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Relationship between rotational barriers and structures in N–C axially chiral 3,4-dihydroquinolin-2-one and 3,4-dihydrobenzoquinolin-2-one

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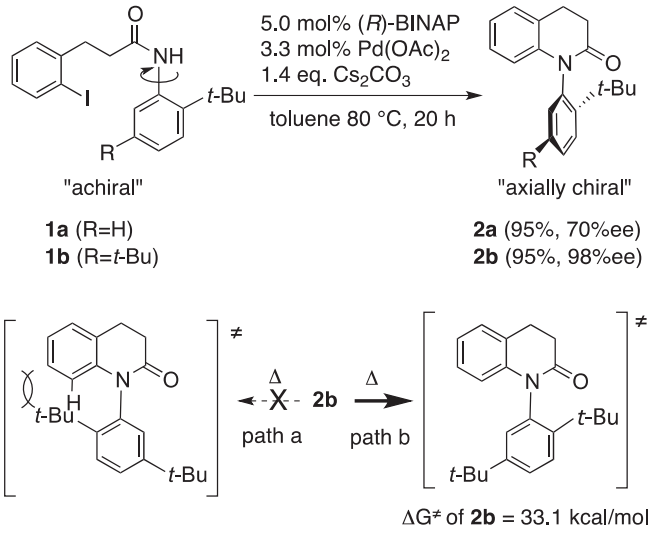
ABSTRACT

The rotational barrier around the N–C chiral axis in *N*-(2-*tert*-butylphenyl)-3,4-dihydrobenzoquinolin-2-one was found to be 6 kcal/mol lower than that in *N*-(2-*tert*-butylphenyl)-3,4-dihydroquinolin-2-one. X-ray crystal structures and ^{1}H NMR spectra of both compounds indicate that the significant decrease in the rotational barrier in benzoquinolinone is brought about by destabilization of the ground state which is highlighted by a considerable distortion of the N-C chiral axis.

Atropisomeric compounds with an N–C chiral axis have received much attention as novel chiral molecules.[1] In particular, recent noteworthy topics in this field are their catalytic enantioselective syntheses. Various N–C axially chiral compounds have been prepared with high enantioselectivity through catalytic asymmetric reaction, and used as chiral building blocks and chiral ligands.[2,3]

In 2005, we succeeded in the highly enantioselective synthesis of *N*-(*ortho*-*tert*-butylphenyl)-3,4-dihydroquinolin-2-one derivatives **2** through (*R*)-BINAP-Pd(OAc)$_2$ catalyzed intramolecular Buchwald–Hartwig amination of NH-anilide **1** (Scheme 1).[2c,d] This reaction was the first practical catalytic asymmetric synthesis of N–C axially chiral compounds. The quinolinones **2** are stable atropisomeric compounds which can be stored without any ee decrease for several months at rt. Slow racemization of **2b** occurred in refluxing toluene ($\Delta G^{\neq}$ of **2b** = 33.1 kcal/mol at 110 °C).

DFT calculation indicates that the thermal racemization proceeds through the rotation of the *ortho*-*tert*-butyl group toward the carbonyl group (path b, Scheme 1).[4] The path a through the rotation of the *ortho*-*tert*-butyl group toward benzene C8 side has an extremely high activation energy in comparison with path b arising from the strong steric repulsion between C8-hydrogen and the *ortho*-*tert*-butyl group.



Scheme 1. Catalytic enantioselective synthesis of N–C axially chiral 3,4-dihydroquinolin-2-ones and the possible mechanism for thermal racemization.

On the basis of these results, we expected that *N*-(*ortho*-*tert*-butylphenyl)-3,4-dihydrobenzoquinolin-2-one **2c** would present a higher rotational barrier than quinolinone **2a**. In **2c**, in addition

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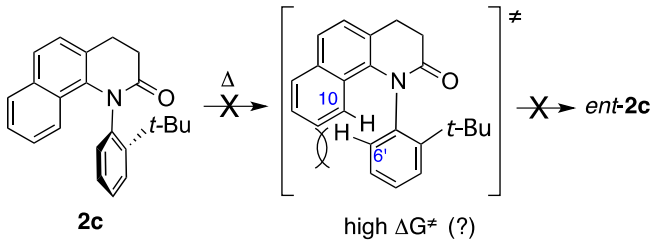


Scheme 2. N–C Axially chiral *N*-(2-*tert*-butylphenyl)-3,4-dihydrobenzoquinolin-2-one **2c**.

to the already existing steric repulsion between carbonyl oxygen and *ortho*-*tert*-butyl group, a strong increase of the steric repulsion is expected from the interaction between the C6′-hydrogen (*ortho*-hydrogen) and the C10-hydrogen on a naphthyl ring in the transition state (Scheme 2).

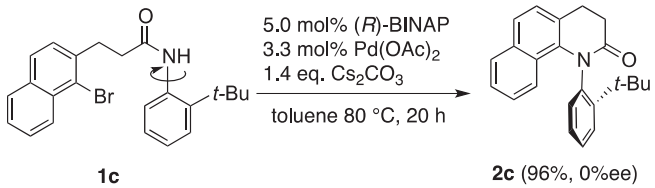
In this Letter, we report an unexpected low rotational barrier in *N*-(2-*tert*-butylphenyl)-3,4-dihydrobenzoquinolin-2-one **2c** in comparison with *N*-(2-*tert*-butylphenyl)-3,4-dihydroquinolin-2-one **2a** and discuss the origin of the decrease in the rotational barrier.

Under the conditions shown in Scheme 1, catalytic enantioselective intramolecular Buchwald–Hartwig amination with the precursor **1c** proceeded smoothly to give the desired benzoquinolinone **2c** in an excellent yield (96%, Scheme 3). However, in sharp contrast with Scheme 1, racemic **2c** was obtained. A racemization due to unexpected low rotational barrier in **2c** was thus envisioned.

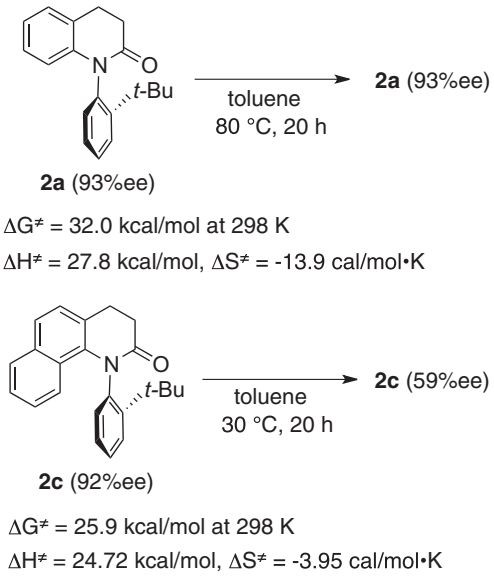
When an optically pure form of **2c** separated through HPLC method using a Chiralpak AD-H column (0.46 cm × 25 cm) was standing for a few hours at room temperature, the ee decreased to 92%. Furthermore, the ee of **2c** (92%ee) dropped to 59% after 20 h at 30 °C in toluene (Scheme 4). The rotational barrier around the chiral axis in **2c** in toluene was evaluated to be 25.9 kcal/mol at 25 °C, 6 kcal/mol lower than that of **2a** ($\Delta G^{\neq}$ = 32.0 kcal/mol at 25 °C). Since partial racemization of **2c** occurred at nearby room temperature, the methodology using Buchwald–Hartwig amination (Scheme 3),[5] which requires long heating, is not applicable to the asymmetric synthesis of **2c**.

The rotational barriers of **2a** and **2c** calculated at the B3LYP5/6-31G* level nicely matched the experimental values. The transition state structures **TS-2A** and **TS-2C** evaluated by the DFT method were not significantly different (Fig. 1).[6] These results may indicate that the origin of the difference of the rotational barriers is located in the ground state structures.

Subsequently, X-ray crystal structure analyses of **2a** and **2c** were performed (Fig. 2).[7] In both compounds **2a** and **2c**, the *ortho*-*tert*-butylphenyl group is nearly perpendicular to the lactam ring (<C2–N1–C1′–C2′ = −108.6° and −76.2°), and the amide part has almost a planar structure (<O–C2–N1–C1′ = 9.8° and 10.5°, total of three bond angles around nitrogen atom = 357° and 357.6°, the possibility of the decrease in the rotational barrier due to the twisting of the amide bond and a full pyramidalization of the nitrogen atom was excluded[8]). No noticeable difference in bond length of the three N—C bonds and the three bond angles



Scheme 3. Attempt for catalytic enantioselective synthesis of **2c**.



Scheme 4. The rotational barriers of N–C axially chiral quinolinone **2a** and benzoquinolinone **2c**.

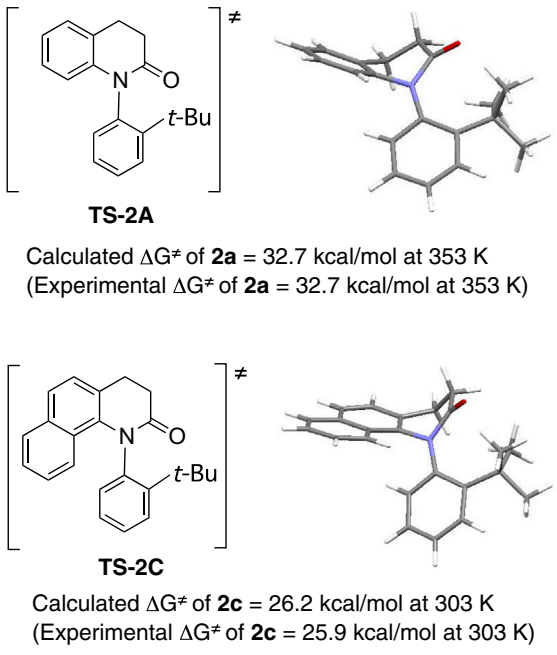


Figure 1. The $\Delta G^{\neq}$ values and the transition state structures during the N—C bond rotation evaluated by DFT calculation at the B3LYP5/6-31G* level.

around the nitrogen atom was observed between **2a** and **2c**. A remarkable difference in the X-ray structure of **2a** and **2c** is found in the high out of plane distortion of the chiral axis from the naphthalene plane in **2c**. The benzene ring and the chiral axis are almost coplanar (<C1′–N1–C8a–C8 = 7.7°) in quinolinone **2a** while the torsion angle between the chiral axis and the naphthalene ring (<C1′–N1–C10b–C10a) is −38.8° in benzoquinolinone **2c**.[9]

The structure found in the crystal might be as well maintained in solution (Fig. 3). In the ^{1}H NMR of **2a** in $CDCl_3$, the C8-hydrogen appears at high field (6.22 ppm) from the shielding effect of the perpendicular 2-*tert*-butylphenyl group (C8 hydrogen is facing the 2-*tert*-butylphenyl plane), while the remarkable high field shift