Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4447-4450, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00928-3

An Efficient Synthesis of Optically Active Axially Chiral Anilide and Its Application to Iodine-mediated Asymmetric Diels-Alder Reaction

Osamu Kitagawa, Hirotaka Izawa, and Takeo Taguchi*

Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

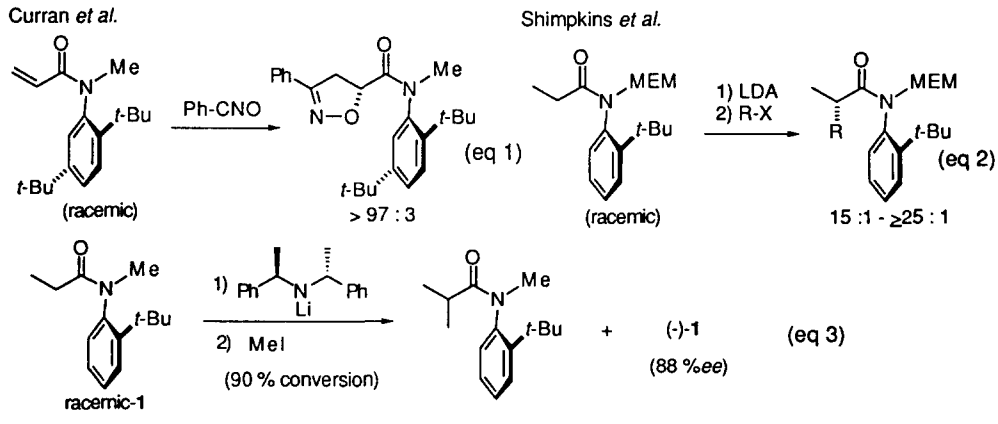
Motoo Shiro

Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima, Tokyo 196, Japan

Abstract: A new axially chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide with high optical purity (96-97 %*ee*) was prepared in good yield from (*S*)-*O*-acetyl lactic acid and *N*-allyl *o*-*t*-butylaniline. Iodine-mediated Diels-Alder reaction of the axially chiral *N*-acryl anilide with cyclopentadiene or isoprene proceeded with high diastereoselectivity. © 1997 Elsevier Science Ltd.

Recently, Curran and co-workers reported highly atropselective radical reaction and 1,3-dipolar cycloaddition reaction with axially chiral anilide as a new stereo-controlled method (Scheme 1, eq 1).[1a, 2] The reaction using similar anilides was also applied to enolate chemistry by Shimpkins *et al*, and a high level of atropselectivity was achieved in alkylation or aldol reaction (eq 2).[1b] However, in these reactions, the racemic axially chiral anilides which can not be applied to an asymmetric reaction were used. Although Shimpkins *et al* tried to prepare an optically active form through the kinetic resolution of racemic anilide **1** by a chiral lithium amide, the chiral anilide with insufficient optical purity (88 %*ee*) was obtained in poor yield at the stage of about 90 % conversion (eq 3).[1b] In addition, there is no report regarding determination of the absolute configuration of this anilide. In this paper, we report an efficient synthesis of chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide with high optical purity (96-97 %*ee*). Furthermore, an asymmetric Diels-Alder reaction of this anilide which proceeds with high diastereoselectivity through an iodine-mediated activating process is also described.

Scheme 1



In order to prepare an axially chiral anilide with high optical purity and definite absolute configuration, the optical resolution based on the formation of a diastereomeric derivative with a certain optically active compound was investigated. After a survey of various optically active carboxylic acids, we found that the resolution through the formation of a carboxamide **2** from *N*-allyl-*o*-*tert*-butylaniline and (*S*)-*O*-acetyl lactic acid[3] can be carried out most effectively (Scheme 2). These diastereomeric anilides **2a** and **2b**[4] on the basis of the axial chirality of the *o*-*tert*-butylanilide moeity and the chiral carbon of lactic acid can be easily separated by column chromatography [TLC (SiO_2), $\Delta Rf = 0.13$, hexane / AcOEt = 3], readily affording a diastereomerically pure anilide. In this condensation reaction, the use of 2 equiv. of lactic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as a condensation reagent, and a highly concentrated solution (1.5 M) were required to get the products **2** in good yield. Under the conditions, **2a** and **2b** were obtained in a ratio of 3 : 1 in 74 % yield, while the use of DCC, $(EtO)_2P(O)CN$, $(PhO)_2P(O)N_3$ and mixed anhydride gave **2** in poor yield ($\leq$ 20 %).[5]

The stereochemistries of these anilides **2a** and **2b** were determined on the basis of X-ray crystallography of **2b** (Figure). The X-ray crystal structure indicates that the planes of the amide and aryl group are twisted by 83 °.

Scheme 2

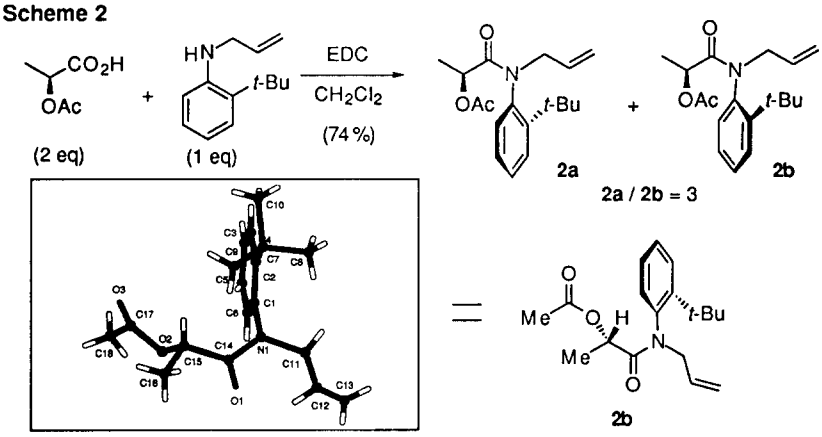
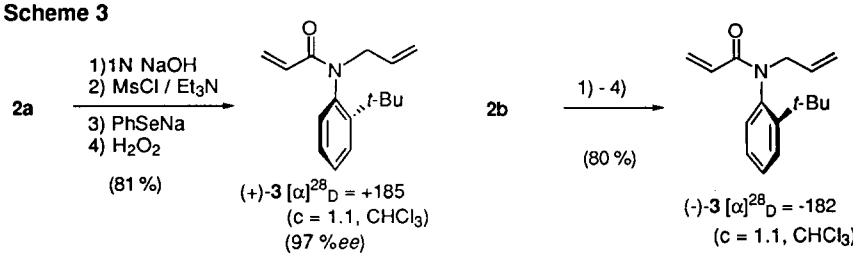


Figure X-ray crystal structure of **2b**.

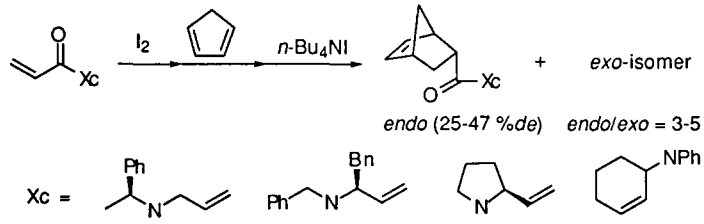
To utilize axially chiral anilide in asymmetric reaction, anilides **2a** and **2b** were converted to the corresponding *N*-acryl anilides (+)-**3** and (-)-**3** in good yields in accordance with Scheme 3, respectively. The physical data[6] of (+)-**3** completely coincided with (-)-**3** except for the sign of $[\alpha]_D$. The *ee* of (+)-**3** having $[\alpha]_D$=+185 was estimated to be 97 % by HPLC analysis using a CHIRALPAK AS column [0.1 % *i*-PrOH in hexane, (+)-**3**; t_R = 20.6 min, (-)-**3**; t_R = 15.5 min]. The optical purity of (+)-**3** did not change after standing for one month at rt, while racemization was observed at 80 °C ($t_{1/2}$ = 33h).

Scheme 3

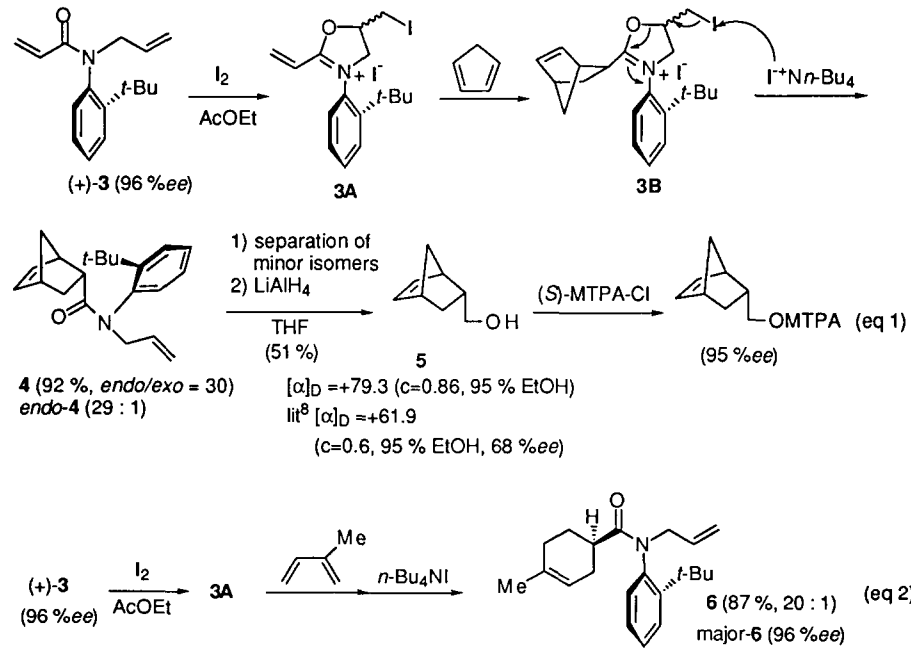


An application of this anilide **3** to an asymmetric Diels-Alder reaction is shown in Scheme 5. We have recently found that the Diels-Alder reaction of *N*-allylic enamide proceeds in good yields through iodine-mediated activating process.[7] As an application of the present reaction to asymmetric reaction, although various chiral *N*-allylic enamides were prepared and the diastereoselectivities in the reaction with cyclopentadiene were investigated, high *endo*- and diastereofacial-selectivities could not be achieved by the use of these substrates (Scheme 4). In contrast to these results, the reaction of anilide (+)-**3** in the presence of I_2 proceeded with high *endo*- and diastereoselectivity [*endo*/*exo* = 30, *endo*-**4** (29 : 1)] to give *endo*-**4** in good yield (92 %) as the major isomer (Scheme 5, eq 1). The observed diastereoselectivity can be rationalized based on the structure of the cyclic imidate intermediate **3A**; that is, the attack of the diene should preferentially occur from the opposite side of the *t*-Bu group in **3A** to give the product with high selectivity. The absolute configuration and *ee* of the product **4** were determined based on the comparison of the $[\alpha]_D$ and Mosher's analysis[8] after conversion to known alcohol **5**[8] by $LiAlH_4$ reduction. The reaction of (+)-**3** with isoprene also gave good yield (87 %) of the adduct **6**[9] with high selectivity (20 : 1, Scheme 5, eq 2).

Scheme 4



Scheme 5



In conclusion, we have succeeded in the synthesis of chiral *N*-acryl-*N*-allyl-*o*-*tert*-butylanilide with high optical purity and a definite absolute configuration. As shown in the above iodine-mediated asymmetric Diels-Alder reaction and the atropselective reactions using the racemic axially chiral anilide[1], this chiral anilide should be efficiently applied to various asymmetric reactions.

References and Notes

1. (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131-3132. (b) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607-7610.
2. Atropselective reactions of axially twisted *N*-(*o*-*t*-butylphenyl)maleimides (σ-symmetric compounds) have been also reported. Ref. 1a and Kishikawa, K.; Tsuru, I.; Kohmoto, S.; Yamamoto, M. Yamada, K. *Chem. Lett.* **1994**, 1605-1606.
3. (*S*)-*O*-Acetyl lactic acid was purchased from Kanto Chemicals Co.
4. **2a**: white crystals; mp 44 °C; $[\alpha]_D$ = +55 (c = 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.29 (3H, d, *J* = 6.4 Hz), 1.38 (s, 9H), 1.98 (3H, s), 3.36 (1H, dd, *J* = 8.1, 14.1 Hz), 4.95 (1H, tdd, *J* = 1.5, 4.9, 14.1 Hz), 5.02 (1H, q, *J* = 6.4 Hz), 5.11 (1H, md, *J* = 17.0 Hz), 5.18 (1H, dd, *J* = 0.8, 10.2 Hz), 5.99 (1H, dddd, *J* = 4.9, 8.1, 10.2, 17.0 Hz), 7.06 (1H, dd, *J* = 1.6, 7.9 Hz), 7.15 (1H, dt, *J* = 1.5, 7.8 Hz), 7.32 (1H, ddd, *J* = 1.6, 7.2, 7.8 Hz), 7.56 (1H, dd, *J* = 1.6, 7.2 Hz); ^{13}C-NMR ($CDCl_3$) δ: 15.7, 20.8, 32.2, 36.1, 54.7, 67.6, 118.9, 126.3, 128.9, 130.1, 131.9, 137.9, 146.0, 169.2, 169.4; Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found; C, 71.35; H, 8.30; N, 4.56.
   2b: white crystals; mp 94-95 °C; $[\alpha]_D$ = -99 (c = 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H, d, *J* = 6.5 Hz), 1.35 (s, 9H), 2.02 (3H, s), 3.34 (1H, dd, *J* = 8.2, 14.1 Hz), 4.95 (1H, tdd, *J* = 1.3, 5.0, 14.1 Hz), 5.08 (1H, q, *J* = 6.5 Hz), 5.09 (1H, md, *J* = 17.1 Hz), 5.18 (1H, d, *J* = 10.4 Hz), 5.98 (1H, m), 6.92 (1H, dd, *J* = 1.5, 7.8 Hz), 7.19 (1H, dt, *J* = 1.4, 7.4 Hz), 7.34 (1H, dt, *J* = 1.5, 7.4 Hz), 7.58 (1H, dd, *J* = 1.5, 8.2 Hz); ^{13}C-NMR ($CDCl_3$) δ: 17.8, 20.9, 31.9, 36.1, 54.4, 67.7, 119.1, 126.5, 128.9, 130.4, 131.5, 131.9, 137.8, 146.4, 169.7, 169.8; Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found; C, 71.25; H, 8.30; N, 4.42.
   In ^{1}H and ^{13}C NMR spectra of **2a** and **2b**, the minor signals which may be due to existence of the amide C-N rotamers were also observed in a ratio of 20 : 1 and 10 :1, respectively.
5. The low reactivity of this aniline with *O*-acetyl lactic acid may be attributed to the bulkiness of the ortho-*tert*-butyl group. On the other hand, although anilides **2a** and **2b** were obtained in quantitative yield from *N*-allyl-*o*-*tert*-butyl aniline and (*S*)-acetoxypropionyl chrolide (commercially available), the preparation of **3** through this method gave **3** with lower optical purity (82 %ee).
6. (+)-**3**: white crystals; mp 41-42 °C; $[\alpha]_D$ = +185 (c = 1.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.38 (9H, s), 3.41 (1H, dd, *J* = 8.1, 14.1 Hz), 5.00 (1H, tdd, *J* = 1.3, 5.1, 14.1 Hz), 5.10 (1H, md, *J* = 17.1 Hz), 5.17 (1H, d, *J* = 9.9 Hz), 5.47 (1H, dd, *J* = 2.1, 10.3 Hz), 5.90 (1H, dd, *J* = 10.3, 16.8 Hz), 6.03 (1H, dddd, *J* = 5.1, 8.1, 9.9, 17.1 Hz), 6.37 (1H, dd, *J* = 2.1, 16.8 Hz), 6.94 (1H, dd, *J* = 1.5, 7.8 Hz), 7.18 (1H, dt, *J* = 1.5, 7.4 Hz), 7.33 (1H, dt, *J* = 1.5, 7.3 Hz), 7.57 (1H, dd, *J* = 1.5, 8.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 31.9, 35.7, 54.0, 118.5, 126.6, 127.2, 128.4, 128.7, 129.4, 131.9, 132.2, 139.0, 146.5, 165.3; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found; C, 79.06; H, 8.55; N, 5.61.
7. Kitagawa, O.; Aoki, K.; Inoue, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 593-596.
8. Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 5513-5538.
9. The stereochemistry and *ee* of the major adduct **6** were determined on the basis of X-ray crystallography and HPLC analysis using CHIRALPAK AS column (1 % *i*-PrOH in hexane), respectively.

(*Received in Japan* 18 *April* 1997; *revised* 8 *May* 1997; *accepted* 9 *May* 1997)