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Highly Enantioselective Synthesis of Atropisomeric Anilide Derivatives through Catalytic Asymmetric N-Arylation: Conformational Analysis and Application to Asymmetric Enolate Chemistry

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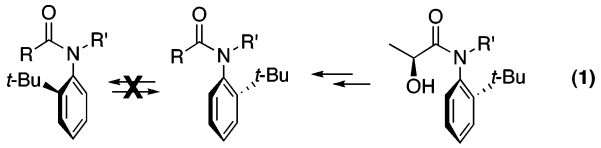
Abstract: In the presence of (*R*)-DTBM-SEGPHOS−$Pd(OAc)_2$ catalyst, N-arylation (aromatic amination) of various *o*-*tert*-butylanilides with *p*-iodonitrobenzene proceeds with high enantioselectivity (88−96% ee) to give atropisomeric *N*-(*p*-nitrophenyl)anilides having an N−C chiral axis in good yields. Atropisomeric anilide products highly prefer to exist as the *E*-rotamer which has trans-disposed *o*-*tert*-butylphenyl group and carbonyl oxygen. The application of the present catalytic enantioselective N-arylation to an intramolecular version gives atropisomeric lactam derivatives with high optical purity (92−98% ee). The reaction of the lithium enolate prepared from the atropisomeric anilide and lactam products with various alkyl halides gives α-alkylated products with high diastereoselectivity (diastereomer ratio = 13:1 to 46:1).

Introduction

N-Substituted *o*-*tert*-butylanilide derivatives are known to exist as stable atropisomers at room temperature and have a large N−Ar torsion angle (∼90°) toward the amide plane (eq 1).[1] In 1994, Curran et al. showed that N−C axial chirality of such anilides highly controls the formation of a new chiral center.[2] Since this report, atropisomeric anilides have received much attention as novel atropiosomeric molecules having an N−C chiral axis.[3] On the other hand, in early studies on diastereoselective (atropselective) reactions reported by Curran et al. followed by other groups, since racemic anilide derivatives were employed,[2,4] application of such anilides to an asymmetric reaction had to wait until their optically pure forms were available.

In 1997, we succeeded in the first synthesis of atropisomeric *o*-*tert*-butylanilide with high optical purity (96% ee) and definite absolute configuration through optical resolution of diastereomeric anilide derived from (*S*)-lactic acid derivative (eq 1).[5a,b] Following our publications, although synthesis of various optically active atropisomeric anilide derivatives was also reported by other groups, in most cases, a multistep sequence from a chiral pool precursor or HPLC separation using a chiral column was required.[6] Uemura and Simpkins reported the highly enantioselective synthesis of atropisomeric *o*-disubstituted anilides and *N*-(*o*-*tert*-butylphenyl)imides by an enantiotopic selec-



(1)

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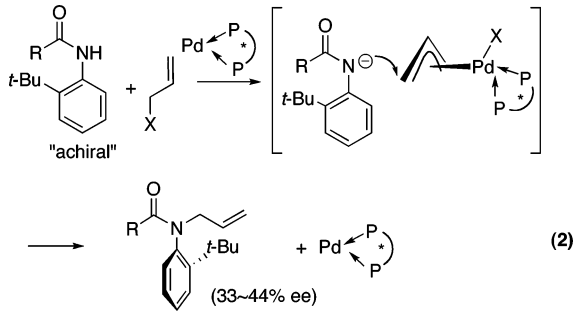
tive deprotonation method with a chiral lithium amide.[7−9] However, these enantioselective reactions using a stoichiometric chiral base could not be applied to the synthesis of *o*-mono-*tert*-butylanilide which effectively works as a chiral molecule (chiral auxiliary). Thus, there still remain some problems from the standpoint of synthesis of anilide products which can be used to asymmetric reaction, as well as asymmetric catalysis of the reaction.

The first catalytic asymmetric synthesis of atropisomeric anilide through enantioselective N-allylation of achiral *o*-*tert*-butyl-NH-anilide was independently found by us and Curran's group.[10,11] However, in these catalytic reactions based on a chiral π-allyl palladium chemistry, high enantioselectivity could not be achieved (eq 2).



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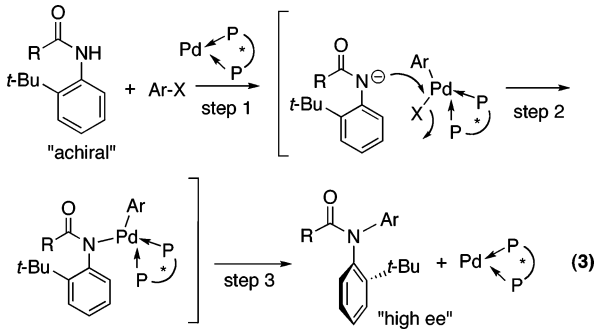
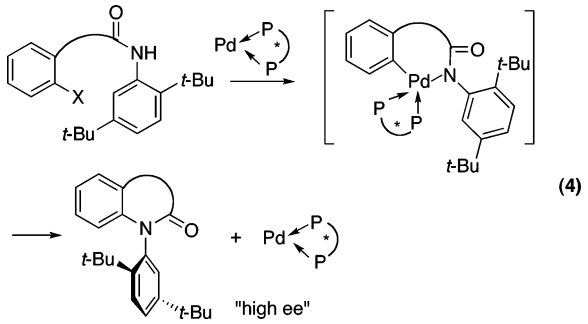
Quite recently, we succeeded in the efficient catalytic asymmetric synthesis of atropisomeric anilides through enantioselective N-arylation of achiral NH-anilide (eq 3).[12] This



(3)

reaction proceeded with high enantioselectivity (89−95% ee) upon using (*R*)-DTBM-SEGPHOS−Pd(OAc)$_2$ catalyst and provided various atropisomeric anilides in good yields. Furthermore, we found that atropisomeric lactam derivatives with high optical purity could be obtained by applying the present catalytic asymmetric N-arylation to an intramolecular version (eq 4).[12] The present reaction is the first practical catalytic



(4)

asymmetric synthesis of atropisomeric compounds having an N−C chiral axis, and it should be also noted as the first asymmetric catalysis of aromatic amination with an achiral substrate.

We report here a full article of our work in relation to highly enantioselective synthesis of atropisomeric anilides through catalytic asymmetric N-arylation. In addition to detailing the scope and limitations of the reaction, this paper describes new insights such as the remarkable *E*-rotamer preference of anilide products and their application to asymmetric enolate chemistry.

Results and Discussion

1.1. Optimization of Reaction Conditions. In the reaction with π-allyl palladium chemistry shown in eq 2, high enantiocontrol of the N−C axial chirality of the anilide by a chiral phosphine ligand may be difficult, because a soft nucleophile, such as an anilide anion, attacks the π-allyl carbon from the opposite side of the Pd atom.[13] We thus paid attention to Pd-catalyzed N-arylation (Buchwald−Hartwig reaction) which proceeds via attack of a nitrogen nucleophile to the Pd atom (step 2 in eq 3) followed by reductive elimination of the resulting Pd(II)-amide complex (step 3 in eq 3).[14] In this reaction, since N−C bond formation occurs near the chiral phosphine ligand, high asymmetric induction was expected.

Although aromatic amination has been widely investigated by many groups,[14] there has been no report dealing with an enantioselective version with an achiral substrate.[15] In addition, N-arylation of bulky and less reactive anilide nucleophiles such as *o*-*tert*-butylanilides has yet to be reported.[16] Therefore, prior to enantioselective reaction, N-arylation of *o*-*tert*-butyl-NH-anilide **1a** with *racemic*-BINAP−Pd(OAc)$_2$ catalyst was examined in the presence of various aryl halides. The reaction

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(12) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc*. **2005**, *127*, 3676.
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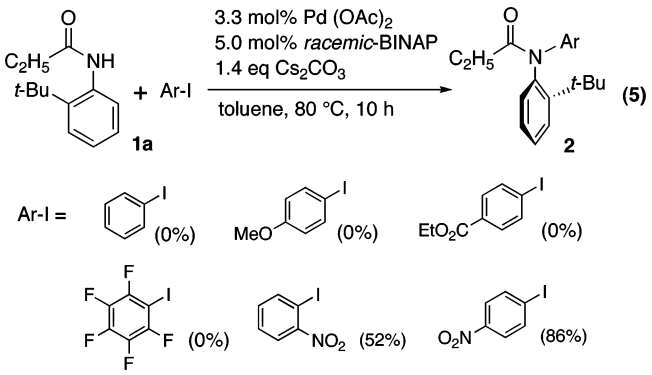
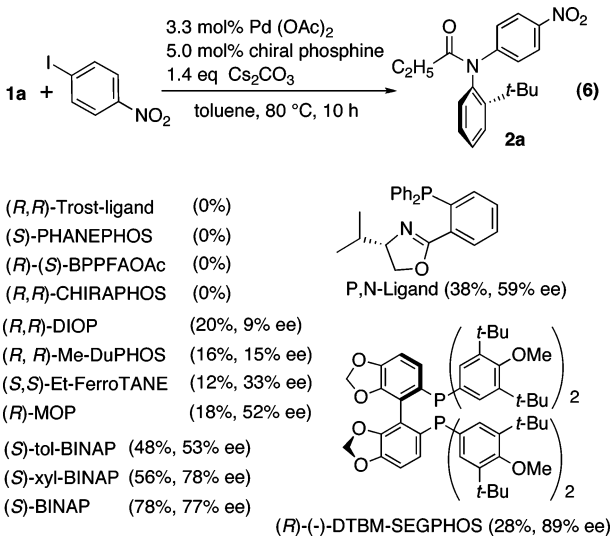
(15) Kinetic resolution of racemic dibromoparacyclophane through PHANEPHOS−Pd catalyzed amination has been reported (only one example), while to the best of our knowledge, there has been no paper in relation to catalytic asymmetric aromatic amination with achiral substrates. Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem*. **1997**, *62*, 6462.
(16) As far as we know, Pd-catalyzed N-arylation with ortho-alkylated anilide derivatives has not been reported.

was conducted for 10 h at 80 °C in toluene using Cs_2CO_3 as a base. As shown in eq 5, no N-arylated products were obtained except for the reaction with iodonitrobenzene derivatives. The use of *p*-iodonitrobenzene as an aryl halide gave the best result; in this case, product **2a** was obtained in 86% yield.

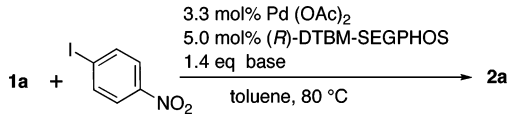


Subsequently, enantioselective *N*-*p*-nitrophenylation of **1a** was examined in the presence of various chiral phosphine ligands (eq 6). The reaction with (*S*)-BINAP[17] gave atropisomeric anilide product **2a** with a relatively good chemical yield (78%) and enantioselectivity (77% ee). In the reaction with (*R*)-DTBM-SEGPHOS,[18] although **2a** was obtained with the best enantioselectivity (89% ee), a considerable decrease in chemical yield (28%) was observed in comparison with that of BINAP.



The chemical yield was improved by the survey of bases (Table 1). The reaction using *t*-BuOK as a base proceeded for 2 h at 80 °C to give **2a** in 84% yield (entry 4). Furthermore, the use of *t*-BuOK brought about an increase in not only chemical yield but also enantioselectivity (93% ee, entry 4). On the other hand, prolonged reaction time (10 h at 80 °C) resulted in a slight decrease in the ee because of racemization of anilide product **2a** (90% ee, entry 5).[19] The rotational barrier

Table 1. Survey of Base and Reaction Time

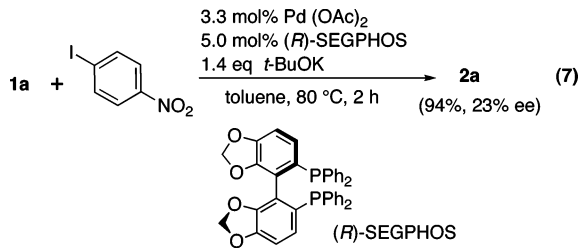


entry	base	time	**2a** yield (%)[a]	ee (%)[b]
1	Cs_2CO_3	10 h	28	89
2	NaH	4 h	45	93
3	*t*-BuONa	4 h	44	93
4	*t*-BuOK	2 h	84	93
5	*t*-BuOK	10 h	90	90
6	*t*-BuOK	1 h	50	94

[a] Isolated yield. [b] The ee was determined by HPLC analysis using a chiral column.

of **2a** for racemization was estimated to be 29.4 kcal/mol ($t_{1/2}$ at 80 °C = 54.5 h).[20] Thus, it is obvious that in the present reaction, excessive heating should be avoided.

The high enantioselectivity observed in the use of (*R*)-DTBM-SEGPHOS may be due to the bulky 4-methoxy-3,5-di-*tert*-butylphenyl group on the phosphorus atoms, since the reaction with (*R*)-SEGPHOS,[18] having a diphenylphosphino group, proceeded with poor enantioselectivity (23% ee) (eq 7).



1.2. Scope and Limitations of the Reaction. Catalytic enantioselective N-arylation with various *p*-nitrohalobenzene and NH anilides was examined under the optimized conditions mentioned above [3.3 mol % $Pd(OAc)_2$, 5.0 mol % (*R*)-DTBM-SEGPHOS, 1.4 equiv *t*-BuOK in toluene] (Table 2). All the reactions were finished within 2−6 h at 80 °C to prevent decrease in the ee of the products **2** by racemization.

Although a slight decrease in chemical yield was observed (79% and 75%), the reaction with *p*-bromo- or inexpensive *p*-chloronitrobenzene also proceeded with similar high enantioselectivity (95% ee and 94% ee) to give the product **2a** (entries 2 and 3). In contrast, with *p*-fluoronitrobenzene, only a trace amount (3%) of **2a** was obtained in racemic form (entry 4).

The reactions of various NH anilides with *p*-iodonitrobenzene were further investigated. Similar to **1a**, the reactions of anilides **1b** and **1c**, derived from aliphatic normal chain carboxylic acid, gave the atropisomeric products **2b** and **2c** with high enantioselectivties (90% ee and 94% ee) and in good yields (75% and 84%), respectively (entries 5 and 6). With anilides from α-branching carboxylic acid, good enantioselectivities (88% ee and 89% ee) and chemical yields (72% and 68%) were also

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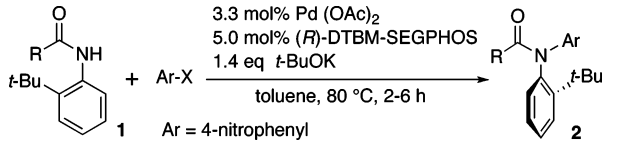
(18) (a) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (b) Sumi, K.; Kumobayashi, K. *Top. Organomet. Chem.* **2004**, *6*, 63.

(19) Addition and correction: Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 6910.

(20) The rate constants (k) for the racemization of **2a** and **2o** were measured at three different temperatures (75.9 °C, 80.4 °C, 85.1 °C) in toluene. The observed values ($k \times 10^4$) were as follows: (**2a**) 1.30 ± 0.03 s^{-1} (75.9 °C), 2.33 ± 0.01 s^{-1} (80.4 °C), 3.69 ± 0.11 s^{-1} (85.1 °C); (**2o**) 1.02 ± 0.02 s^{-1} (75.9 °C), 1.86 ± 0.01 s^{-1} (80.4 °C), 3.27 ± 0.02 s^{-1} (85.1 °C). These data were subjected to an Eyring plot to determine the rotational barrier of the racemization.

Table 2. Catalytic Enantioselective N-Arylation of Various NH-Anilides



entry	1	R	X	2	yield (%)[a]	ee (%)[b]	$[\alpha]_D$[c]
1	**1a**	C_2H_5	I	**2a**	84	93	+238.9
2	**1a**	C_2H_5	Br	**2a**	79	95	
3	**1a**	C_2H_5	Cl	**2a**	75	94	
4	**1a**	C_2H_5	F	**2a**	3	0	
5	**1b**	CH_3	I	**2b**	75	90	+254.1
6	**1c**	$Ph(CH_2)_2$	I	**2c**	84	94	+198.7
7	**1d**	$(CH_3)_2CH$	I	**2d**	72	88	+187.2
8	**1e**	cyclohexyl	I	**2e**	68	89	+187.5
9	**1f**	$CH_2{=}CH(CH_2)_2$	I	**2f**	72	92	+239.7
10	**1g**	$HC{\equiv}C(CH_2)_3$	I	**2g**	48	92	+255.5
11	**1h**	$CH_3C{\equiv}C(CH_2)_2$	I	**2h**	82	96	+254.4
12	**1i**	$MeO(CH_2)_3$	I	**2i**	87	93	+220.5
13	**1j**	$MOMO(CH_2)_3$	I	**2j**	84	94	+217.8
14	**1k**	$PhCH{=}CH$	I	**2k**	40	94	+323.0
15	**1l**	$CH_3CH{=}CH$	I	**2l**	40	89	+355.0
16	**1m**	Ph	I	**2m**	10	25	+7.2
17	**1n**	COOMe	I	**2n**	0	-	-

[a] Isolated yield. [b] The ee was determined by HPLC analysis using a chiral column. [c] $[\alpha]_D$ value was measured in $CHCl_3$ (c = 1.0).

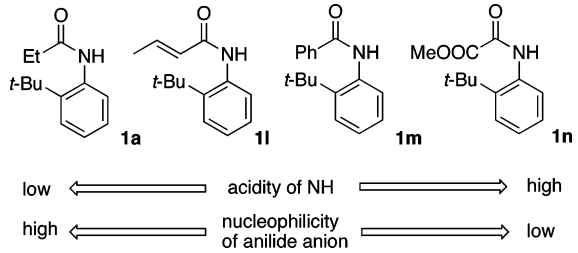


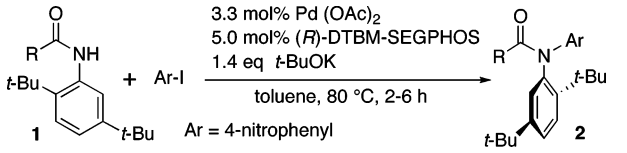
Figure 1. Acidity and nucleophilicity of several anilides.

observed (entries 7 and 8). The present reaction can be applied to anilide substrates having various functional groups. For example, anilides **1f**, **1h**, **1i**, and **1j** having alkenyl, alkynyl, ether, and acetal groups proceeded with high enantioselectivity (92−96% ee) to give the products **2f**, **2h**, **2i**, and **2j** in good yield (72−87%) (entries 9, 11−13). Although **1g** possessing terminal alkynyl group also gave **2g** with excellent enantioselectivity (92% ee), a considerable decrease in chemical yield owing to the formation of a Sonogashira coupling product was observed (48%) (entry 10).

The reaction of α,β-unsaturated amides **1k** and **1l** also resulted in a decrease in the chemical yield (40%), while the products **2k** and **2l** were obtained with high enantioselectivity (94% ee and 89% ee) (entries 14 and 15). With benzamide **1m**, decreases in both enantioselectivity and chemical yield were observed (10% yield, 25% ee) (entry 16). The reaction of the ester amide **1n** did not proceed at all (entry 17). The reactivity of these anilides may be rationalized on the basis of the nucleophilicity of the corresponding anilide anions (conjugated bases). That is, the chemical yield of the product **2** reduced with the decrease in the nucleophilicity of anilide anion (the increase in the acidity of NH-hydrogen) (Figure 1).

In the reactions of entries 1−16, a trace amount (≤3%) of *N*-(*p*-nitrophenyl)-2-*tert*-butylaniline was formed as a side product.

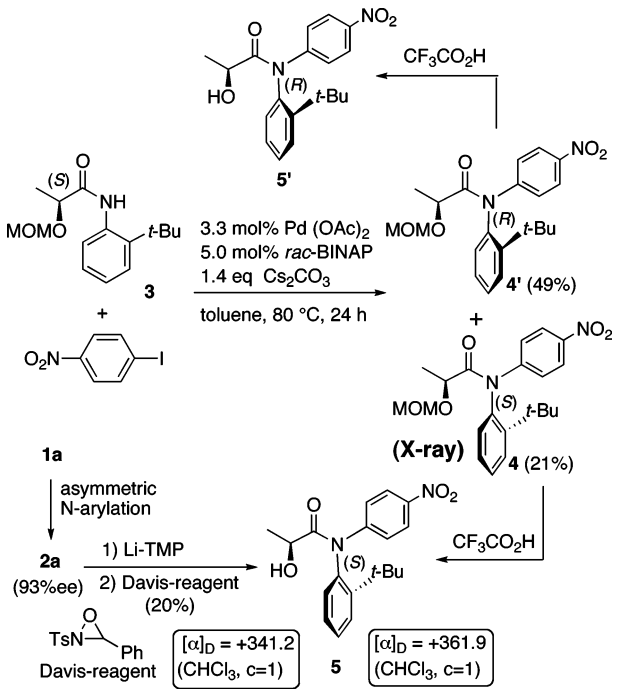
Table 3. Catalytic Enantioselective N-Arylation of 2,5-Di-*tert*-butylanilides



entry	1	R	2	yield (%)[a]	ee (%)[b]	$[\alpha]_D$[c]
1	**1o**	C_2H_5	**2o**	81	95	+338.6
2	**1p**	CH_3	**2p**	85	94	+323.1
3	**1q**	$(CH_3)_2CH$	**2q**	76	91	+302.5
4	**1r**	$CH_2{=}CH(CH_2)_2$	**2r**	70	95	+291.7

[a] Isolated yield. [b] The ee was determined by HPLC analysis using a chiral column. [c] $[\alpha]_D$ value was measured in $CHCl_3$ (c = 1.0).

Scheme 1. Stereochemical Assignment of Anilide Product **2a**

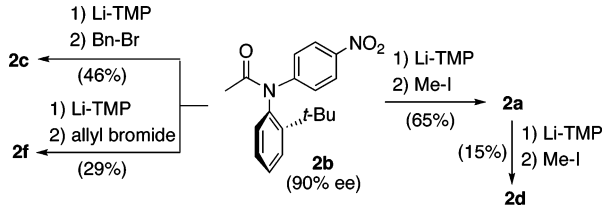


Under the same conditions, N-arylation with 2,5-di-*tert*-butylanilides **1o**−**r** also gave the atropisomeric products **2o**−**r** with excellent enantioselectivity (91−95% ee) (Table 3). In all reactions shown in Table 3, the higher enantioselectivities than those (**2a**: 93% ee, **2b**: 90% ee, **2d**: 88% ee, **2f**: 92% ee) of corresponding mono-*tert*-butylanilides **1a**, **1b**, **1d**, **1f** (entries 1, 5, 7, and 9 in Table 2) were observed. The increase in the enantioselectivity by using 2,5-di-*tert*-butylphenylanilides is also observed in the intramolecular reactions (vide infra). The rotational barrier of bis-*tert*-butyl derivative **2o** for racemization showed a slightly higher value (30.0 kcal/mol) in comparison with that of mono-*tert*-butyl derivative **2a** (29.4 kcal/mol).[20]

1.3. Determination of Absolute Stereochemistries of Anilide Products. The absolute stereochemistries of axial chirality in atropisomeric anilide products **2** were determined in accordance with chemical correlation to the compounds shown in Schemes 1 and 2.

NH-anilide **3** derived from (*S*)-lactic acid was converted to lactamide **5** and **5′** through *N*-*p*-nitrophenylation of **3** followed

Scheme 2. Stereochemical Assignment of Anilide Products **2b**−**2d** and **2f**



by the separation of the resulting diastereomeric anilides **4** and **4′**, and subsequent demethoxymethylation (Scheme 1). The stereochemistries of axial chirality of **5** and **5′** were confirmed to be (*S*)- and (*R*)-configurations, respectively, based on the X-ray analysis of **4**.[21] Next, **5** was prepared with almost complete diastereoselectivity through the reaction of the lithium enolate prepared from **2a** (93% ee) and lithium 2,2,6,6-tetramethylpiperidide (Li-TMP) with Davis reagent. Thus, the absolute stereochemistry of axial chirality in **2a** obtained by using (*R*)-DTBM-SEGPHOS was determined to be (*S*).

The major enantiomers of **2b**−**d** and **2f** were also confirmed to be (*S*)-configuration on the basis of the correlation of each compound shown in Scheme 2. The absolute stereochemistries of other anilides **2e** and **2g**−**l** which have large positive $[\alpha]_D$ values like **2a**−**d** and **2f** were also predicted to be the (*S*)-configuration.

2. Conformational Analysis of Atropisomeric Anilides. The elucidation of the preferential rotamer of anilides **2** is crucial for the development of the stereoselective reaction using **2**, because in the *E* and *Z* rotamers, each *o*-*tert*-butyl group shields an opposite face of the molecule (Figure 2).[4b,c] In addition, since conformational analysis of *N*,*N*-diarylated amides has not been reported except for only one example,[22] such a study would attract much attention in the field of structural organic chemistry.

We initially investigated the conformational analysis of anilide **2a** by X-ray diffraction of single crystals and a NOESY experiment in $CDCl_3$. In a crystalline state, **2a** was confirmed to exist as an *E*-rotamer (Figure 2). The *E*-rotamer preference of **2a** was also found in solution. That is, in the NOESY spectrum of **2a** in $CDCl_3$, NOE between Ha and Hb observed was stronger than that between Ha and Hc (Figure 2). Since a similar NOE was also observed in acetamide **2b** and isobutyramide **2d**, the *E*-rotamer preference may be a common character of anilide **2** (Figure 3). Moreover, when ^{1}H NMR of **2a** was measured at −50 °C (223 K) in CD_2Cl_2, the broadening of the signals and the formation of signals corresponding to another rotamer were not observed.[23,24] This result may indicate that in anilides **2**, an equilibrium between *E* and *Z* rotamers does not take place, but **2** exists as an almost completely single rotamer.

The remarkable *E*-rotamer preference of **2** was also supported by the *E*/*Z* energy differences ($\Delta H_{E-Z} = \Delta H_E - \Delta H_Z$) based on a MO calculation. The ab initio calculations with the HF/6-31G* basis set showed the large relative stability values of *E*-**2** (ΔH_{E-Z} of **2a**, **2b**, **2d** = 2.76, 2.46, 2.24 kcal/mol) which

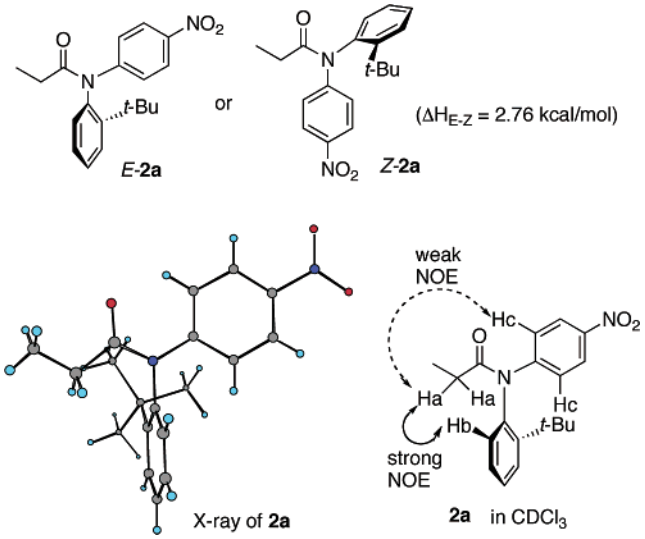


Figure 2. X-ray crystal structure and NOESY experiment of **2a**.

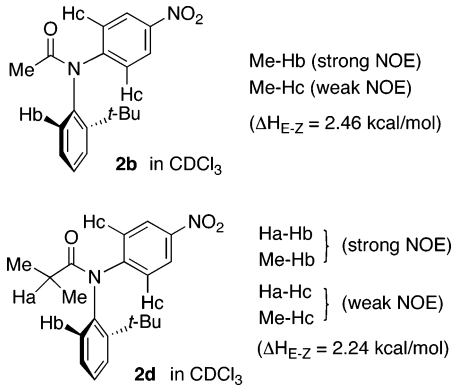


Figure 3. NOESY experiment of anilide products **2b** and **2d**.

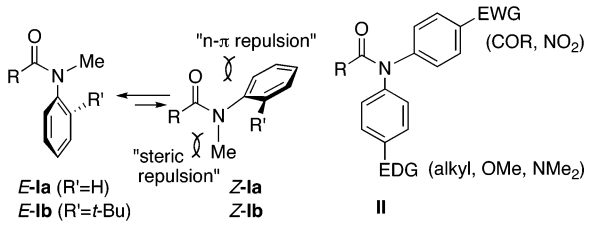


Figure 4. Preferential rotamer of N-methylated or N-arylated anilide derivatives.

correspond to the values *E*-**2a**/*Z*-**2a** = 507, *E*-**2b**/*Z*-**2b** = 258, and *E*-**2d**/*Z*-**2d** = 157 at 223 K (Figures 2 and 3).[25]

The preferential rotamers of nonatropisomeric *N*-methyl anilides **Ia** (R′ = H, Figure 4)[26] and atropisomeric N-alkylated *o*-*tert*-butylanilides **Ib** (R′ = *t*-Bu) have been reported to be the *E*-conformation.[4b,c,5b] These *E*-rotamer preferences have been rationalized on the basis of the destabilization of the *Z*-rotamer by steric repulsion between the R and Me (Ar group behaves

(21) See Supporting Information in preliminary Communication (ref 12).
(22) Yamasaki, R.; Tanatani, A.; Azumaya, I.; Saito, S.; Yamaguchi, K.; Kagechika, H. *Org. Lett.* **2003**, *5*, 1265.
(23) Among the *N*-nitrophenylated products **2a**−**r**, only the NMR spectrum of benzanilide **2m** showed a broadening of the signals which may be due to the equilibrium between the *E*- and *Z*-rotames.
(24) ^{1}H NMR chart of **2a**, **6a**−**8a** at room temperature and 223 K (−50 °C) are shown in Supporting Information.
(25) All calculations were carried out by using GAMESS (US) package. Schmidt, M. W.; Baldridge, K. K.; Elbert, Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. M. *J. Comput. Chem.* **1993**, *14*, 1347.
(26) (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, 2995. (b) Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297. (c) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177.

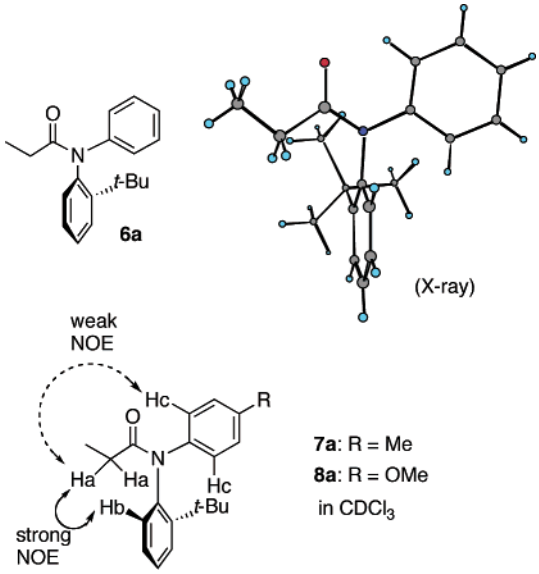


Figure 5. X-ray crystal structure of **6a** and NOESY experiment of **7a** and **8a**.

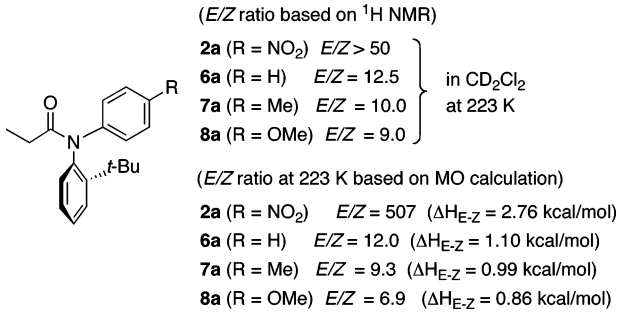


Figure 6. *E*/*Z* ratio of **2a**, **6a**−**8a** based on ^{1}H NMR and MO calculation.

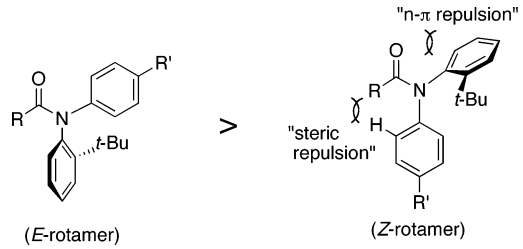


Figure 7. Model for *E*-rotamer preference.

as a small group in comparison with the Me group because of its twisted arrangement), and $n-\pi$ repulsion between the lone pairs on the oxygen and benzene ring owing to the twisting of *N*-phenyl group (Figure 4).[26] In a conformational study of *N*,*N*-diarylated amides, only one example with regard to nonatropisomeric amides has been reported by Azumaya and Kagechika et al.[22] They found that the electron-rich aromatic ring prefers to be placed toward an alkyl (R) site, while the electron-deficient aromatic ring prefers cis-disposition toward the carbonyl oxygen (Figure 4, **II**). Can the *E*-rotamer preference of atropisomeric anilide **2** having an electron-rich *o*-*tert*-butylphenyl group and electron-deficient nitrophenyl group also be explained on the basis of this electronic effect?

To elucidate the conformational restriction factors of anilide **2**, the preferential rotamers of *o*-*tert*-butylanilides **6a**−**8a** (racemic forms) having various para-substituted phenyl groups (Figure 5) were analyzed. *N*-Phenyl derivative **6a** was found to exist as an *E*-rotamer in the crystalline state.[27] *N*-*p*-Methylphenyl and *N*-*p*-methoxyphenyl derivatives **7a** and **8a** were also confirmed to prefer *E*-rotamer in a solution by NOESY experiment.

Meanwhile, ^{1}H NMR spectra of **6a**−**8a** at room temperature showed a broadening of signals which may be due to the equilibrium between the *E* and *Z* rotamers.[24] Indeed, in the ^{1}H NMR spectra of **6a**−**8a** at 223 K in CD_2Cl_2, a small amount of *Z*-rotamers was observed in *E*/*Z* ratios = 12.5, 10.0, and 9.0 for **6a**, **7a**, and **8a**, respectively (Figure 6).[24] The *E*/*Z* ratios determined in low temperature ^{1}H NMR measurements related well with the values (*E*/*Z* ratios of **6a**, **7a**, **8a** = 12.0, 9.3, 6.9) based on *E*/*Z* energy differences (ΔH_{E-Z}) calculated by MO calculation (ab initio calculations with HF/6-31G* basis set) (Figure 6).[25] Thus, the increase in the electron density of the *p*-substituted phenyl group resulted in a decrease in the *E*/*Z* ratios of the anilide rotamer, while it was also obvious that the electronic effect is not a major factor for the *E*-rotamer preference of **2**.

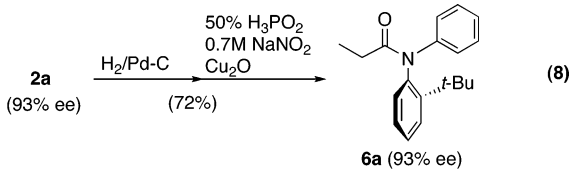
The *E*-rotamer preference of *o*-*tert*-butylanilide derivatives irrelevant to the electronic effect may be rationalized as follows. X-ray crystal structures of **2a** and **6a** showed large twisting of the *o*-*tert*-butylphenyl group (twist angles of *tert*-butylphenyl group: 81.0° for **2a** and 78.2° for **6a**), and small twisting of *p*-nitrophenyl and phenyl groups (twist angles of *p*-nitrophenyl and phenyl groups = 26.5° and 26.0°) (Figures 2 and 5). Such tendency of twist angles may also occur in the case of the *Z*-rotamer. Accordingly, in the *Z*-rotamer, steric repulsion between the alkyl (R) group and aryl group having small twist angle, and $n-\pi$ repulsion between lone pairs on oxygen and twisted *o*-*tert*-butylphenyl group, should be stronger than those of the *E*-rotamer (Figure 7). Such destabilization of the *Z*-rotamer may lead to the *E*-rotamer preference.

3. Application to Asymmetric Enolate Chemistry. After publication of our preliminary communication in relation to the present chemistry,[12] highly enantioselective syntheses of atropisomeric anilides using catalytic asymmetric Friedel−Crafts amination and chiral Rh-catalyzed asymmetric [2 + 2 + 2] cycloaddition were reported by two groups.[28,29] However, atropisomeric naphthyl amides and *o*-2,6-disubstituted anilides, which were obtained through these reactions, may be difficult to use as a chiral molecule (chiral auxiliary) in an asymmetric reaction. Therefore, we attempted the synthetic application (application to asymmetric enolate chemistry) of atropisomeric anilide product **2a** (93% ee) which was obtained through our catalytic enantioselective N-arylation.

Since the reaction of the lithium enolate from N-nitrophenylated anilide **2a** with some electrophilic reagents brought about in the decrease in the chemical yield because of the existence of the nitro group (Schemes 1 and 2), the reaction with N-phenylated propanamide **6a** was investigated. **6a** (93% ee) was prepared from **2a** (93% ee) without racemization as shown in eq 8.

(27) NOESY experiment of **6a** was not investigated because of an overlap of the ortho-hydrogen (Hc) in the *N*-phenyl group with an other aromatic hydrogen.

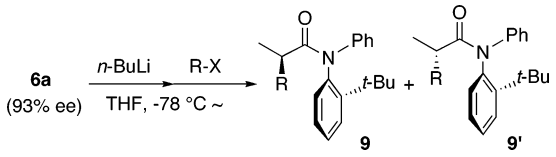
(28) Brandes, S.; Bella, M.; Kjoersgaard, A.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147.
(29) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586.



(8)

The reaction of lithium enolate prepared from **6a** and *n*-BuLi with various alkyl halides proceeded with high diastereoselectivity (diastereomer ratio = 23:1 to 46:1) to give diastereomeric α-alkylated products **9** and **9′** in good yields (73−94%) (Table 4). Minor diastereomers **9′** were also confirmed by thermal atropisomerization of major diastereomers **9**. For example, diastereomerically pure **9d** changed to an equilibrium mixture of **9d** and **9d′** (**9d**/**9d′** = 1:1.3) after heating for 13 h at 90 °C. The present reaction can be applied to not only reactive alkyl halides (entries 1−4) but also less reactive halides such as propyl iodide (entry 5).

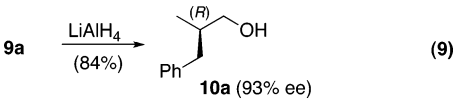
Table 4. Diastereoselective α-Alkylation of **6a** with Various Alkyl Halides



entry	R–X	**9** and **9′**	yield[a]	**9**/**9′**[b]
1	$PhCH_2-Br$	**9a**, **9a′**	94%	46:1
2	(*E*)-$PhCH{=}CHCH_2-Br$	**9b**, **9b′**	85%	42:1
3	$CH_2{=}CH-CH_2-Br$	**9c**, **9c′**	79%	39:1
4	CH_3OCH_2-I	**9d**, **9d′**	92%	23:1
5	$CH_3(CH_2)_2-I$	**9e**, **9e′**	73%	23:1

[a] Isolated yield. [b] The diastereomer ratio based on isolated yield.

The removal of the aniline moiety from the alkylation product **9a** was achieved by LAH reduction, and in this case known alcohol **10a** [30] was obtained in good yield (eq 9). By this conversion, the absolute stereochemistry of the α-carbon in major product **9a** was determined to be the (*R*)-configuration. Likewise, the stereochemistries of the other major diastereomers **9b**−**e** were also confirmed to be the (*R*)-configuration through a similar conversion (see Supporting Information). Moreover, the ee (93% ee) of alcohol **10a** indicates that α-alkylation reaction with the enolate from **6a** (93% ee) proceeded without the racemization (Table 4 and eq 9).



(9)

10a: $[\alpha]_D$ = +10.2 (c = 1.15, C_6H_6)
lit: $[\alpha]_D$ = +11.0 (c = 1.15, C_6H_6)

Since the C=C part of the amide enolate is well known to prefer the *Z*-form,[31] (*R*)-stereoselectivity observed in the present alkylation should be due to the *E*-rotamer preference of the lithium enolate. That is, attack of alkyl halides to *Z*-enolate

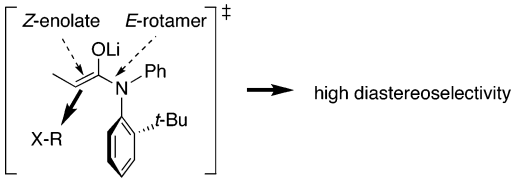


Figure 8. Model for diastereoselective α-alkylation with Li-enolate from **6a**.

having *E*-conformation [C(O)−N bond] should preferentially occur from the *β*-face (opposite face of *o*-*tert*-butyl group) to give alkylated product **9** having an α-chiral carbon of (*R*)-configuration with high stereoselectivity (Figure 8). Simpkins et al. reported on the highly diastereoselective reaction of lithium enolate prepared from atropisomeric propanamide with various electrophiles.[4b,6b] In this reaction, the use of an anilide having an *N*-methoxyethoxymethyl (*N*-MEM) group which can freeze the rotation around C(O)−N bond by chelation to Li atom is required for high diastereoselectivity (dr = 15:1 to >25:1), while the reaction of the N-methylated anilide resulted in a decrease in diastereoselectivity because of the contribution of both the *E*- and *Z*-rotamers (dr = 2:1 to 4:1).[4b] Thus, in our reaction, it should be noted that the α-alkylation of N-phenylated enolate, which does not have a chelation functional group (such as MEM) to freeze the conformation, proceeded with high diastereoselectivity.

4. Catalytic Asymmetric Intramolecular N-Arylation. We next investigated the application of the present catalytic asymmetric N-arylation to an intramolecular version (eq 4).[32] That is, chiral Pd-catalyzed intramolecular N-arylation of NH-anilides having a haloaryl group should provide efficient synthesis of cyclic atropisomeric anilide derivatives. Atropisomeric six-membered lactams, which have a higher rotational barrier than that of five-membered lactams, were chosen as target cyclic atropisomeric anilides.[5f,33]

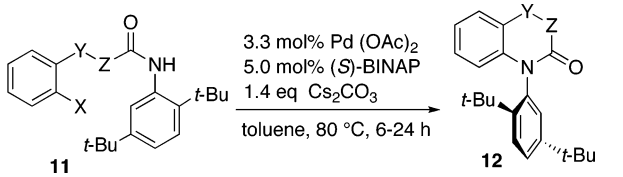
The intramolecular N-arylation reaction with NH-anilide **11a** prepared from 3-(2-iodophenyl)propanoate was initially examined in the presence of various chiral phosphine ligands and $Pd(OAc)_2$. The reaction was conducted for 20 h at 80 °C in toluene using Cs_2CO_3 as a base. Among the phosphine ligands, the use of BINAP derivatives gave a relatively good result, in these cases, atropisomeric lactam **12a** was obtained in good yields (67−95%) with moderate enantioselectivities (68−72% ee) (eq 10). With (*R*)-DTBM-SEGPHOS, which gave excellent results in an intermolecular reaction, no asymmetric induction was observed. Although the survey of bases (NaH, *t*-BuOK) and solvents (DMF, dioxane) was further performed, the enantioselectivity was not improved.

Under the same conditions using (*S*)-BINAP, the reaction with urea derivative **11b** also gave product **12b** with similar moderate enantioselectivity (63% ee) (eq 11).

The enantioselectivity was remarkably improved by using 2,5-di-*tert*-butylanilide substrates (Table 5). For example, the reaction of di-*tert*-butylanilide **11c** proceeded with excellent enantioselectivity (96% ee) to give lactam **12c** in 95% yield (entry 1). Although a slight decrease in chemical yield was

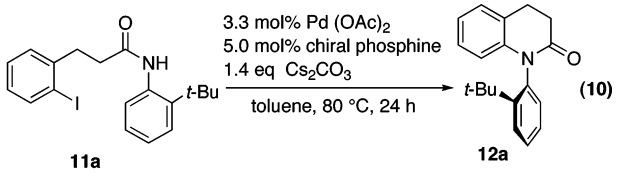
(30) Tyrrell, E.; Skinner, G. A.; Janes, J.; Milsom, G. *Synlett* **2002**, 1073
(31) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857. (c) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.
(32) Examples of intramolecular aromatic amination: (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35.
(33) In a previous paper (ref 5f), we reported that the larger bond angle [C(O)−N−C] of a six-membered lactam than that of a five-membered lactam resulted in a higher rotational barrier around the N−Ar bond.

Table 5. Catalytic Asymmetric Intramolecular N-Arylation of Several Bis-*tert*-butylanilides

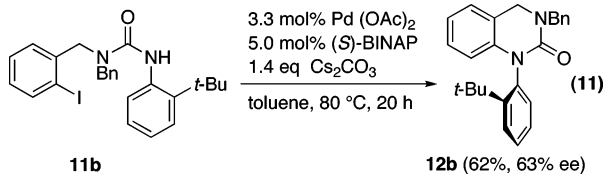


entry	11	X	Y	Z	12	yield (%)[a]	ee (%)[b]	$[\alpha]_D$[c]
1	**11c**	I	CH_2	CH_2	**12c**	95	96	+82.2
2	**11d**	Br	CH_2	CH_2	**12c**	85	98	
3	**11e**	Cl	CH_2	CH_2	**12c**	13	98	
4	**11f**	I	CH_2	NBn	**12f**	82	92	+58.3
5	**11g**	I	NBn	CH_2	**12g**	71	95	+22.6

[a] Isolated yield. [b] The ee was determined by HPLC analysis using a chiral column. [c] $[\alpha]_D$ value was measured in $CHCl_3$ (c = 1.0).



(*R*,*R*)-Trost-ligand	(0%)	(*R*)-MOP	(97%, 17% ee)
P,N-Ligand	(0%)	(*S*)-tol-BINAP	(67%, 72% ee)
(*R*,*R*)-Me-DUPHOS	(0%)	(*S*)-xyl-BINAP	(87%, 68% ee)
(*R*,*R*)-CHIRAPHOS	(0%)	(*S*)-BINAP	(95%, 70% ee)
(*S*)-DIOP	(0%)		
(*S*)-PHANEPHOS	(11%, 0% ee)		
(*S*,*S*)-Et-FerroTANE	(29%, 69% ee)		
(*R*)-(-)-DTBM-SEGPHOS	(12%, 0% ee)		



observed (85%), the reaction of **11d** having a bromophenyl group also gave **12c** with similar excellent enantioselectivity (98% ee) (entry 2). The reaction with less reactive chlorophenyl derivative **11e** resulted in a considerable decrease in the chemical yield (13%), while the enantioselectivity was excellent, similar to iodo- and bromophenyl derivatives **11c** and **11d** (98% ee) (entry 3). The remarkable increase in the enantioselectivity by using 2,5-di-*tert*-butylanilide substrates was also observed in the reactions with **11f** and **11g** having a nitrogen-containing tether. In these reactions, cyclic urea **12f** and piperadinone **12g** were obtained in 92% ee and 95% ee, respectively (entries 4 and 5). In contrast, the reaction with anilide substrates shown in Figure 9 resulted in the formation of a complex mixture or quantitative recovery of starting anilides.

In these intramolecular reactions, although prolonged heating (6−24 h at 80 °C) in comparison with intermolecular N-nitrophenylation (2−6 h) was required, high enantiomeric excess of the products **12c**−**e** may indicate that the racemization of **12** hardly occurred under the reaction conditions. Indeed, even when isolated **12a** (70% ee) and **12c** (96% ee) were heated for 24 h at 80 °C in toluene, appreciable change in the ee was not

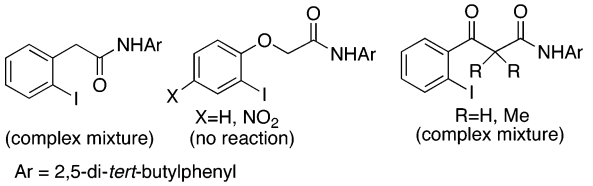
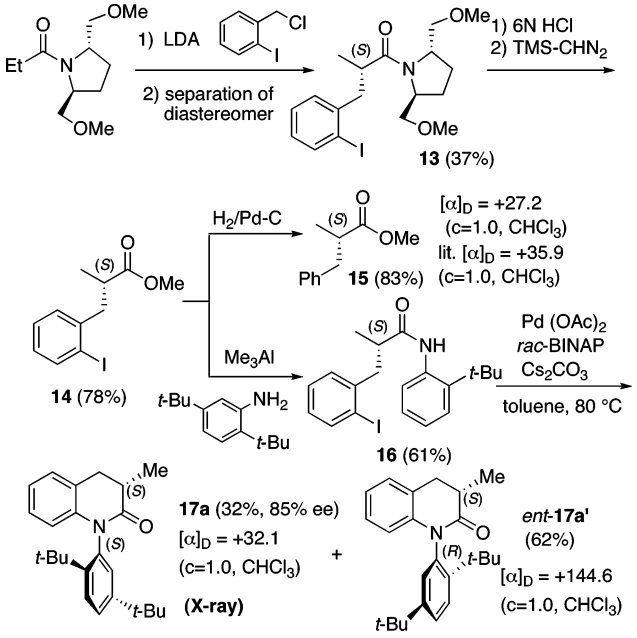


Figure 9. Anilide substrates which gave negative results.

Scheme 3. Stereochemical Assignment of Lactam Product



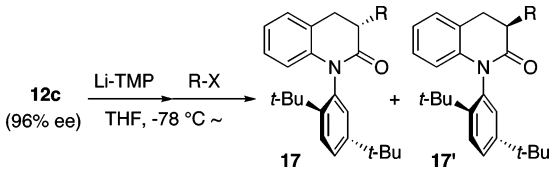
observed. Higher rotational barrier of lactams **12a** and **12c** than that of acyclic anilide **2a** may be due to the existence of hydrogen at the C-8 position which results in the strong steric repulsion during rotation around the N−Ar bond.

5. Stereochemical Assignment of Atropisomeric Lactam and the Application to Asymmetric Enolate Chemistry. The absolute stereochemistry of atropisomeric anilide product **12c** was determined as follows. α-Methylated lactam **17a** (85% ee) was prepared from (2*S*,5*S*)-*N*-propionyl-2,5-di(methoxymethyl)-pyrrolidine as shown in Scheme 3. The authentic lactam **17a**, which was confirmed to possess (*S*,*S*)-configuration by the X-ray crystal analysis[21] and derivation to the known ester **15**[34] from the intermediacy **14**, was compared with **17a** prepared by α-methylation of lithium enolate from **12c** (96% ee) (Table 6, entry 1). Thus, the axial chirality of **12c** obtained by using (*S*)-BINAP was determined to be (*S*)-configuration. The absolute stereochemistries of other cyclic anilides **12a**−**b**,**f**,**g**, which have positive $[\alpha]_D$ values such as **12c**, were also tentatively assigned to be the (*S*)-configuration.

In α-methylation with **12c** mentioned above, relatively high diastereoselectivity was observed. That is, the reaction of the lithium enolate prepared from **12c** and Li-TMP with iodomethane gave diastereomeric α-methylated lactams **17a** and **17′a** in a ratio of 13:1 (Table 6, entry 1). It was expected: the reaction using more bulky alkyl halides may proceed with higher diastereoselectivity.[5e,35] Indeed, the reaction with benzyl bromide and allyl bromide gave the products **17b** and **17c** with higher

(34) Davis, S. G.; Doisneau, G. J.; Prodger, J. C.; Samganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2373.

Table 6. Diastereoselective α-Alkylation of Atropisomeric Lactam



entry	R–X	**17** and **17′**	yield[a]	**17**/**17′**[b]
1	Me−I	**17a**, **17a′**	72%	13:1
2	$PhCH_2$−Br	**17b**, **17b′**	86%	48:1
3	CH_2=CH−CH_2−Br	**17c**, **17c′**	83%	38:1
4	$CH_3(CH_2)_2$−I	**17d**, **17d′**	73%	32:1

[a] Isolated yield. [b] The diastereomer ratio based on isolated yield.

diastereoselectivities (**17b**/**17b′** = 48:1, **17c**/**17c′** = 38:1) (entries 2 and 3). The reaction with less reactive propyl iodide also efficiently proceeded to give **17d** with high stereoselectivity (**17d**/**17d′** = 32:1) (entry 4). Minor diastereomers **17′** were identified by thermal atropisomerization of major isomers **17**. For example, diastereomerically pure **17d** changed to the diastereomeric mixture of **17d** and **17d′** (3:1) after heating for 24 h at 140 °C.

Stereochemistries of α-carbon in major products **17b**−**d** were assigned as (*S*)-configurations, because NOEs between α-hydrogen on the lactam ring and *o*-*tert*-butyl group were detected. The high (*S*)-selectivity should be rationalized that the attack of alkyl halides to the lactam enolate preferentially occurred from the opposite site of *o*-*tert*-butyl group.

(35) Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walke, M. D.; Wilson, C. *Tetrahedron* **2004**, *60*, 4491.

Conclusion

We succeeded in the development of an efficient synthetic method of optically active atropisomeric anilides through catalytic enantioselective N-arylation of achiral *o*-*tert*-butyl NH anilide. The present reaction, which proceeds with high enantioselectivity in the presence of (*R*)-DTBM-SEGPHOS−Pd-$(OAc)_2$ catalyst, can be applied to the preparation of various atropisomeric anilides. The application of the present catalytic asymmetric N-arylation to an intramolecular reaction provides highly enantioselctive synthesis of atropisomeric lactam derivatives (92−98% ee). Furthermore, we have shown the *E*-rotamer preference of N-arylated atropisomeric anilide products and highly diastereoselective reaction of the lithium enolate prepared from the anilide and lactam products with various alkyl halides. The present study should be noted not only as the first practical catalytic asymmetric synthesis of atropisomeric molecules possessing an N−C chiral axis but also as the first example of catalytic enantioselective aromatic amination with achiral substrates.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^{1}H NMR spectra of **2a**, **6a**−**8a** at room temperature and 223 K (PDF); X-ray analytical data of **2a** and **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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