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Stereoselective synthesis of separable amide rotamers using π-allyl-Pd catalyst and their thermodynamic behavior

Nobutaka Ototake [a], Takeo Taguchi [a], Osamu Kitagawa [b,*]

[a] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
[b] Department of Applied Chemistry, Shibaura Institute of Technology, 3-7-5 Toyosu, Kohto-ku, Tokyo, Japan

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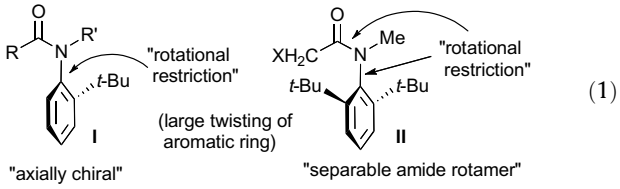
ABSTRACT

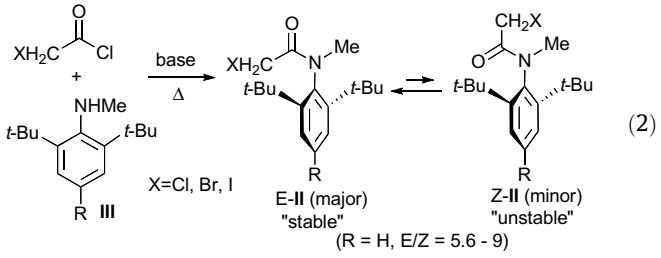
Separable amide rotamers were prepared with moderate to excellent *Z*-selectivities by N-allylation of 2,4,6-tri-*tert*-butyl-NH-anilides using a π-allyl-Pd catalyst. The present allylation proceeded through a unique mechanism involving O-allylation and the subsequent *O*,*N*-allylic rearrangement. The prepared amide rotamers of *Z*-major changed to equilibrium mixtures of *E*-major when heated in toluene.

N-Substituted *ortho*-*tert*-butylanilide derivatives often show interesting structural properties. For example, *ortho*-mono-*tert*-butylanilides **I** are stable atropisomeric compounds due to the rotational restriction of the N–Ar bond, and have recently received much attention as a new class of chiral molecules having an N–C chiral axis (Eq. 1).[1]



(1)

On the other hand, in 2,6-di-*tert*-butylanilide derivatives **II** (achiral), the amide rotational isomer can be isolated by rotational restriction around the C(O)–N bond (the rotational barriers = 27–28 kcal/mol) as well as the N–Ar bond (Eq. 1).[2] Although such anilides **II**, which were reported by Chupp et al. in 1967, should be noted as rare examples of separable amide rotamers,[2,3] systematic investigation using other anilide substrates except for α-haloacetanilides **II** (X = Cl, Br, I) have not been performed. Moreover, since their synthesis through the acylation of *N*-methyl-2,6-di-*tert*-butylaniline **III** requires high reaction temperature (100–140 °C) because of the low reactivity of **III**, the mixtures of *E*- and *Z*-rotamers were obtained in a near equilibrium ratio (*E*/*Z* = 5.6–9, Eq. 2). Thus, the stereoselective synthesis of the thermodynamically unstable *Z*-rotamer (*Z*-**II**) has not yet been established.



(2)

In connection with our study on atropisomeric *ortho*-mono-*tert*-butylanilides,[4] we felt an interest in 2,6-di-*tert*-butylanilide derivatives. In this Letter, we report *Z*-rotamer-selective synthesis of various N-allylated 2,4,6-tri-*tert*-butylanilides through allylation using a π-ally-Pd catalyst. Furthermore, unique reaction mechanism of the present allylation, involving O-allylation and subsequent *O*,*N*-allylic rearrangement, and investigation on isomerization of these anilide rotamers under thermal conditions are also described.

2,6-Di- and 2,4,6-tri-*tert*-butyl-NH-anilides are known to exist as equilibrium mixture of *Z*-major ($Z/E \simeq 8$) in solution.[5] Accordingly, it was expected that *Z*-rotamer may be obtained as a major isomer by N-alkylation of 2,6-di- or 2,4,6-tri-*tert*-butyl-NH-anilide. N-Allylation with NH-anilide **1a** prepared from commercially available 2,4,6-tri-*tert*-butylaniline was initially examined. However, the reaction of the amide anion from **1a** and NaH with allyl bromide in DMF gave O-allylated imidate **3a** in a good yield in place of the desired N-allylated anilide **2a** (Eq. 3). This unusual O-allylation should be specific to 2,6-di-*tert*-butyl derivatives, because allylation with *ortho*-mono-*tert*-butylanilide under the same conditions gave a quantitatively N-allylated product.

* Corresponding author. Tel.: +81 3 5859 8161; fax: +81 3 5859 8101.
E-mail address: kitagawa@shibaura-it.ac.jp (O. Kitagawa).

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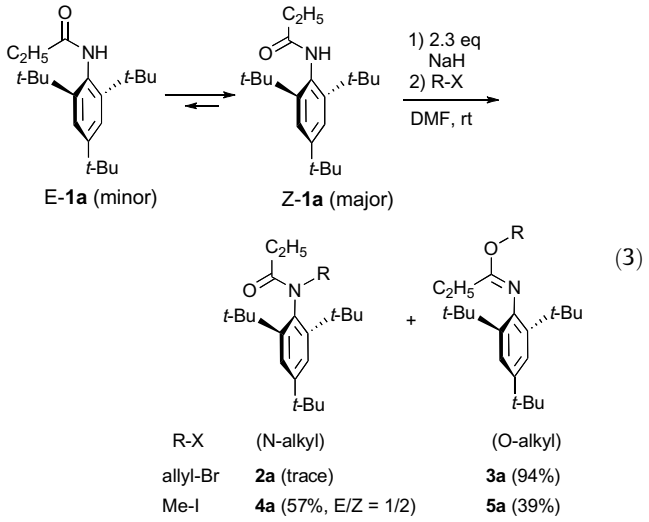
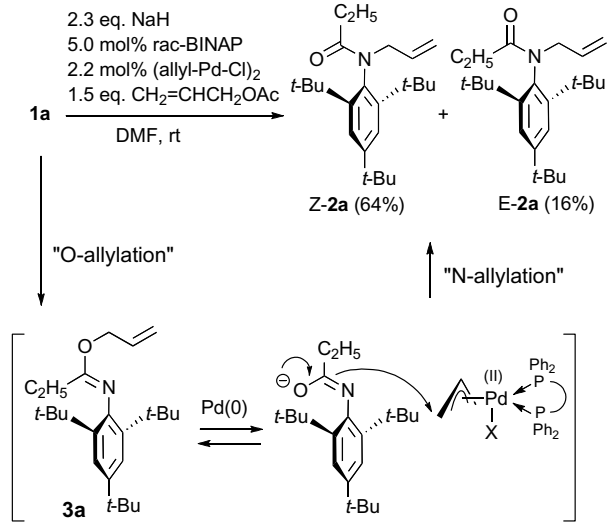


The formation of such an O-alkylation product was also observed in the reaction of **1a** with iodomethane, in this case, a mixture of N- and O-methylation products **4a** and **5a** was obtained in 57% and 39% yields, respectively (Eq. 3). The steric crowd around the amide nitrogen atom by two *ortho-tert*-butyl groups should cause the unusual O-alkylation of **1a**.

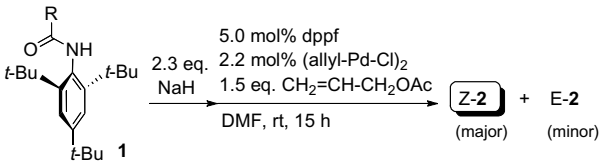
After surveying several reactions, we found that the N-allylation of **1a** efficiently proceeds by using π-allyl-Pd complex.[6] That is, when amide anion prepared from **1a** and NaH (2.3 equiv) was treated with allyl acetate in the presence of rac-BINAP-(allyl-Pd-Cl)$_2$ catalyst in DMF at rt, anilide **2a** was obtained in a good yield (80%) without the formation of imidate **3a** (Scheme 1). Furthermore, in the present reaction, *Z*-**2a** was obtained as a major rotamer (*Z*/*E* = 4).

By careful TLC monitoring, it was found that in the present reaction, imidate **3a** is initially formed and then the resulting **3a** changes to anilide **2a** via reproduction of π-allyl-Pd complex and anilide anion (Scheme 1). Indeed, smooth conversion to N-allylated amide **2a** was observed by treating isolated **3a** with BINAP-Pd catalyst and NaH (1 equiv). As far as we know, in allylations of amide derivatives using a π-allyl-Pd complex, there has been no report on a reaction which proceeds via such O-allylation and subsequent *O*,*N*-allylic rearrangement.[7,8]



Scheme 1. N-Allylation of 2,4,6-tri-*tert*-butyl-NH-anilide using π-allyl-Pd catalyst.

Table 1
Z-Selective N-allylation of various 2,4,6-tri-*tert*-butyl anilides



Entry	1	R	2	Yield[a] (%)	*Z*/*E*[b]
1	**1a**	Et	**2a**	99	4.9
2	**1b**	Me	**2b**	91	3.2
3	**1c**	Me_2CH	**2c**	99	>50
4	**1d**	Cyclohexyl	**2d**	81	>50
5	**1e**	MeO_2C	**2e**	85	>50
6	**1f**	*p*-Br–C_6H_4	**2f**	38	>50
7	**1g**	MeCH=CH	**2g**	70	3

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

The use of dppf as a phosphine ligand led to a further increase in the chemical yield and *Z*-rotamer selectivity, in this case, **2a** was obtained with an excellent yield (99%) in a ratio of *Z*/*E* = 4.9 (Table 1, entry 1). Under optimized conditions [NaH (2.3 equiv), allyl acetate (1.5 equiv), dppf (5.0 mol %) and (allyl-Pd-Cl)$_2$ (2.2 mol %) in DMF at rt], N-allylations of various 2,4,6-tri-*tert*-butyl-NH-anilides **1** were further examined (Table 1).[9] In the reaction with acetanilide derivative **1b**, a slight decrease in *Z*-rotamer selectivity was observed (*Z*-**2b**/*E*-**2b** = 3.2, entry 2). On the other hand, the reaction of anilides **1c** and **1d** prepared from α-branched carboxylic acid proceeded in almost a complete *Z*-selective manner (entries 3 and 4). The reaction with amidester **1e** and benzamide **1f** also gave *Z*-**2e** and *Z*-**2f** with almost complete selectivity (entries 5 and 6), while with α,β-unsaturated amide **1g**, product **2g** was obtained with moderate *Z*-selectivity (*Z*/*E* = 3, entry 7). These reactions proceeded with good to excellent yields (70–99%, entries 1–5 and 7) except for that of benzamide **1f** (entry 6, 38%).[10]

Z-Selectivity observed in the present reaction may be rationalized in accordance with the transition state model shown in Figure 1.[11] The transition state (TS-E) for *E*-**2** may be disfavored in comparison with TS-Z for *Z*-**2** because of the steric repulsion between substituent R and the *ortho-tert*-butyl group in the iminoalcoholate intermediate. In the reactions of **1c** and **1d** having bulky substituent R, such as isopropyl and cyclohexyl groups, excellent *Z*-selectivity would be observed by further destabilization of TS-E.

Next, the thermodynamic behavior of the obtained various N-allyl anilides **2a**–**g** was investigated. **2a**–**g** existed without isomerization between the *E*- and *Z*-rotamers for several days at

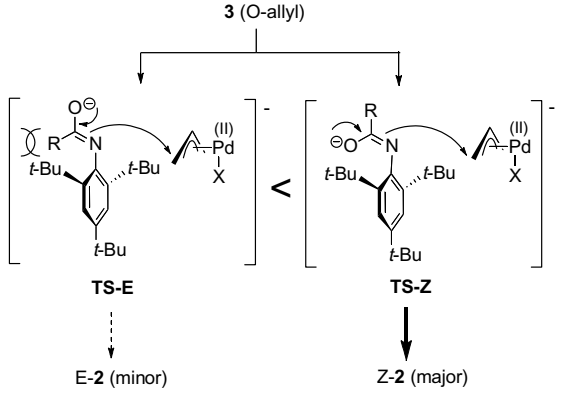
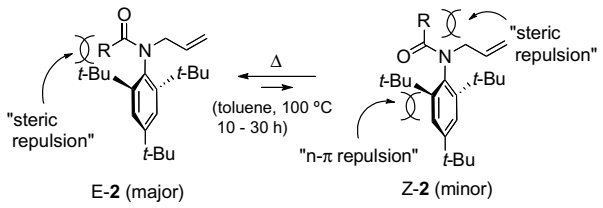


Figure 1. Transition state model for *Z*-selective N-allylation.



2a (R = Et, E/Z =6), **2b** (R = Me, E/Z = 10), **2c** (R = Me_2CH, E/Z= 1.4),
2d (R = cyclohexyl, E/Z = 1.4), **2e** (R = CO_2Me, E/Z = 4),
2f (R = p-Br-C_6H_4, E/Z = 3), **2g** (R = MeCH=CH, E/Z = 5)

Figure 2. Thermal isomerization between *E*-**2** and *Z*-**2**.

rt. Meanwhile, **2a–g** of *Z*-major changed to equilibrium mixture of *E*-major when heated for 10–30 h at 100 °C in toluene (Fig. 2). The equilibrium ratio (*E*/*Z* = 1.4–10) considerably depended on substituent R. The *E*-rotamer preference of **2** may be explained on the basis of n–π repulsion between the lone pairs on the carbonyl oxygen and aromatic ring, and steric repulsion between R and allyl group (Fig. 2).[12] Namely, the destabilization of the *Z*-rotamer due to both the n–π repulsion and the steric repulsion may bring about the *E*-rotamer preference.[4c,12,13] In the cases of **1c** and **1d** having bulky substituent R, the decrease in the *E*/*Z* ratio of **2** should be observed because of strong steric repulsion between R and the *tert*-butylphenyl group in *E*-**2** (*E*/*Z* = 1.4).

In conclusion, we succeeded in the development of stereoselective synthetic method of separable amide rotamer through N-allylation using π-allyl-Pd catalyst. This result should be noted as very few examples of kinetically controlled stereoselective synthesis of separable amide rotamers.[3c,d,14] Furthermore, the interesting mechanism of the present N-allylation, which proceeds via O-allylation and subsequent *O*,*N*-allylic rearrangement, and the thermodynamic stabilities of the various prepared amide rotamers were clarified. Rotamers based on an amide C(O)–N bond play an important role in the regulation of the actions in biologically active peptides and functional molecules having amide skeletons.[15] Thus, the present work should provide broad interest from the viewpoint of structural organic chemistry as well as unique stereoselective reaction (*rotamer-selective reaction*) and π-allyl-Pd chemistry.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.017.

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8. It is obvious that the present *O*,*N*-allylic rearrangement does not proceed via aza-Claisen reaction, but via reproduction of π-allyl-Pd complex, because the reaction through aza-Claisen mechanism should give *E*-rotamer. Typical papers on Pd-catalyzed conversions from *O*-allyl imidates to *N*-allyl amides: (a) Overman, L. E. *Acc. Chem. Res* **1980**, *13*, 218; (b) Ikariya, T.; Ishikawa, Y.; Hirai, K.; Yoshikawa, S. *Chem. Lett.* **1982**, 1815; (c) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058; (d) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, C. G. *J. Org. Chem.* **1997**, *62*, 1449.
9. *General procedure for N-allylation of 2,4,6-tri-tert-butyl-NH-anilide* **1**. Under an Ar atmosphere, to **1b** (752 mg, 2.48 mmol) in DMF (10 mL) was added NaH (228 mg, 5.7 mmol, 60% assay). After being stirred for 5 min at rt, the suspension of (allyl-Pd-Cl)$_2$ (19.8 mg, 0.054 mmol), dppf (68.7 mg, 0.124 mmol), and allyl acetate (0.4 mL, 3.72 mmol) in DMF (3.0 mL) was added to the mixture, and then the reaction mixture was stirred for 15 h at rt. 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 the mixture of *Z*-**2b** and *E*-**2b** (787 mg, 92%, *E*/*Z* = 3.2). *Z*-**2b** (more polar) and *E*-**2b** (less polar) were separated by MPLC (hexane/AcOEt = 7). *Z*-**2b:** mp 141–143 °C; IR (KBr) 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.39 (2H, s), 5.41 (1H, tdd, *J* = 6.7, 10.2, 17.0 Hz), 5.16 (1H, qd, *J* = 1.3, 17.0 Hz), 5.02 (1H, qd, *J* = 1.3, 10.2 Hz), 4.23 (2H, td, *J* = 1.3, 6.7 Hz), 2.11 (3H, s), 1.37 (18H, s), 1.28 (9H, s);^{13}C NMR ($CDCl_3$) δ: 172.9, 148.3, 146.4, 132.1, 131.7, 125.4, 118.5, 56.2, 37.3, 34.6, 33.1, 31.3, 23.7; MS (*m*/*z*) 344 (MH^+). Anal. Calcd for $C_{23}H_{37}NO$: C, 80.41; H, 10.86; N, 4.08. Found: C, 80.33; H, 10.58; N, 3.96. *E*-**2b**: mp 70–73 °C; IR (KBr) 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.42 (2H, s), 5.38 (1H, tdd, *J* = 6.8, 10.2, 17.1 Hz), 5.19 (1H, qd, *J* = 1.5, 17.1 Hz), 5.01 (1H, qd, *J* = 1.5, 10.2 Hz), 4.27 (2H, br d, *J* = 6.8 Hz), 1.85 (3H, s), 1.34 (18H, s), 1.31 (9H, s);^{13}C NMR ($CDCl_3$) δ: 171.7, 149.4, 146.7, 132.9, 132.1, 125.9, 118.8, 53.5, 37.6, 34.7, 33.4, 31.3, 24.4; MS (*m*/*z*) 344 (MH^+). Anal. Calcd for $C_{23}H_{37}NO$: C, 80.41; H, 10.86; N, 4.08. Found: C, 80.34; H, 10.75; N, 3.98.
10. Unfortunately, under the same conditions, the reaction with 2,4,6-tri-*tert*-butylchloroacetanilide gave a complex mixture.
11. The stereochemistries of **2a** and **2e** were determined by NOESY experiment. In *Z*-**2a** and *Z*-**2e**, strong NOE between allylic hydrogen and α-hydrogen (**2a**) or ester Me group (**2e**) was observed. Stereochemistries of **2b–d**, **2f**, and **2g** were determined on the basis of chemical shifts of α-hydrogens or *ortho*-hydrogens in ^{1}H NMR. That is, α-hydrogens and *ortho*-hydrogens of *E*-rotamers appeared in higher field than those of *Z*-rotamers because of an anisotropy effect by the *tert*-butylphenyl group having large twist angle.[3]
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