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Catalytic enantioselective synthesis of key intermediates for NET inhibitors using atropisomeric lactam chemistry

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Abstract

An atropisomeric lactam which was prepared with high enantioselectivity by catalytic asymmetric intramolecular N-arylation, was efficiently converted to synthetic intermediates for NET inhibitors through highly diastereoselective α-alkylation followed by hydration and trans-*tert*-butylation.

N-Substituted *ortho*-*tert*-butylanilide derivatives have received much attention as novel atropisomeric compounds possessing an N–C chiral axis.[1] The synthesis of such optically active atropisomeric anilides and their application to asymmetric reactions have been reported by many groups.[2] On the other hand, there have been very few reports on the synthesis of natural products and biologically active compounds using these atropisomeric anilides.[2n]

In the course of our study on optically active atropisomeric anilide chemistry,[2b,k] we recently succeeded in highly enantioselective synthesis of atropisomeric anilides and lactams through chiral Pd-catalyzed inter- and intramolecular N-arylation (catalytic asymmetric Buchwald–Hartwig amination[3]) of achiral NH-anilides.[4,5] Furthermore, highly diastereoselective α-monoalkylation with lithium enolates prepared from these anilides and lactams was also found.[4] In this Letter, we report catalytic asymmetric synthesis of biologically active dihydroquinolin-2-one derivatives using our atropisomeric lactam chemistry. This work shows a new utility of atropisomeric anilide derivatives.

Various biologically active compounds possessing a dihydroquinolin-2-one skeleton have been found so far.[6] For example, Camp and co-workers reported *N*-phenyl-α-substituted dihydroquinolin-2-one derivatives **I** having potent norepinephrine transporter (NET) inhibitory activity.[7] An enantiomer of **I** ($R' = H$) was also found to be 20-fold more NET active than the antipode, while the absolute configurations were not determined. We expected that catalytic asymmetric synthesis of key intermediates **II** for such NET inhibitors **I** may be achieved through our enantioselective intramolecular N-arylation followed by diastereoselective α-alkylation of the resulting atropisomeric lactam **2** and the removal of the *tert*-butyl group by trans-*tert*-butylation (retro-Friedel–Crafts reaction)[8] (Scheme 1).

To realize the synthetic pathway shown in Scheme 1, *N*-(*ortho*-mono-*tert*-butylphenyl)lactam **III** ($R = H$) having high optical purity is essential, because the *meta*-*tert*-butyl group in 2,5-di-*tert*-butyl derivative **III** ($R = t$-Bu) is difficult to remove.[8b] However, as described in a previous paper,[4] the intramolecular N-arylation of the *ortho*-mono-*tert*-butylanilide **1** ($R = H$) resulted in a considerable decrease in enantioselectivity in comparison with that of 2,5-di-*tert*-butyl derivative **1** ($R = t$-Bu) ($R = H$: 70% ee, $R = t$-Bu: 96% ee, Scheme 1). In addition, stereoselective construction of quaternary α-carbon in **III** ($R' = Me$) and efficient removal of the *ortho*-*tert*-butyl group in **III**, which have not yet been examined, are necessary.

Initially, the improvement of the enantioselectivity in the reaction with mono-*tert*-butylanilide **1a** was investigated. After reinvestigation of the chiral phosphine ligands,

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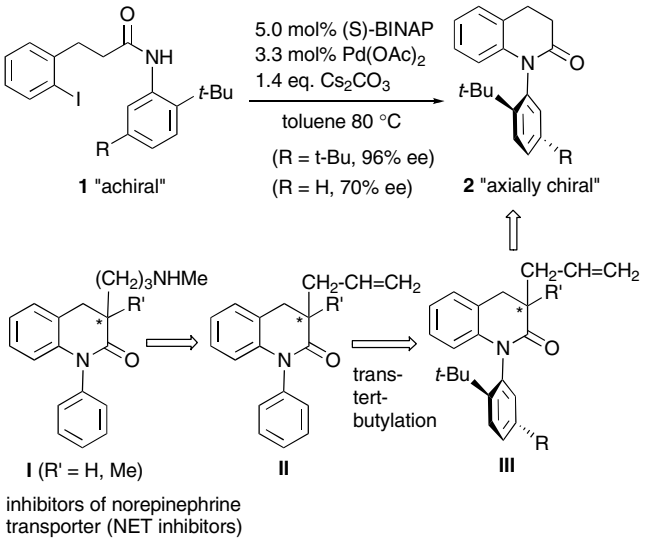


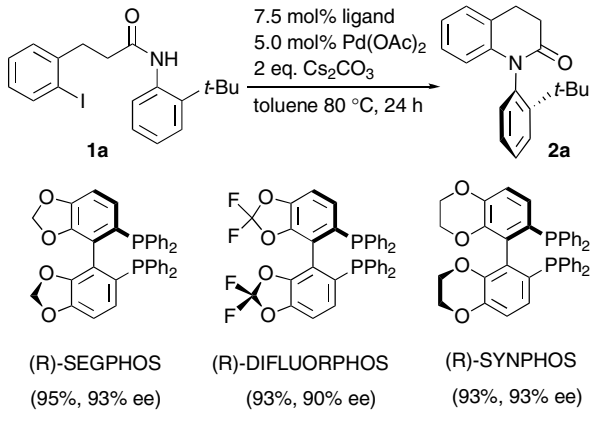
Scheme 1. Catalytic asymmetric synthesis of atropisomeric lactam and its conversion to NET inhibitors.

it was found that the use of SEGPHOS-like ligands such as (*R*)-SEGPHOS, (*R*)-DIFLUORPHOS and (*R*)-SYNPHOS led to a remarkable increase in enantioselectivity (90–93% ee, Scheme 2).[9] This result is in striking contrast to that of intermolecular N-arylation, which proceeded with poor enantioselectivity (23% ee) in the presence of the (*R*)-SEGPHOS ligand.[4,10]

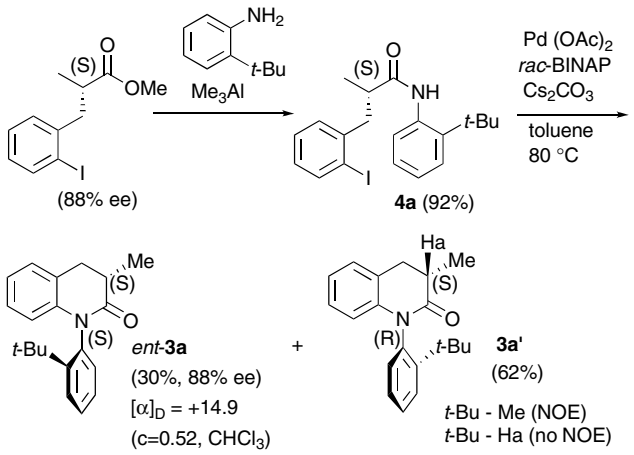
The absolute stereochemistry of the axial chirality in lactam product **2a** was confirmed to be (*R*)-configuration by comparison of **3a** in Scheme 4 with *ent*-**3a** prepared in accordance with Scheme 3.[4b]

The α-alkylation with mono-*tert*-butyl lactam product **2a** (93% ee) proceeded with higher diastereoselectivity (dr = 31:1–50:1) than that with 2,5-di-*tert*-butyl lactam (dr = 13:1–48:1), which was previously reported.[4,11] The attack of alkyl halides to the lactam enolate preferentially occurs from the opposite site of the *ortho*-*tert*-butyl group to afford products **3a**–**c** having α-chiral carbon of (*R*)-configuration (Scheme 4).

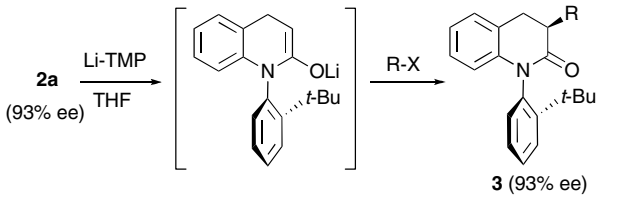
Furthermore, we newly found that the present α-alkylation can be applied to the stereoselective construction of



Scheme 2. Catalytic asymmetric intramolecular N-arylation of *ortho*-mono-*tert*-butyl-NH-anilide **1a**.



Scheme 3. Stereochemical assignment of lactam product.

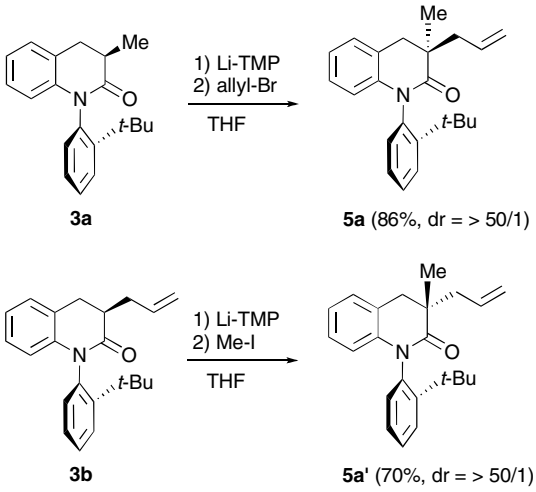


R-X	3	yield (%)	dr	
Me-I	**3a**	82	31/1	$[\alpha]_D$ = -17.0 (c=0.92, $CHCl_3$)
allyl-Br	**3b**	83	> 50/1	
$PhCH_2$-Br	**3c**	85	> 50/1	

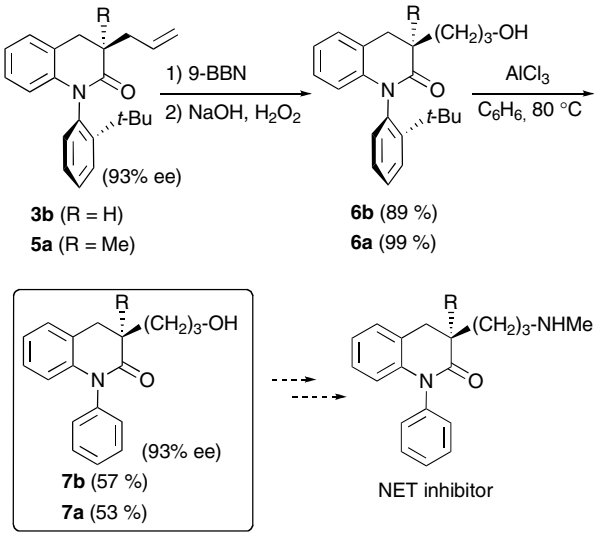
Scheme 4. Diastereoselective α-alkylation with atropisomeric lactam **2a**.

a quaternary carbon. That is, α-allylation and α-methylation of α-methyl lactam **3a** and α-allyl lactam **3b** gave diastereomeric α-methyl-α-allyl lactams **5a** and **5a**′with almost complete diastereoselectivities, respectively (Scheme 5). The stereochemistries of products **5a** and **5a**′ show that the second alkylation also selectively occurs from the opposite site of the *ortho*-*tert*-butyl group.[12]

For conversion to synthetic intermediates **II** (Scheme 1), the removal of the *ortho*-*tert*-butyl group in α-allylated lac-



Scheme 5. Diastereoselective α-alkylation with α-substituted lactams.



Scheme 6. Conversion to synthetic intermediates for NET inhibitors.

tams **3b** (R = H) and **5a** (R = Me) was next investigated. In accordance with the procedure of trans-*tert*-butylation reported by Simpkins et al.,[8c] although **3b** and **5a** were treated with $AlCl_3$ (10 equiv) in C_6H_6 at 80 °C, desired *N*-phenyl lactams were not obtained. In these reactions, the formation of complex mixtures accompanied by the disappearance of the alkene part was observed. The *tert*-butyl group could be removed by trans-*tert*-butylation of the resulting hydroxy lactams **6b** and **6a** after *anti*-Markovnikov hydration of **3b** and **5a** (Scheme 6). The obtained *N*-phenyl lactams **7b** and **7a** are also synthetic intermediates for NET inhibitors, which have been reported by Camp et. al.[7]

α-Alkylations in Schemes 4 and 5, and hydration and trans-*tert*-butylation in Scheme 6 proceeded without any racemization to give intermediates **7b** and **7a** of same ee as that of starting lactam **2a**.

In conclusion, we succeeded in the catalytic asymmetric synthesis of key intermediates for NET inhibitors using optically active atropisomeric lactam obtained through highly enantioselective intramolecular N-arylation.[13,14] The present work shows a new development in atropisomeric anilide chemistry.

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10. Interestingly, the use of (*R*)-DTBM-SEGPHOS which gave the best results in intermolecular reaction, was not effective in the intramolecular reaction with **1a** (12% yield, 0% ee).
11. Similar stereoselective α-mono-alkylation with *racemic* atropisomeric N-(*ortho-tert*-butylphenyl)-5,6-dehydropiperidin-2-one has been reported by Simpkins and co-workers (Ref. 8c).
12. Stereochemistries of lactams **5a** and **5a′** were determined by NOESY experiment. In **5a′**, NOE between the *ortho-tert*-butyl group and alkenyl hydrogen was observed, while in **5a**, NOE between these groups was not observed.
13. *General procedure of catalytic asymmetric intramolecularN-arylation*: Under Ar atmosphere, to **1a** (407 mg, 1.0 mmol) in toluene (3.0 mL) was added Cs_2CO_3 (651 mg, 2.0 mmol). After being stirred for 5 min at rt, the suspension of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and (*R*)-SEGPHOS (45.8 mg, 0.075 mmol) in toluene (2.0 mL) was added to the mixture, and then the reaction mixture was vigorously stirred for 24 h at 80 °C (When the reaction mixture was heated for several hours, some solids adhered to the flask's walls above the solution. The solids, including active catalyst, had to be resuspended in the reaction solution by shaking the flask). 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 = 10) gave **2a** (267 mg, 95%). The ee (93% ee) of **2a** was determined by HPLC analysis using a CHIRALPACK AD-H column [25 cm × 0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (−)-**2a** (major); t_R = 11.3 min, (+)-**2a** (minor); t_R = 12.6 min]. Compound **2a**: $[\alpha]_D$ −77.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR of lactam **2a** coincided with that reported in our previous paper.[4]
14. Spectral data of key compounds **3b**, **5a**, **6b**, **6a**, **7b** and **7a**. Compound **3b** (93% ee): white solid; $[\alpha]_D$ −58.4 (*c* 1.0, $CHCl_3$); mp 78–82 °C; IR (KBr) 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.63 (1H, dd, *J* = 1.5, 8.1 Hz), 7.39 (1H, dt, *J* = 1.5, 8.1 Hz), 7.30 (1H, dt, *J* = 1.5, 7.6 Hz), 7.19 (1H, d, *J* = 7.0 Hz), 7.04 (1H, dt, *J* = 1.5, 7.6 Hz), 6.97 (1H, dt, *J* = 1.2, 7.6 Hz), 6.88 (1H, dd, *J* = 1.5, 7.6 Hz), 6.19 (1H, dd, *J* = 1.0, 8.0 Hz), 5.84 (1H, dddd, *J* = 6.1, 8.1, 10.2, 17.0 Hz), 5.10 (1H, d, *J* = 10.2 Hz), 5.06 (1H, qd, *J* = 1.6, 17.0 Hz), 3.15 (1H, dd, *J* = 5.4, 15.6 Hz), 2.89 (1H, dd, *J* = 6.7, 15.6 Hz), 2.81 (1H, m), 2.61 (1H, m), 2.23 (1H, td, *J* = 8.1, 14.0 Hz), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$): δ 172.6, 147.9, 141.9, 136.1, 135.3, 132.0, 129.6, 128.6, 128.4, 127.7, 127.0, 123.6, 122.8, 117.5, 116.9, 40.8, 35.9, 33.8, 31.6, 29.6; MS (*m*/*z*) 320 (MH^+); Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.75; H, 7.94; N, 4.47. Compound **5a** (93% ee): colourless oil; $[\alpha]_D$ −122.6 (*c* 1.0, $CHCl_3$); IR (neat) 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.60 (1H, dd, *J* = 1.6, 8.0 Hz), 7.38 (1H, dt, *J* = 1.6, 7.3 Hz), 7.31 (1H, dt, *J* = 1.6, 7.3 Hz), 7.16 (1H, d, *J* = 7.1 Hz), 7.03 (1H, dt, *J* = 1.2, 7.5 Hz), 6.97 (1H, dt, *J* = 1.2, 7.3 Hz), 6.87 (1H, dd, *J* = 1.6, 7.5 Hz), 6.15 (1H, dd, *J* = 1.0, 8.0 Hz), 5.80 (1H, tdd, *J* = 7.4, 10.0, 17.0 Hz), 5.10 (1H, qd, *J* = 1.0, 10.0 Hz), 4.99 (1H, qd, *J* = 1.0, 17.0 Hz), 2.96 (1H, d, *J* = 15.8 Hz), 2.86 (1H, d, *J* = 15.8 Hz), 2.29 (1H, dd, *J* = 7.1, 14.6 Hz), 2.21 (1H, dd, *J* = 7.8, 14.6 Hz), 1.32 (3H, s), 1.22 (9H, s); ^{13}C NMR ($CDCl_3$): δ 174.8, 147.7, 142.0, 136.6, 133.0, 132.3, 129.4, 128.5, 128.3, 127.6, 126.9, 123.7, 122.7, 118.7, 116.5, 40.8, 40.0, 37.2, 35.8, 31.5, 22.3; MS (*m*/*z*) 334 (MH^+); Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.53; H, 8.10; N, 3.98. Compound **6b** (93% ee): white solid; $[\alpha]_D$ −44.0 (*c* 1.0, $CHCl_3$); mp 91–92 °C; IR (KBr) 3420, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.63 (1H, dd, *J* = 1.5, 8.1 Hz), 7.39 (1H, dt, *J* = 1.5, 7.6 Hz), 7.31 (1H, dt, *J* = 1.5, 7.6 Hz), 7.20 (1H, d, *J* = 7.0 Hz), 7.04 (1H, dt, *J* = 1.5, 7.6 Hz), 6.98 (1H, dt, *J* = 1.2, 7.3 Hz), 6.87 (1H, dd, *J* = 1.5, 7.6 Hz), 6.19 (1H, d, *J* = 7.6 Hz), 3.60–3.70 (2H, m), 3.21 (1H, dd, *J* = 5.1, 15.3 Hz), 2.88 (1H, dd, *J* = 6.8, 15.3 Hz), 2.82 (1H, m), 2.01 (1H, br s), 1.88 (1H, m), 1.55–1.82 (3H, m), 1.25 (9H, s); ^{13}C NMR ($CDCl_3$): δ 173.3, 147.9, 141.7, 136.0, 131.8, 129.7, 128.7, 128.4, 127.8, 127.1, 123.8, 122.9, 117.0, 62.4, 40.8, 35.9, 31.6, 30.9, 30.1, 26.1; MS (*m*/*z*) 338 (MH^+); Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.16; H, 7.90; N, 3.98. Compound **6a** (93% ee): colourless oil; $[\alpha]_D$ −145.7 (*c* 0.2, $CHCl_3$); IR (neat) 3443, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.60 (1H, dd, *J* = 1.5, 8.1 Hz), 7.37 (1H, dt, *J* = 1.5, 7.6 Hz), 7.30 (1H, dt, *J* = 1.5, 7.6 Hz), 7.17 (1H, d, *J* = 7.1 Hz), 7.03 (1H, t, *J* = 7.6 Hz), 6.96 (1H, dt, *J* = 1.0, 7.3 Hz), 6.85 (1H, dd, *J* = 1.5, 7.6 Hz), 6.15 (1H, d, *J* = 8.0 Hz), 3.55 (2H, t, *J* = 5.8 Hz), 3.01 (1H, d, *J* = 15.8 Hz), 2.86 (1H, d, *J* = 15.8 Hz), 1.50–1.67 (5H, m), 1.33 (3H, s), 1.21 (9H, s); ^{13}C NMR ($CDCl_3$): δ 175.0, 147.8, 141.8, 136.6, 132.2, 129.4, 128.5, 128.3, 127.7, 127.0, 123.7, 122.7, 116.5, 63.0, 40.6, 38.1, 35.9, 32.2, 31.5, 27.3, 22.5; MS (*m*/*z*) 352 (MH^+); HRMS: (MH^+) calcd for $C_{23}H_{30}NO_2$, 352.2277; found, 352.2288. Compound **7b** (93% ee): white solid; $[\alpha]_D$ +15.6 (*c* 0.4, $CHCl_3$); mp 106–108 °C; IR (KBr) 3420, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, t, *J* = 7.6 Hz), 7.41 (1H, tt, *J* = 1.2, 7.6 Hz), 7.18–7.22 (3H, m), 7.04 (1H, dt, *J* = 1.5, 7.6 Hz), 6.99 (1H, dt, *J* = 1.2, 7.6 Hz), 6.34 (1H, dd, *J* = 1.2, 7.8 Hz), 3.62–3.72 (2H, m), 3.13 (1H, dd, *J* = 5.4, 15.4 Hz), 2.92 (1H, dd, *J* = 9.8, 15.4 Hz), 2.80 (1H, m), 1.98 (1H, m), 1.58–1.82 (4H, m); ^{13}C NMR ($CDCl_3$): δ 172.7, 141.1, 138.6, 129.8, 129.0, 128.1, 128.1, 127.1, 124.9, 123.0, 116.8, 62.4, 40.7, 31.3, 30.2, 25.9; MS (*m*/*z*) 304 (MNa^+); HRMS: (MNa^+) calcd for $C_{18}H_{19}NO_2Na$, 304.1313; found, 304.1305. Compound **7a** (93% ee): white solid; $[\alpha]_D$ −12.8 (*c* 1.0, $CHCl_3$); mp 82–85 °C; IR (KBr) 3435, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, t, *J* = 7.5 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.16–7.20 (3H, m), 7.03 (1H, dt, *J* = 1.5, 7.5 Hz), 6.98 (1H, dt, *J* = 1.0, 7.5 Hz), 6.28 (1H, dd, *J* = 1.0, 8.0 Hz), 3.59 (2H, t, *J* = 5.7 Hz), 3.02 (1H, d, *J* = 15.7 Hz), 2.88 (1H, d, *J* = 15.7 Hz), 1.63–1.78 (5H, m), 1.27 (3H, s); ^{13}C NMR ($CDCl_3$): δ 174.7, 140.8, 138.8, 129.8, 129.0, 128.4, 128.0, 127.0, 124.0, 122.9, 116.2, 62.8, 40.6, 37.8, 32.6, 27.5, 22.5; MS (*m*/*z*) 296 (MH^+); HRMS: (MH^+) calcd for $C_{19}H_{22}NO_2$, 296.1651; found, 296.1678.