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Synthesis of Optically Active Atropisomeric Anilide Derivatives through Diastereoselective *N*-Allylation with a Chiral Pd−π-Allyl Catalyst

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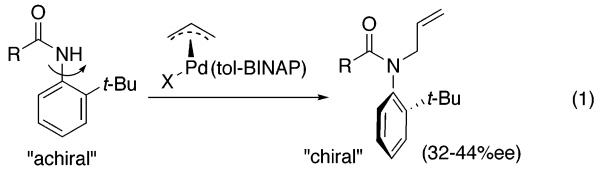
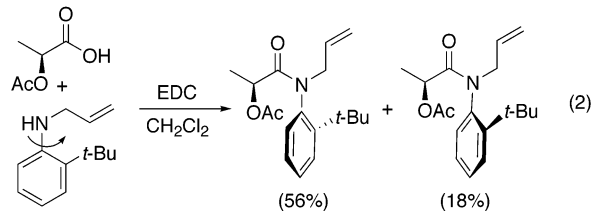
Abstract: *N*-Allylation of *o*-*tert*-butyl anilides derived from *o*-*tert*-butyl aniline and (*S*)-lactic acid or (*S*)-mandelic acid proceeded with high diastereoselectivity in the presence of a (BINAP)Pd−π-allyl catalyst to give atropisomeric *N*-allyl *o*-*tert*-butyl anilide derivatives.

Since Curran's report in 1994,[1] *N*-substituted *o*-*tert*-butyl anilide derivatives have received much attention as new atropisomeric compounds[2] and have also been applied to several asymmetric reactions.[3,4] Optically active forms of such atropisomeric anilides have so far been prepared through optical resolution by the formation of a diastereomeric derivative or HPLC separation using a chiral column.[3,4] Quite recently, we and Curran's group reported the synthesis of optically active atropisomeric anilides through enantioselective *N*-allylation of *N*-nonsubstituted *o*-*tert*-butyl anilide with a chiral Pd−π-allyl complex (eq 1).[5,6] As far as we know, these reports are the first example of catalytic asymmetric synthesis of atropisomeric compounds having a N−C chiral axis.[7] Unfortunately, although various reaction conditions involving a survey of many known chiral phosphine ligands were investigated, high enantioselectivity could not be achieved [maximum up to 44% ee (our reaction) and 53% ee (Curran's reaction)].[8]



(1)

On the other hand, not only the enantioselective synthesis, but also diastereoselective construction of optically active atropisomeric anilides has been so far uncommon. For example, as the first synthesis of an atropisomeric anilide with high optical purity and definite absolute configuration, we reported optical resolution of diastereomeric atropisomeric lactamide prepared from *N*-allyl-*o*-*tert*-butylaniline and (*S*)-*O*-acetyl lactic acid, while the diastereoselectivity in the condensation reaction was not high (50% de) (eq 2).[4a,b] If a highly diastereoselective preparation of diastereomeric lactamides which can be easily separated by column chromatography can be achieved, it should provide a useful synthetic method of optically active atropisomeric anilides. In this paper, we report an efficient synthesis of atropisomeric anilides with high optical purity (≥97% ee) through diastereoselective *N*-allylation of lactamide and mandelamide using a (BINAP)Pd−π-allyl catalyst. Furthermore, a transition state model for the origin of the diastereoselectivity is also proposed.



(2)

We expected that asymmetric induction due to the chirality of the substrate would be possible in *N*-allylation of a chiral carboxamide such as *N*-*o*-*tert*-butylphenyl lactamide with the Pd−π-allyl catalyst. As the substrates for the diastereoselective *N*-allylation, lactamide and

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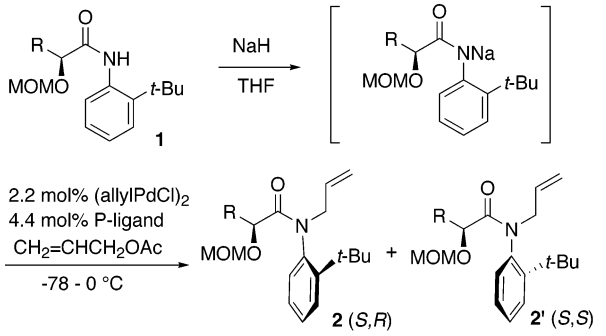
TABLE 1. Diastereoselective *N*-Allylation of Lactamide or Mandelamide

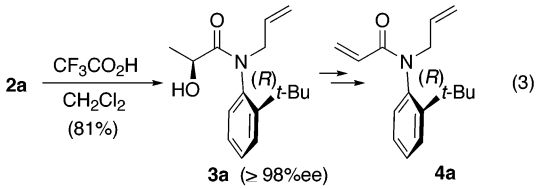


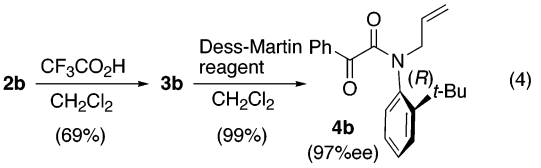
entry	1	P-ligand	2 and 2'	yield (%)[a]	ratio(2/2')[b]
1	**1a** (R = CH_3)	dppf	**2a** and **2a'**	97	6.8
2	**1a** (R = CH_3)	(*R*)-BINAP	**2a** and **2a'**	95	15.9
3	**1a** (R = CH_3)	(*S*)-BINAP	**2a** and **2a'**	95	5.2
4	**1b** (R = Ph)	dppf	**2b** and **2b'**	94	5.1
5	**1b** (R = Ph)	(*R*)-BINAP	**2b** and **2b'**	93	13.5
6	**1b** (R = Ph)	(*S*)-BINAP	**2b** and **2b'**	92	3.2

[a] Isolated yield. [b] The ratio was determined by 300 MHz ^{1}H NMR.

mandelamide which are prepared from *o*-*tert*-butylaniline and cheap lactic acid or mandelic acid, were chosen (Table 1). Initially, *N*-allylation of the amide anion prepared from (*S*)-*O*-methoxymethyl lactamide **1a** and NaH was conducted in the presence of allyl palladium chloride dimer (2.2 mol %), dppf ligand (4.4 mol %), and allyl acetate (1 equiv) in THF (Table 1, entry 1). The reaction proceeded with moderate diastereoselectivity (**2a**/**2a′** = 6.8) to give diastereomeric atropisomeric *N*-allyl lactamides **2a** and **2a′** in excellent yield (97%). The stereochemistry of the atropisomerism part of the major isomer **2a** was confirmed to be the (*R*)-configuration after the conversion to known lactamide **3a**[4a,b] (eq 3). It should be noted that the (*R*)-selectivity of this Pd-catalyzed *N*-allylation is in contrast to (*S*)-selectivity in the case of the amide-forming reaction shown in eq 2. For further improvement of the diastereoselectivity, although a survey of protective groups (Bn, Me, Ac, TBDPS) on the α-oxygen atom, phosphine ligand (dppe), solvent (toluene, CH_2Cl_2), and base (*n*-BuLi, KH) was performed, improvement of the selectivity and yield compared to those in entry 1 was not realized.

We next attempted the improvement of the selectivity on the basis of a double stereodifferentiation method.[9] In our previous paper concerning enantioselective *N*-allylation of achiral anilide,[5] we reported that the use of the (*S*)-BINAP−Pd catalyst always gives (*S*)-configurated *N*-allyl anilide in 32−44% ee. Accordingly, the reaction of (*S*)-lactamide **1a** with an (*R*)-BINAP−Pd catalyst [10] may bring about an increase in the diastereoselectivity





by (*R*)-selectivity due to the chirality of both the substrate and the catalyst. Indeed, the reaction with (*R*)-BINAP gave **2a** and **2a′** with high diastereoselectity (**2a**/**2a′** = 15.9, entry 2), while the use of mismatched (*S*)-BINAP resulted in a decrease in the diastereoselectivity (**2a**/**2a′** = 5.2, entry 3).

The increase in the diastereoselectivity by such double stereodifferentiation was also observed in the reaction of (*S*)-mandelamide **1b**. That is, the *N*-allylation of **1b** with the matched (*R*)-BINAP−Pd catalyst gave the products **2b** and **2b′** with higher diastereoselectivity (**2b**/**2b′** = 13.5, entry 5) than that in the reaction with an achiral dppf−Pd catalyst (**2b**/**2b′** = 5.1, entry 4). The reaction with mismatched (*S*)-BINAP gave **2b** and **2b′** with lower diastereoselectivity (**2b**/**2b′** = 3.2, entry 6). The (*R*)-configuration of the atropisomeric part of the major isomer **2b** was determined after conversion to known ketoamide **4b**[4d] (eq 4).

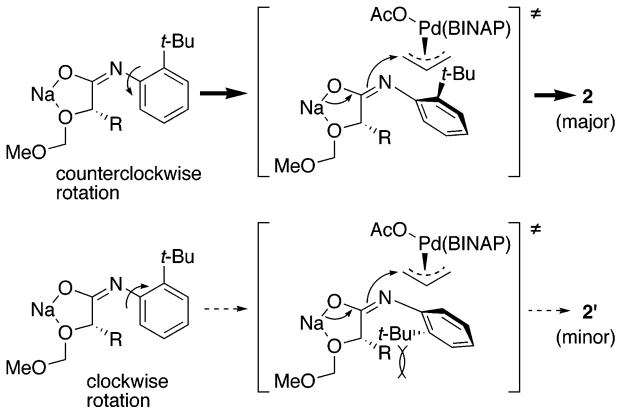


FIGURE 1. Transition-state model for the origin of the diastereoselectivity.

(*R*)-Selectivity on the basis of the substrate control may be rationalized according to the transition-state model shown in Figure 1. During *N*-allylation of the sodium imino alcoholate intermediate, rotation of a coplanar *tert*-butylphenyl group to the imine plane may simultaneously occur to produce the *N*-allyl anilide having a perpendicular *tert*-butylphenyl group to the amide plane. The clockwise rotational transition state which gives **2′** having an (*S*)-configuration should result in steric repulsion between the α-substituent and the *o*-*tert*-butyl group. Accordingly, the reaction may preferentially proceed through the counterclockwise rotational transition state to give (*R*)-atropisomeric *N*-allyl anilide **2** as a major isomer.

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As regards stereoselective synthesis of optically active atropisomeric *o*-*tert*-butylanilide by other groups, only one example has been reported by Curran's group.[3i,11] However, the ee of anilides obtained by their method using crystallization-induced asymmetric transformation is not sufficient for application to asymmetric reaction (maximum 93% ee, 77% ee). On the other hand, by the use of our method, anilides **3a** (**4a**) and **4b** which are already found to effectively work as chiral molecules[4b,d] can be obtained in ≥97% ee.

In conclusion, we have succeeded in the diastereoselective synthesis of atropisomeric anilide derivatives with high optical purity (≥97% ee) through double stereodifferentiative *N*-allylation of *N*-*o*-*tert*-butylphenyl lactamide or −mandelamide using a (BINAP)Pd catalyst. In addition, we also proposed plausible transition state model for the origin of the diastereoselectivity based on substrate control. The present reaction should provide new and efficient methodology for the synthesis of optically active atropisomeric anilide derivatives.

Experimental Section

General procedure for diastereoselective *N*-Allylation with BINAP−Pd Catalyst. Under Ar atmosphere, to a suspension of NaH (20 mg, 0.5 mmol) in THF (2 mL) was added (*S*)-lactamide **1a** (133 mg, 0.5 mmol). After being stirred for 10 min at room temperature, allylpalladium chloride dimer (4 mg, 0.011 mmol), (*R*)-BINAP (14 mg, 0.022 mmol), and allyl acetate (81 μL, 0.75 mmol) in THF (1 mL) were added to the mixture at −78 °C, and then the reaction mixture was stirred for 15 h from −78 to 0 °C. The mixture was poured into 2% HCl solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 12) gave **2a′** (less polar, 9 mg, 6%) and **2a** (more polar, 137 mg, 90%).

(*S*,*R*)- and (*S*,*S*)-*N*-Allyl-*N*-2-(*tert*-butyl)phenyl 2-Methoxymethoxypropanamide (2a) and (2a′). 2a: white solid; $[\alpha]_D = -104.6$ ($c = 1.0$, $CHCl_3$); mp 34−35 °C; IR (KBr) 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (1H, dd, $J = 1.2$, 7.9 Hz), 7.33 (1H, dt, $J = 1.2$, 7.3 Hz), 7.17 (1H, dt, $J = 1.2$, 7.3 Hz), 6.93 (1H, dd, $J = 1.2$, 7.9 Hz), 5.97 (1H, dddd, $J = 5.0$, 8.8, 10.0, 17.0 Hz), 5.16 (1H, d, $J = 10.0$ Hz), 5.08 (1H, dd, $J = 0.6$, 17.0 Hz), 4.98 (1H, dd, $J = 5.0$, 14.1 Hz), 4.60 (1H, d, $J = 7.0$ Hz), 4.52 (1H, d, $J = 7.0$ Hz), 4.04 (1H, q, $J = 6.5$ Hz), 3.32 (1H, dd, $J =$ 8.8, 14.1 Hz), 3.30 (3H, s), 1.40 (9H, s), 1.30 (3H, d, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 146.3, 137.9, 132.2, 131.9, 130.3, 128.6, 126.2, 118.7, 94.7, 70.8, 55.7, 54.5, 36.5, 32.5, 18.8; MS (*m*/*z*) 328 ($M^+ + Na$); Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.73; H, 8.95; N, 4.51. In the ^1H and ^{13}C NMR spectra of **2a**, the minor signals on the basis of the existence of the amide C−N rotamer were also observed in a ratio of 15:1. **2a′**: white solid; $[\alpha]_D = +75.0$ ($c = 1.0$, $CHCl_3$); mp 59−60 °C; IR (KBr) 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, dd, $J = 1.5$, 8.2 Hz), 7.32 (1H, dt, $J = 1.8$, 8.2 Hz), 7.18 (1H, dt, $J = 1.5$, 7.9 Hz), 7.12 (1H, dd, $J = 1.8$, 7.9 Hz), 6.03 (1H, dddd, $J = 5.0$, 8.2, 10.0, 17.0 Hz), 5.17 (1H, d, $J = 10.0$ Hz), 5.09 (1H, dd, $J = 0.9$, 17.0 Hz), 4.95 (1H, dd, $J = 5.0$, 14.1 Hz), 4.48 (1H, d, $J = 7.0$ Hz), 4.19 (1H, d, $J = 7.0$ Hz), 3.91 (1H, q, $J = 6.2$ Hz), 3.33 (1H, dd, $J = 8.2$, 14.1 Hz), 3.28 (3H, s), 1.37 (9H, s), 1.34 (3H, d, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.9, 146.1, 138.3, 132.4, 132.0, 129.8, 128.5, 126.2, 118.8, 96.3, 71.8, 55.8, 54.8, 36.3, 32.6, 17.7; MS (*m*/*z*) 328 ($M^+ + Na$). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.62; H, 9.08; N, 4.59.

(*S*,*R*)- and (*S*,*S*)-*N*-Allyl-*N*-2-(*tert*-butyl)phenyl 2-Methoxymethoxyphenylacetamide (2b) and (2b′). 2b and **2b′** were prepared from **1b** (164 mg, 0.5 mmol) in accordance with the general procedure. Purification by column chromatography (hexane/AcOEt = 4) and subsequent MPLC (hexane/AcOEt = 5) gave **2b′** (less polar, 9 mg, 5%) and **2b** (more polar, 162 mg, 88%). **2b**: white solid; $[\alpha]_D = -2.0$ ($c = 1.0$, $CHCl_3$); mp 58 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (1H, dd, $J = 1.5$, 8.0 Hz), 7.20−7.29 (4H, m), 7.06 (2H, dd, $J = 1.5$, 8.0 Hz), 6.89 (1H, dt, $J = 1.5$, 8.0 Hz), 6.09 (1H, dd, $J = 1.5$, 8.0 Hz), 5.83 (1H, dddd, $J = 5.0$, 8.5, 10.1, 17.4 Hz), 5.04 (1H, d, $J = 10.1$ Hz), 4.99 (1H, tdd, $J = 1.2$, 5.0, 14.4 Hz), 4.96 (1H, dd, $J = 1.2$, 17.4 Hz), 4.91 (1H, s), 4.55 (1H, d, $J = 7.0$ Hz), 4.41 (1H, d, $J = 7.0$ Hz), 3.30 (1H, dd, $J = 8.5$, 14.4 Hz), 3.26 (3H, s), 1.46 (9H, s); ^{13}C NMR ($CDCl_3$) δ 169.4, 146.5, 137.6, 135.6, 133.6, 132.3, 129.9, 129.5, 128.7, 128.6, 128.2, 126.0, 118.6, 93.4, 75.8, 55.9, 54.3, 36.4, 32.4; MS (*m*/*z*) 390 ($M^+ + Na$). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.21; H, 7.93; N, 3.83. **2b′**: colorless oil; $[\alpha]_D = +141.3$ ($c = 1.0$, $CHCl_3$); IR (neat) 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, dd, $J = 1.5$, 8.0 Hz), 7.38 (1H, dt, $J = 1.8$, 8.0 Hz), 7.23−7.29 (6H, m), 7.17 (1H, dd, $J = 1.5$, 8.0 Hz), 6.02 (1H, dddd, $J = 5.3$, 8.2, 9.9, 17.2 Hz), 5.18 (1H, d, $J = 9.9$ Hz), 5.09 (1H, dd, $J = 1.0$, 17.2 Hz), 5.06 (1H, s), 5.03 (1H, tdd, $J = 1.0$, 5.3, 14.0 Hz), 4.57 (1H, d, $J = 7.0$ Hz), 4.50 (1H, d, $J = 7.0$ Hz), 3.29 (3H, s), 3.26 (1H, dd, $J = 8.2$, 14.0 Hz), 1.04 (9H, s); ^{13}C NMR ($CDCl_3$) δ 169.2, 146.9, 137.7, 135.4, 132.6, 131.7, 130.6, 129.2, 128.7, 128.7, 128.2, 126.4, 119.1, 94.7, 75.0, 55.7, 54.7, 35.9, 31.9; MS (*m*/*z*) 390 ($M^+ + Na$). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.99; H, 7.75; N, 3.85.

Supporting Information Available: Experimental procedures for the preparation and characterization data of **1a**, **1b**, **3a**, **3b**, and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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