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## Efficient synthesis of various atropisomeric amides in optically pure forms and their application to asymmetric reactions

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## Abstract

Various atropisomeric amides were prepared in optically pure forms ( $\geq$ 98% ee) through the optical resolution of the amide ester derived from (*R*)-pantolactone, *N*-allyl-*ortho-tert*-butylaniline and oxalyl chloride. Asymmetric carbonyl addition reaction of an alkyllithium and asymmetric iodolactonization with these atropisomeric amides proceeded with high stereoselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

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*N*-Substitued anilide derivatives bearing a large substituent such as a *tert*-Bu group at the *ortho*position are pointed out to have axial chirality due to the high rotation barrier of the N-Ar bond.<sup>1a,d</sup> Recently, Curran and several other groups have reported highly stereoselective reactions (atroposelective reactions) using such atropisomeric anilides,<sup>1</sup> while these reactions could not be applied to asymmetric reactions because of the use of racemic anilides. We have succeeded in the first synthesis of an atropisomeric amide (+)-**2a** with high optical purity (96% ee) and definite absolute configuration, and the development of iodine-mediated asymmetric Diels-Alder reaction with (+)-**2a**.<sup>2a,b,3</sup> Although the synthesis of the optically active amide (+)-**2a** was achieved through the optical resolution of the amide derived from (S)-O-acetyllactic acid and N-allyl-ortho-tert-butylaniline (Scheme 1), this method is limited to the preparation of only acrylamide as substrate. In addition, (S)-O-acetyllactic acid cannot be reused as an optical resolution reagent, because the synthetic pathway involves the loss of the chiral center. In this paper, we report an efficient and general synthetic method of optically pure forms of various atropisomeric amides **2**-**4** (Scheme 2). Furthermore, the results of asymmetric reactions with atropisomeric amides **3** and **4** are also described.

We designed the axially chiral amide methyl ester 6 as a common intermediate for the synthesis of various optically active atropisomeric amides (Scheme 3). The optically pure form of 6 was found to be efficiently synthesized through the optical resolution of the amide ester prepared from (R)-pantolactone, N-allyl-ortho-tert-butylaniline and oxalyl chloride. That is, diastereomeric amide ester 5 and 5', on

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## Scheme 2.

the basis of the chiral center of pantolactone and axial chirality of anilide, can be easily separated by recrystallization (from Et<sub>2</sub>O-hexane) to give the diastereomerically pure amide **5** in 30% yield overall. The pantolactone ester part could be selectively converted to the methyl ester to obtain an optically pure form of amide methyl ester (-)-**6** (85% yield,  $\geq$ 98% ee). Racemization of (-)-**6** in the solution or the crystalline state was not observed after standing for more than 3 weeks at room temperature (more than 1 year in a freezer). The optical purity of (-)-**6** was determined by HPLC analysis using CHIRALPAK AS column [25×0.46 cm i.d.; solvent, 1% *i*-PrOH in hexane, (-)-**6**;  $t_{\rm R}$ =16.3 min, (+)-**6**;  $t_{\rm R}$ =18.9 min]. Amide ester (-)-**6** can be converted into various  $\alpha$ -ketoamides **3** and  $\alpha$ ,  $\beta$ -unsaturated amides **2**<sup>4</sup> without racemization in accordance with a reaction pathway shown in Scheme 3;<sup>2a,b</sup> thus, (-)-**6** should be a useful synthetic intermediate for the preparation of various atropisomeric amides. The absolute configuration of (-)-**6** was determined from the [ $\alpha$ ]<sub>D</sub> value of acrylamide (-)-**2a**, which was previously reported by us.<sup>2a,b</sup>



In the above protocol for the synthesis of atropisomeric amides, the following points are noteworthy: (1) cheap (R)-pantolactone can be used as an optical resolution reagent, and in our study it was recovered without racemization and reused; (2) an efficient optical resolution by recrystallization makes large-scale preparation possible; (3) various axially chiral amides can be prepared by the appropriate choice of Grignard reagents (Grignard reagents preferentially attack the ester site and not the amide part); (4) all

the reactions in this synthetic pathway proceeded without racemization to give atropisomeric amides in optically pure forms ( $\geq$ 98% ee).

This synthetic method supplies various axially chiral amides as useful chiral molecules. For example, addition reactions of methyllithium and *n*-butyllithium to  $\alpha$ -ketoamide 3d, which was obtained by the reaction of amide ester (-)-6 with PhMgBr, proceeded with high diastereoselectivity to give  $\alpha$ -hydroxyamides 7d (86% de) and 8d ( $\geq$ 96% de), respectively (Scheme 4).<sup>5</sup> It should be noted that in the reaction with this atropisomeric amide, high diastereoselectivity could be achieved by simply treating with alkyllithium without any assistance such as from Lewis acid.<sup>5,6</sup> The stereochemistries of 7d and 8d were determined from the [ $\alpha$ ]<sub>D</sub> values after conversion to the known hydroxyaldehyde 10d<sup>7</sup> and diol 13d,<sup>8</sup> respectively. The observed diastereoselectivities may be rationalized on the basis of the conformation of 3d found by X-ray crystallography. The X-ray crystal structure indicates an orthogonal conformation between the ketone and amide carbonyl groups,<sup>9</sup> a *trans*-relationship between the amide oxygen and the *tert*-butylphenyl group, and a large torsion angle (80.8°) between the amide and the *tert*-butylphenyl group (Fig. 1). In this conformer, alkyllithium should preferentially attack from the *si*-face of ketone (path a), because the attack from the *re*-face brings about steric repulsion with the *tert*-butylphenyl group (path b, Fig. 2).



Scheme 4.



Figure 1. Chem 3D drawing of 3d obtained by X-ray analysis. Hydrogen atoms have been omitted for clarity



Figure 2. The origin of diastereoselectivity

Asymmetric iodolactonization reaction with  $\alpha, \alpha$ -bis-allylhydroxyacetanilide 14 which was prepared via hydrogenation of 6 and subsequent allylation, was also found to proceed with high diastereotopic-group selectivity (Scheme 5). We previously reported an enantiotopic-group selective iodolactonization with similar  $\alpha, \alpha$ -bis-allyl- $\alpha$ -hydroxyacetic acid which proceeds in the presence of Ti–(*R*,*R*)-TADDOL complex to give iodolactone *cis*-(-)-15 of 65% ee.<sup>10</sup> In the diastereotopic-group selective iodolactonization nization with amide 14, *cis*-(+)-15 of 82% ee and *trans*-(+)-15 of 91% ee were obtained in a ratio of 2:1, respectively.<sup>11,12</sup> The enantioselectivity of the present reaction may be explained on the basis of the transition state model shown in Fig. 3. The reaction may proceed through transition state  $A^{\neq}$  to preferentially give *cis*-(+)-15, because the reaction through transition state  $B^{\neq}$  brings about steric repulsion between the *ortho-tert*-butyl and allyl groups.



Figure 3. The origin of the enantioselectivity in the asymmetric iodolactonization

In conclusion, we have succeeded in the development of an efficient synthetic method of various optically pure atropisomeric amides ( $\geq$ 98% ee). Furthermore, it was also found that the asymmetric carbonyl addition reaction of an alkyllithium and asymmetric iodolactonization with these atropisomeric amides proceeds with high stereoselectivity.

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