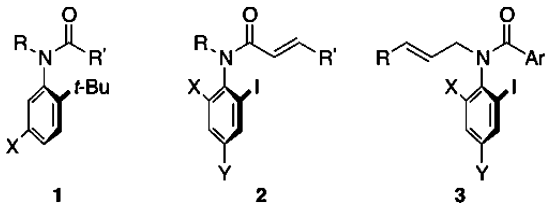

Figure 1. Axially chiral anilides.

For this reason, the development of novel catalytic asymmetric methods for the synthesis of different types of axially chiral anilides is highly desirable.

Our target structures of axially chiral anilides in catalytic asymmetric synthesis are *o*-iodoacrylanilides **2** and *N*-allyl-*o*-iodoanilides **3** (Figure 1), which are useful chiral building blocks for organic synthesis. Although the synthetic utility of these chiral compounds has been elegantly demonstrated by Curran in the chemistry of memory of axial chirality,[3,9] optical resolution or a stoichiometric amount of chiral reagent is required to obtain the optically active axially chiral anilides, and the catalytic asymmetric methods for the synthesis of these compounds are still unknown. Here we report a valuable example of catalytic asymmetric synthesis of axially chiral *o*-iodoanilides via phase-transfer catalyzed *N*-alkylations.[10,11]

We first examined the screening of binaphthyl-modified chiral ammonium salts (*S*)-**5**[12] as phase-transfer catalysts for asymmetric alkylation of *o*-iodoacrylanilide **4** (Table 1). Attempted reaction of *o*-iodoacrylanilide **4a** and benzyl bromide with solid KOH (2.0 equiv) in diisopropyl ether[13] under the influence of catalyst (*S*)-**5a** or (*S*)-**5b** (2 mol %) at 0 °C for 24 h afforded the axially chiral *o*-iodoacrylanilide **2a** in high yields with moderate enantioselectivities (34−52% ee, Table 1, entries 1 and 2). Switching the catalyst to (*S*)-**5c** and (*S*)-**5d**, which possess radially extended aromatic substituents (Ar), improved the enantioselectivities, and the product **2a** was obtained with good enantioselectivities (82−83% ee, entries 3 and 4). Next, the effect of alkyl chain length (R) in catalyst (*S*)-**5** was carefully examined (entries 4−8), and the catalyst (*S*)-**5f** possessing hexyl groups gave higher enantioselectivity (89% ee, entry 6). This was not improved by the screening of solvents (entries 9−13). The highest enantioselectivity was attained when lower temperature (−20 °C) was employed in diisopropyl ether as a solvent with catalyst (*S*)-**5f** (90% ee, entry 14). The absolute configuration of product **2a** was determined by X-ray diffraction (XRD) analysis.[14,15]

With these optimum reaction conditions in hand, we studied the substrate generality of asymmetric alkylation of *o*-iodoacrylanilides **4** under the influence of chiral phase-transfer catalyst (*S*)-**5f** (Scheme 1). Various types of *o*-iodoacrylanilides **4** were found to be employable for the reaction to give axially chiral anilides **2a**−**2d** in good to high enantioselectivities (80−96% ee). Furthermore, a series of alkyl halides were tolerated in this reaction, thus allowing the preparation of structurally diverse, enantioenriched axially chiral *o*-iodoacrylanilides (**2e**−**2h**, 80−92% ee). The introduction of different substituents at the ortho- and para-positions (X and Y) of anilide **4** also worked well to give high enantioselectivities (**2i**−**2l**, 92−95% ee).[16]

To expand the utility of this synthetic method, we also examined asymmetric allylation of *o*-iodoanilides **6** to give axially chiral *N*-allyl-*o*-iodoanilides **3** as useful chiral building blocks (Scheme 2).[3] Not only allyl bromide but also crotyl bromide and methallyl bromide were employable for the reaction to give axially chiral anilides **3a**−**3d** in good to high enantioselectivities (88−90% ee). The allyl bromide possessing a functional group was also employable for the reaction

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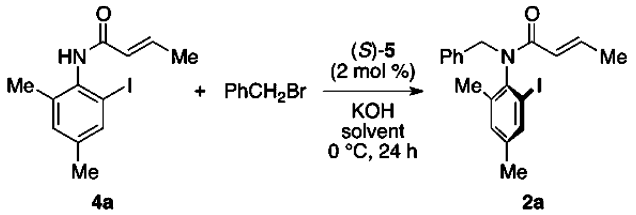
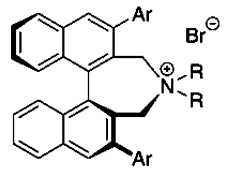
Table 1. Optimization of the Reaction Conditions[a]



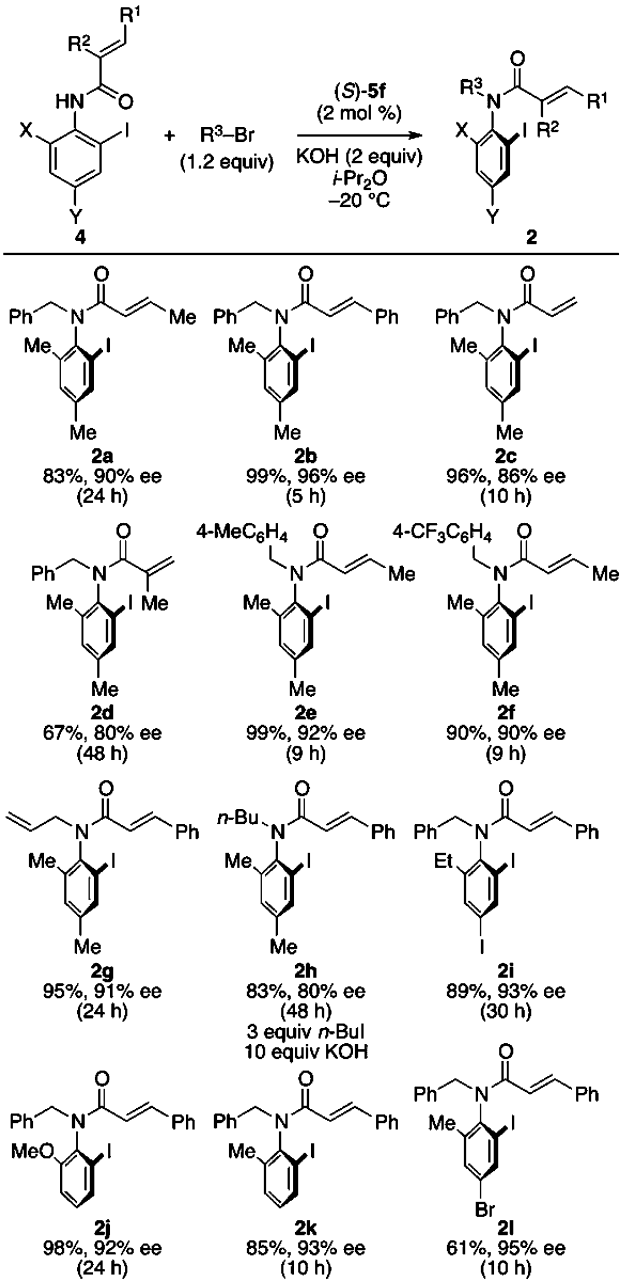


(*S*)-**5a**: Ar = 3,5-$(CF_3)_2$-C_6H_3, R = *n*-Bu
(*S*)-**5b**: Ar = 3,5-$(t\text{-Bu})_2$-C_6H_3, R = *n*-Bu
(*S*)-**5c**: Ar = 3,5-[3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Bu
(*S*)-**5d**: Ar = 3,5-[3,5-$(t\text{-Bu})_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Bu
(*S*)-**5e**: Ar = 3,5-[3,5-$(t\text{-Bu})_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Pen
(*S*)-**5f**: Ar = 3,5-[3,5-$(t\text{-Bu})_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Hex
(*S*)-**5g**: Ar = 3,5-[3,5-$(t\text{-Bu})_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Hep
(*S*)-**5h**: Ar = 3,5-[3,5-$(t\text{-Bu})_2$-C_6H_3]$_2$-C_6H_3, R = *n*-Oct

entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	(*S*)-**5a**	*i*-Pr_2O	86	52
2	(*S*)-**5b**	*i*-Pr_2O	90	34
3	(*S*)-**5c**	*i*-Pr_2O	77	82
4	(*S*)-**5d**	*i*-Pr_2O	82	83
5	(*S*)-**5e**	*i*-Pr_2O	97	88
6	(*S*)-**5f**	*i*-Pr_2O	85	89
7	(*S*)-**5g**	*i*-Pr_2O	83	87
8	(*S*)-**5h**	*i*-Pr_2O	98	85
9	(*S*)-**5f**	toluene	72	82
10	(*S*)-**5f**	CCl_4	85	73
11	(*S*)-**5f**	Et_2O	83	83
12	(*S*)-**5f**	CPME[d]	78	83
13	(*S*)-**5f**	*t*-BuOMe	89	70
14[e]	(*S*)-**5f**	*i*-Pr_2O	83	90

[a]Reaction conditions: **4a** (0.050 mmol), benzyl bromide (0.060 mmol), and solid KOH powder (0.10 mmol) in the presence of (*S*)-**5** (2 mol %) in solvent (1.0 mL) at 0 °C for 24 h. [b]Yield of isolated products. [c]Determined by chiral HPLC analysis. [d]CPME = cyclopentyl methyl ether. [e]Reaction was performed at −20 °C.

Scheme 1. Asymmetric Alkylation of *o*-Iodoacrylanilides 4



(**3e**, 93% ee). The absolute configuration of product **3a** was confirmed by comparison of the optical rotation with the literature value.[3b,16]

The obtained axially chiral products can be readily transformed to other useful compounds (Scheme 3). For example, axially chiral *N*-allyl-*o*-iodoanilide **3b** was transformed to 3-methyl indoline **7** via radical cyclization with high chirality transfer from axial chirality to *C*-centered chirality.[3b] Furthermore, *o*-iodoanilide **2a** was transformed to axially chiral phosphine oxide **8**, which was attractive precursor for the design of novel chiral ligands and catalysts,[17] without any loss of stereoinformation.[3g]

To obtain insight into the transition-state structure for the present enantioselective synthesis of axially chiral anilides, we tried XRD analysis of ammonium anilides prepared from chiral ammonium bromides (*S*)-**5** and *o*-iodoanilides **6**. Several kinds of ammonium anilides were prepared to obtain crystals suitable for XRD analysis, and we finally succeeded in obtaining a single-crystal X-ray structure of (*S*)-**5i**, which was prepared from an ammonium bromide (*S*)-**5a** and *o*-iodoanilide **6** (Ar = Ph).[18] The crystal structure of (*S*)-**5i** provides important structural information. The bond lengths of the amide moiety (O−C, 1.348 Å; N−C, 1.351 Å) indicate that the negative charge of the anilide anion is delocalized as shown in Figure 2.[15]

Based on the X-ray crystal structure of (*S*)-**5i**, plausible transition-state models (**A** and **B**) have been proposed to account for the absolute configuration of products **2** and **3** (Figure 2). The transition state **A** might be more favorable than **B** to avoid steric repulsion between aryl group (Ar) on (*S*)-**5** and iodide on anilide anion (**A** ≫ **B** in Figure 2). The binaphthyl unit of catalyst (*S*)-**5** completely shielded the back side of the anilide anion, allowing alkyl halide to approach from the front in transition state **A**, leading to products **2** and **3** with the observed absolute configurations. This explanation of the steric effect of aryl group (Ar) on catalyst (*S*)-**5** to obtain high enantioselectivities was supported by the results in Table 1, which were radially extended bulky aromatic substituents (Ar)

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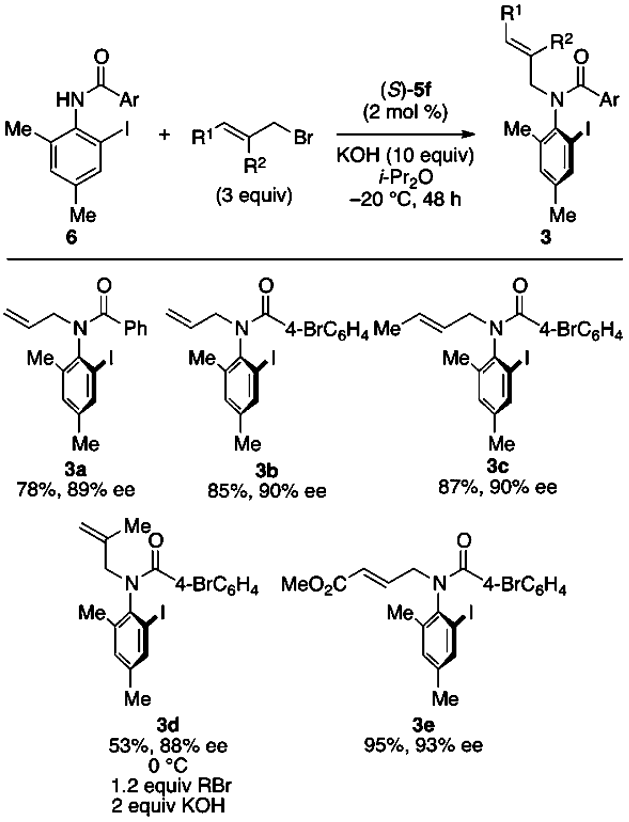
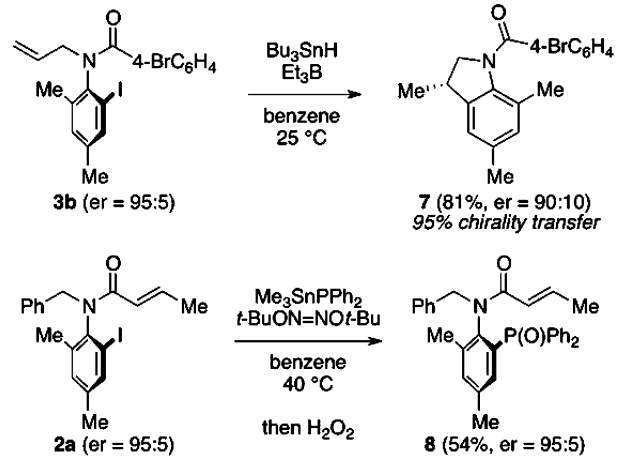
Scheme 2. Asymmetric Allylation of *o*-Iodoanilides 6



Scheme 3. Transformation of the Axially Chiral *o*-Iodoanilides



on catalyst (*S*)-**5**, which gave the higher enantioselectivities (entries 3,4 vs 1,2 in Table 1).

The discussion on transition-state structure in Figure 2 indicates that the catalyst (*S*)-**5** recognizes the steric difference between iodide and methyl groups as ortho-substituents on anilide. Based on this hypothesis, the size effect of ortho-substituent on *o*-iodoanilide was investigated by introducing different halogens (X) to the ortho-position of *o*-iodoanilide **4** (Scheme 4). A clear size effect of ortho-substituent on enantioselectivities was observed (F > Cl > Br),[19] and the results strongly supported our hypothesis.

In summary, we have successfully developed catalytic asymmetric synthesis of axially chiral *o*-iodoanilides as synthetically

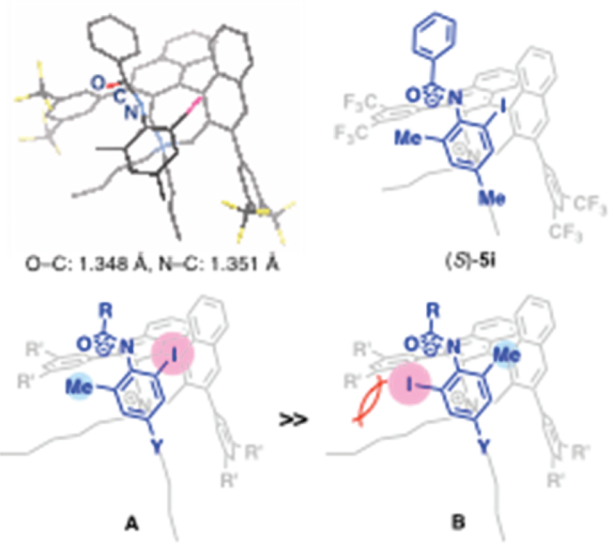
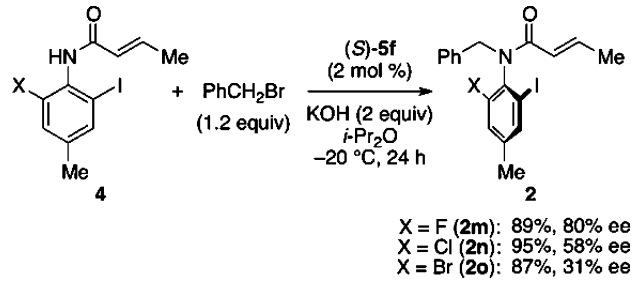


Figure 2. X-ray crystal structure of (*S*)-**5i** and plausible transition-state models.

Scheme 4. Effect of Ortho-Substituent



useful compounds. Furthermore, the transition-state structure of the present reaction has been discussed on the basis of the X-ray crystal structure of ammonium anilide. Future studies will be directed toward further expansion of the reaction scope.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Diisopropyl ether may contain peroxides, which are formed by contact with air, and requires care for treatment.

(14) The crystal structure of **2a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 845829). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

(15) Bond lengths of amide moiety in product **2a**: O—C, 1.223 Å; N—C, 1.379 Å. See also ref 3.

(16) The absolute configurations of products **2b—2o** and **3b—3e** were tentatively assigned by analogy.

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(18) The crystal structure of (*S*)-**5i** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 845830). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

(19) The product **2m** gradually racemized at room temperature ($t_{1/2} \approx$ 3.5 days at 25 °C, $\Delta G \approx$ 25.6 kcal/mol).