Communication

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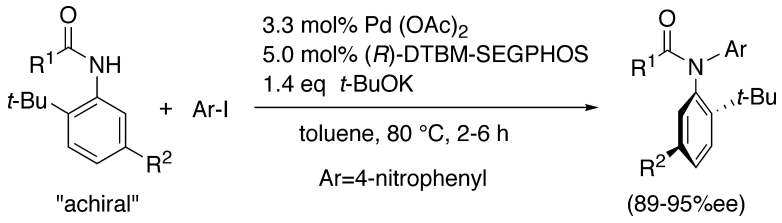

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Efficient Synthesis of Optically Active Atropisomeric Anilides through Catalytic Asymmetric N-Arylation Reaction

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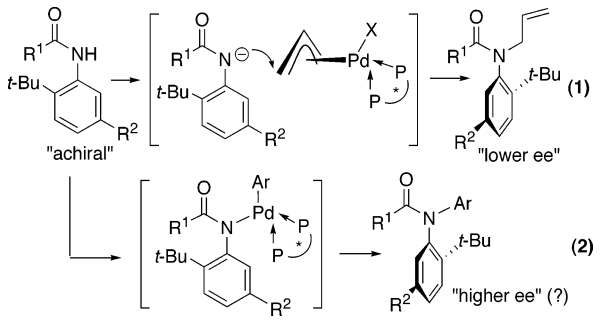
Since Curran's report in 1994, N-substituted *ortho-tert*-butylanilide derivatives have received much attention as novel atropisomeric compounds possessing an N−C chiral axis.[1] On the other hand, the utility of these anilides in asymmetric reaction is limited by the lack of efficient methods for their preparation in high optical purity.[1] To date, although syntheses of several optically active atropisomeric anilides through a multistep sequence from a chiral pool precursor or HPLC separation using a chiral stationary phase have been reported by several groups, including by us,[2] some problems remain in these methods with regard to generality and efficiency.

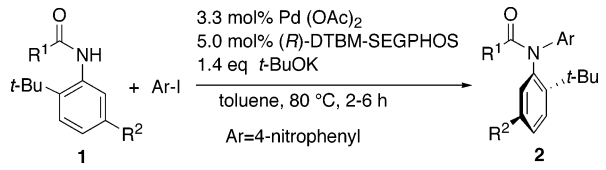
Recently, we and Curran's group reported the first catalytic asymmetric synthesis of atropisomeric anilides through enantioselective N-allylation of achiral *ortho-tert*-butyl-NH-anilide (eq 1).[3,4] However, in this methodology using a chiral π-allyl Pd catalyst, high enantioselectivity could not be achieved (30−53% ee). In this communication, we report a new and efficient catalytic asymmetric synthesis of atropisomeric anilides through enantioselective inter- and intramolecular N-arylation mediated by a chiral Pd catalyst. The present reaction proceeds with high enantioselectivity to give various optically active atropisomeric amides and lactams in good yields. Moreover, this study should be also noted as a rare example of catalytic asymmetric N-arylation.[5]



In N-allylation with an asymmetric π-allyl Pd catalyst, since a soft nucleophile such as anilide anion attacks the π-allyl carbon from the opposite side of the Pd atom, asymmetric induction at the anilide part by a chiral phosphine ligand may be difficult (eq 1). Meanwhile, in the Pd-catalyzed asymmetric N−C coupling, it was expected that high enantioselectivity may be achieved through attack of an anilide nucleophile to the Pd atom followed by reductive elimination of the resulting palladium amide complex (II), because in such reaction, N−C bond formation should occur near the chiral ligand (eq 2).

We chose an aromatic amination reaction that proceeds via such a mechanism (eq 2).[6] Initially, the N-arylation of propanamide **1a** (R^1 = Et) with racemic BINAP-Pd(OAc)$_2$ catalyst was investigated in the presence of various aryl halides and bases. The best result was observed in the reaction using *p*-nitroiodobenzene as an aryl halide and Cs_2CO_3 (1.4 equiv) as a base [in toluene (80 °C, 10 h)];

Table 1. Catalytic Asymmetric Aromatic Amination of Various NH Anilides



entry	1	R^1	R^2	2	yield (%)[a]	ee (%)[b]	abs config
1	**1a**	C_2H_5	H	**2a**	84	93	*S*
2	**1b**	C_2H_5	*t*-Bu	**2b**	81	95	—[c]
3	**1c**	CH_3	H	**2c**	75	90	*S*
4	**1d**	$PhCH_2CH_2$	H	**2d**	84	94	*S*
5	**1e**	cyclohexyl	H	**2e**	68	89	—[c]
6	**1f**	PhCH=CH	H	**2f**	40	94	—[c]
7	**1g**	CH_3CH=CH	H	**2g**	40	89	—[c]

[a] Isolated yield. [b] The ee was determined by HPLC analysis using chiral column. [c] The absolute configuration was not determined.

in this case, racemic anilide **2a** was obtained in 79% yield. Subsequently, asymmetric N-arylation of **1a** with various chiral phosphine ligands was examined under the above conditions.[7] The reaction using (*S*)-BINAP gave **2a** in relatively good chemical yield (78%) and enantioselectivity (77% ee). With (*R*)-DTBM-SEGPHOS,[8] the product **2a** was obtained with high enantioselectivity (89% ee), while considerable decrease in the chemical yield was observed (28%). Improvement of both chemical yield and enantioselectivity was achieved by a survey of the base. That is, in the reaction with (*R*)-DTBM-SEGPHOS, the use of *t*-BuOK instead of Cs_2CO_3 led to the formation of **2a** in excellent enantioselectivity (93% ee) and high yield (84%) (Table 1, entry 1).

Under the optimized conditions [*p*-nitroiodobenzene (1.1 equiv), (*R*)-DTBM-SEGPHOS (5.0 mol %), Pd(OAc)$_2$ (3.3 mol %), and *t*-BuOK (1.4 equiv) in toluene at 80 °C], catalytic asymmetric N-arylation with various NH anilides **1b**−**1g** was further examined (Table 1). Similar to mono-*tert*-butylphenyl derivative **1a**, the reaction with *N*-(2,5-bis-*tert*-butyl)phenyl propanamide **1b** also proceeded with high enantioselectivity (95% ee) to give atropisomeric product **2b** in 81% yield (entry 2). In the reaction with other carboxamides such as acetamide **1c**, phenylpropanamide **1d**, and cyclohexanecarboxamide **1e**, similar high enantioselectivities were also observed (89−94% ee, entries 3−5). Although the reaction of α,β-unsaturated amides **1f** and **1g** brought about a decrease in the chemical yield (40% yield), the products **2f** and **2g** were obtained in high enantioselectivity (94 and 89% ee, entries 6 and 7).

The high enantioselectivities observed in these reactions may indicate that no racemization of the products **2** occurs under the above reaction conditions (heating for 2−6 h at 80 °C). Indeed, when isolated propanamide **2a** (93% ee) was heated for 6 h at 80 °C, no appreciable change in the ee was detected. In addition, the absolute stereochemistries of major enantiomers of anilide products **2a**, **2c**, and **2d** obtained by the use of (*R*)-DTBM-SEGPHOS were

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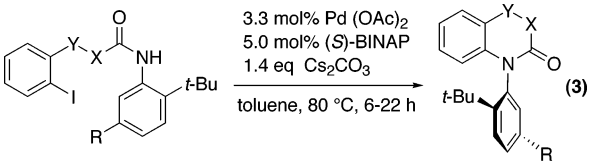
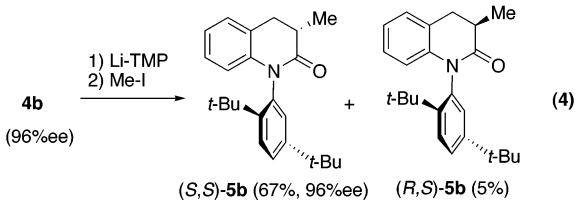
confirmed to be (*S*)-configuration by comparing with authentic sample prepared through a chiral pool route starting from (*S*)-lactic acid (see Supporting Information). The stereochemistries of other anilides—**2b**, **2e**−**2g**, which have positive $[\alpha]_D$ values like **2a**, **2c**, **2d**—were also tentatively predicted to be (*S*)-configuration.

We next attempted the synthesis of optically active atropisomeric lactams by applying the present catalytic asymmetric N-arylation to an intramolecular version. The reaction with anilide **3a** (X = Y = CH_2, R = H) prepared from 3-(2-iodophenyl)propanoate was conducted under various conditions. After an extensive survey of chiral phosphine ligands (SEGPHOS and ligands shown in ref 7), we found that, in the presence of Cs_2CO_3 in toluene, the reaction using (*S*)-BINAP-Pd(OAc)$_2$ catalyst gives the lactam product **4a** in 70% ee and 95% yield (eq 3). Although several bases and solvents were further employed for improvement of the enantioselectivity, better results could not be obtained. On the other hand, the reaction with 2,5-bis-*tert*-butylanilide **3b** (X = Y = CH_2, R = *t*-Bu) led to a remarkable increase in the enantioselectivity; in this case, atropisomeric lactam **4b** of 96% ee was obtained in good yield (95%). The reactions of other 2,5-bis-*tert*-butylanilides **3c** (X = NBn, Y = CH_2) and **3d** (X = CH_2, Y = NBn) also proceeded with excellent enantioselectivity (94 and 95% ee) to give the cyclic urea **4c** and piperazinone **4d** in good yields (82 and 71%), respectively.





Although these lactamizations required prolonged heating (6−22 h at 80 °C) in comparison with intermolecular N-arylation, no racemization of lactams **4a**−**4d** was observed under the present conditions.

Equation 4 is an application of a lactam product to stereoselective reaction. The reaction of lactam enolate from **4b** with MeI proceeded with high diastereoselectivity (13:1) to give (*S*,*S*)-**5b** as a major diastereomer. The absolute stereochemistry of the axial chirality of **4b** was determined as (*S*)-configuration by comparing with an authentic sample (*S*,*S*)-**5b** prepared from (*S*)-3-(2-iodopheny)-2-methylpropanoate (see Supporting Information).

In conclusion, we have succeeded in the synthesis of optically active atropisomeric anilide derivatives through a catalytic asymmetric inter- and intramolecular N-arylation reaction. The present reaction should provide new and efficient methodology for the preparation of various atropisomeric anilides with high optical purity. Furthermore, this study should attract the interest of many chemists as the first example of practical catalytic asymmetric aromatic amination with achiral substrates.

Acknowledgment. We gratefully acknowledge Takasago International Corporation for the supply of chiral phosphine ligands [(*R*)-(−)-DTBM-SEGPHOS].

Supporting Information Available: Experimental procedures and characterization data for compounds **2a**−**2g**, **3a**−**3d**, **4a**−**4d**, and **5b**; X-ray structural data and reaction scheme for the determination of absolute configuration of **2a**, **2c**, **2d**, and **4b**; and a list of chiral phosphine ligands examined (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Asymmetric syntheses of atropisomeric anilides through enantiotopic selective deprotonation with a *stoichiometric* chiral base have been reported by two groups. However, Uemura's method (ref 3a) cannot be applied to the synthesis of *ortho*-mono-*tert*-butylanilide, which can effectively work as a chiral molecule. On the other hand, in Simpkins' method (ref 3b), improvement of the chemical yield (40−56%) and application to other substrates except for *N*-*ortho*-*tert*-butylphenyl maleimide are problems for future study. (a) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett*. **2000**, *2*, 1907. (b) Bennett, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun*. **2004**, 1392.

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(7) Results with other chiral phosphine ligands (see Supporting Information): Trost ligand (0%), CHIRAPHOS (0%), PHANEPHOS (0%), BPPFOAc (0%), DIOP (20%, 9% ee), Me-DuPhos (16%, 15% ee), Et-FerroTANE (12%, 33% ee), MOP (18%, 52% ee), tol-BINAP (48%, 53% ee), xyl-BINAP (56%, 78% ee).

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