

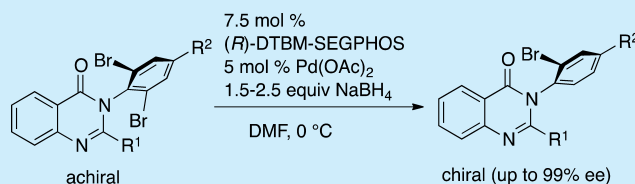
# Catalytic Enantioselective Synthesis of N–C Axially Chiral Mebroqualone and Its Derivatives through Reductive Asymmetric Desymmetrization

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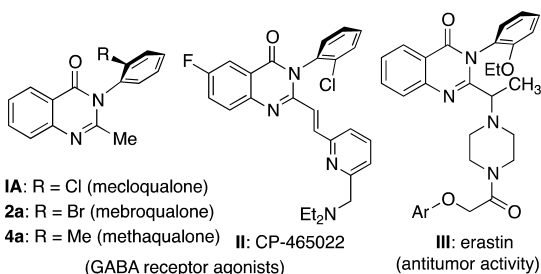
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**S** Supporting Information

**ABSTRACT:** In the presence of (*R*)-DTBM-SEGPHOS-Pd(OAc)<sub>2</sub> catalyst, treatment of various 3-(2,6-dibromophenyl)quinazolin-4-ones with NaBH<sub>4</sub> gave optically active N–C axially chiral quinazolinone (mebroqualone) derivatives through reductive asymmetric desymmetrization (enantioselective monohydrodebromination) followed by kinetic resolution of the resulting monobromophenyl products (up to 99% ee). The enantioselectivity strongly depended on the substituent (R<sup>2</sup>) at the C4' position, amount of NaBH<sub>4</sub>, and reaction temperature.



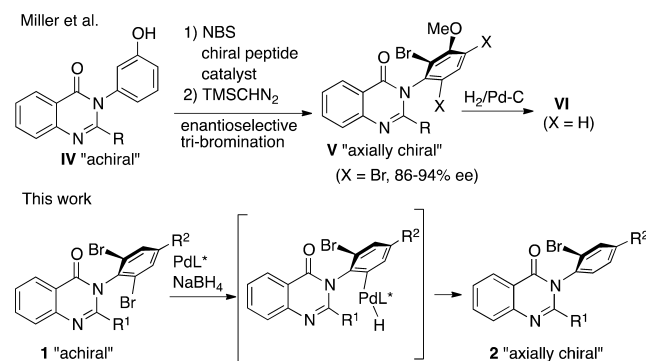
In 2005, we succeeded in the highly enantioselective synthesis of N–C axially chiral anilides and 3,4-dihydroquinolin-2-ones through chiral Pd-catalyzed aromatic amination.<sup>1</sup> After that publication, catalytic asymmetric syntheses of various N–C axially chiral molecules were reported by many groups.<sup>2,3</sup> On the other hand, N–C axially chiral quinazolin-4-one derivatives possessing a GABA-receptor agonist and antitumor activities have also become known (Figure 1),<sup>4</sup> while there have been no reports to date on catalytic enantioselective synthesis of these bioactive quinazolinones.



**Figure 1.** Various bioactive quinazolinone derivatives bearing an N–C axially chiral structure.

Recently, Miller et al. reported the highly enantioselective synthesis of N–C axially chiral quinazolinone derivatives via chiral peptide-catalyzed electrophilic tribromination of 3-(3-hydroxyphenyl)quinazolin-4-ones **IV** (Scheme 1).<sup>5</sup> However, since this reaction requires a hydroxyl group (an electron-donating group) at the C3' position for the tribromination of the *N*-aryl group, the conversion from tribromination products **V** to mebroqualone **2a** and methaqualone **4a** would appear to be difficult. Indeed, although they succeeded in conversion to mebroqualone analogue **VI** through the regioselective hydrodebromination of **V**, removal of the oxygen functional group at the C3' position was not mentioned in their report.

## Scheme 1. Catalytic Asymmetric Synthesis of N–C Axially Chiral Quinazolinones



In this paper, we report direct catalytic enantioselective synthesis of mebroqualone **2a** and its derivatives through chiral palladium (PdL\*)-catalyzed hydrodebromination (reductive asymmetric desymmetrization) of achiral 3-(2,6-dibromophenyl)quinazolin-4-one derivatives **1** (Scheme 1). Furthermore, the determination of the absolute stereochemistry of mebroqualone **2a** and the substituent effect on enantioselectivity are described.

Various 3-(2,6-dibromophenyl)quinazolin-4-one substrates **1a–h** were easily prepared through the reaction of *N*-acylanthranilic acid and 2,6-dibromoaniline derivatives in the presence of PCl<sub>3</sub>.<sup>6</sup> Initially, we attempted enantioselective synthesis of N–C axially chiral quinazolinones via mono C–C cross-coupling of **1** with methyl or phenyl metal species in the presence of chiral Pd catalyst because syntheses of optically active axially chiral biaryl derivatives through asymmetric desymmetrization using chiral Pd-catalyzed cross-coupling

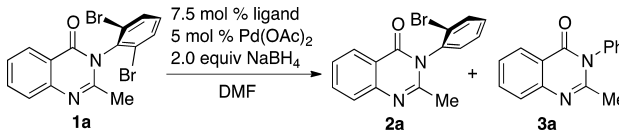
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have already been reported by Hayashi et al.<sup>7,8</sup> However, the methodology with asymmetric cross-coupling did not give a good result for N-C axially chiral quinazolinone. In addition, since this methodology is not applicable to synthesis of mebroqualone **2a** and mecloqualone **1a**, we next tried asymmetric desymmetrization of **1** via chiral Pd-catalyzed hydrodebromination.<sup>9</sup>

In the presence of Pd(OAc)<sub>2</sub> catalyst (5.0 mol %) and NaBH<sub>4</sub> (2.0 equiv) in DMF (50 °C), the reaction conditions for asymmetric desymmetrization with **1a** were optimized (Table 1). After screening of chiral phosphine ligands, it was

**Table 1. Optimization of Reaction Conditions for Catalytic Enantioselective Synthesis of Mebroqualone **2a** through Reductive Asymmetric Desymmetrization**



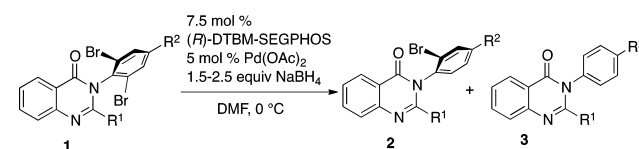
entry	chiral ligand	<i>t</i> (°C)	<b>2a</b> yield <sup>a</sup> (%)	<b>2a</b> ee <sup>b</sup> (%)	<b>3a</b> yield <sup>a</sup> (%)
1	(R)-DIFLUOROPHOS	50	34	0	2
2	(R)-MOP	50	53	0	10
3	(S,S)-CHIRAPHOS	50	59	0	15
4	(S,R)-PPFA	50	61	0	26
5	(R)-SEGPHOS	50	53	9	7
6	(R)-BINAP	50	48	29	8
7	(R)-DTBM-SEGPHOS	50	49	39	20
8	(R)-DTBM-SEGPHOS	40	48	56	31
9	(R)-DTBM-SEGPHOS	30	58	60	23
10	(R)-DTBM-SEGPHOS	0	48	73	27
11 <sup>c</sup>	(R)-DTBM-SEGPHOS	0	76	56	7

<sup>a</sup>The yield was determined by <sup>1</sup>H NMR analysis of the mixture of **2a** and **3a**. <sup>b</sup>The ee was determined by HPLC analysis using a chiral AS-H column. <sup>c</sup>1.5 equiv of NaBH<sub>4</sub> was used.

found that the use of (R)-DTBM-SEGPHOS<sup>10</sup> gives the best enantioselectivity (entry 7). In this case, 39% ee of mebroqualone **2a** was obtained in 49% yield together with over-reduction side product **3a** (20%). The present reaction was significantly influenced by reaction temperature (entries 7–10). That is, the enantioselectivity increased with decreasing reaction temperature, and the reaction at 0 °C gave 73% ee of **2a** (48% yield, entry 10). When NaBH<sub>4</sub> was decreased from 2.0 to 1.5 equiv, a considerable increase in the chemical yield was observed (76%) while the enantioselectivity lowered to 56% ee (entry 11).<sup>11</sup>

Under the optimized conditions [7.5 mol % of (R)-DTBM-SEGPHOS, 5.0 mol % of Pd(OAc)<sub>2</sub>, 1.5–2.5 equiv of NaBH<sub>4</sub> in DMF at 0 °C], asymmetric desymmetrization with various 2',6'-dibromo substrates **1b–h** was further examined (Table 2). In the reaction with 2-ethyl derivative **1b**, an increase in the enantioselectivity was observed in comparison with that with 2-methyl derivative **1a** (entries 1–4). Namely, the reaction of **1b** with 1.5 equiv and 2.0 equiv of NaBH<sub>4</sub> gave **2a** in 68% ee (81% yield) and 89% ee (35% yield), respectively (entries 3 and 4).

**Table 2. Catalytic Asymmetric Desymmetrization of Various 3-(2,6-Dibromophenyl)quinazolin-4-ones**



entry	<b>1</b>	R <sup>1</sup> , R <sup>2</sup>	NaBH <sub>4</sub> <sup>a</sup>	<b>2</b>	<b>2</b> yield <sup>b</sup> (%)	<b>2</b> ee <sup>c</sup> (%)	<b>3</b>	<b>3</b> yield <sup>b</sup> (%)
1	<b>1a</b>	Me, H	1.5	<b>2a</b>	76	56	<b>3a</b>	7
2	<b>1a</b>	Me, H	2.0	<b>2a</b>	48	73	<b>3a</b>	27
3	<b>1b</b>	Et, H	1.5	<b>2b</b>	81	68	<b>3b</b>	11
4	<b>1b</b>	Et, H	2.0	<b>2b</b>	35	89	<b>3b</b>	45
5	<b>1c</b>	Me, Me	1.5	<b>2c</b>	83	77	<b>3c</b>	6
6	<b>1c</b>	Me, Me	2.0	<b>2c</b>	40	98	<b>3c</b>	40
7	<b>1d</b>	Et, Me	1.5	<b>2d</b>	90	77	<b>3d</b>	5
8	<b>1d</b>	Et, Me	2.0	<b>2d</b>	36	99	<b>3d</b>	58
9	<b>1e</b>	Me, <i>i</i> -Pr	1.5	<b>2e</b>	62	73	<b>3e</b>	3
10	<b>1e</b>	Me, <i>i</i> -Pr	2.0	<b>2e</b>	73	80	<b>3e</b>	13
11	<b>1e</b>	Me, <i>i</i> -Pr	2.5	<b>2e</b>	50	91	<b>3e</b>	32
12	<b>1f</b>	Et, <i>i</i> -Pr	2.0	<b>2f</b>	75	74	<b>3f</b>	12
13	<b>1f</b>	Et, <i>i</i> -Pr	2.5	<b>2f</b>	44	98	<b>3f</b>	40
14	<b>1g</b>	Me, OMe	1.5	<b>2g</b>	68 <sup>d</sup>	29	<b>3g</b>	12 <sup>d</sup>
15	<b>1g</b>	Me, OMe	2.0	<b>2g</b>	36 <sup>d</sup>	59	<b>3g</b>	43 <sup>d</sup>
16	<b>1h</b>	Me, Cl	1.5	<b>2h</b>	49 <sup>d</sup>	28	<b>3h</b>	<sup>e</sup>

<sup>a</sup>Equivalents of NaBH<sub>4</sub>. <sup>b</sup>The yield was determined by <sup>1</sup>H NMR analysis of the mixture of **2** and **3**. <sup>c</sup>The ee was determined by HPLC analysis using a chiral column. <sup>d</sup>Isolated yield. <sup>e</sup>The formation of several byproducts was observed, and these structures were not determined.

The enantioselectivity was significantly influenced by the R<sup>2</sup> (C4') substituent on the N3-phenyl group to a greater extent than the R<sup>1</sup> substituent on the quinazolinone ring. For example, the reaction of **1c** and **1d** bearing a 4'-methyl group proceeded with higher enantioselectivity than those of **1a** and **1b** (entries 5–8). In particular, the reactions with 2.0 equiv of NaBH<sub>4</sub> gave products **2c** and **2d** with almost complete enantioselectivity (98% ee and 40% yield, 99% ee and 36% yield, entries 6 and 8).

The reactions of **1e** and **1f** bearing an isopropyl group at the C4' position also proceeded with high enantioselectivity (entries 9–13), while the use of a slightly larger amount of NaBH<sub>4</sub> in comparison with other substrates was required. As shown in entries 11 and 13, the reactions with 2.5 equiv of NaBH<sub>4</sub> gave monobromo products **2e** and **2f** in 91% ee and 98% ee, respectively. Thus, an alkyl substituent at the C4' position was found to bring about the remarkable increase in enantioselectivity.

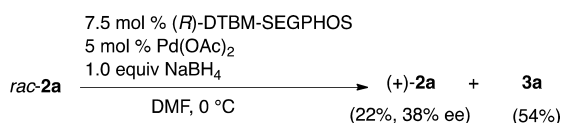
In contrast to **1c–f** bearing an alkyl group at C4', with substrates **1g** and **1h** bearing C4'-methoxy and C4'-chloro groups, a remarkable decrease in the enantioselectivity was observed (entries 14–16). These results may indicate that a significant change in the enantioselectivity by the C4' substituent is caused by the electronic effects (inductive effect) rather than steric factors.

As described in entries 1–15, the enantioselectivity showed an increasing tendency as the amount of NaBH<sub>4</sub> increased. At the same time, it led to a decrease in the yield of desymmetrization product **2** and an increase in the yield of over-reduction side product **3**. Thus, this strongly suggests that the ee of **2** shown in Table 2 was determined not only by the asymmetric desymmetrization process (the first hydrodebromi-

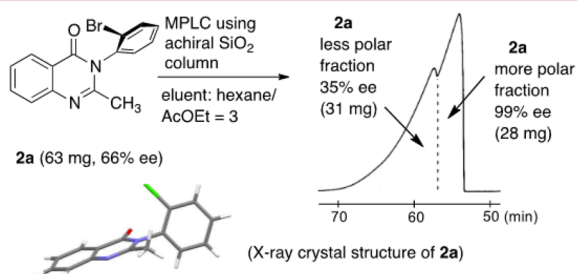
nation) but also by kinetic resolution of the resulting **2** (the second hydrodebromination).<sup>12</sup>

Indeed, when racemic mebroqualone *rac*-**2a** was treated with 1.0 equiv of NaBH<sub>4</sub> in the presence of (*R*)-DTBM-SEGPHOS–Pd(OAc)<sub>2</sub> catalyst, 38% ee of (+)-**2a** was recovered (recovery yield 22%) together with reduction product **3a** (54%, Scheme 2), and the major enantiomer of the recovered (+)-**2a** had the same absolute configuration as product **2a** described in Table 2 (entries 1 and 2).

### Scheme 2. Kinetic Resolution with *rac*-**2a**



Since the absolute stereochemistry of mebroqualone **2a** has yet to be determined, the stereochemical assignment of **2a** was investigated next. We observed significant self-disproportionation of enantiomers (SDE) during MPLC purification of optically active **2a** (66% ee) and could obtain 99% ee of **2a** by the SDE (Figure 2).<sup>13,14</sup> Subsequently, X-ray crystal structural

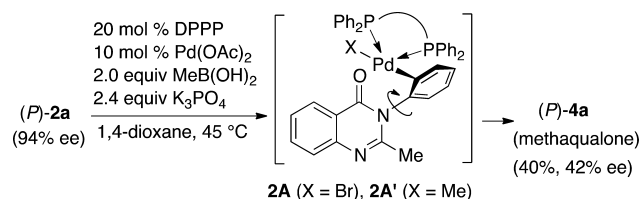


**Figure 2.** SDE observed in MPLC of **2a** (66% ee) and X-ray crystal structure of (+)-(*P*)-**2a**.

analysis of (+)-**2a** (99% ee) was performed, and the major enantiomer was determined to have the (*P*)-configuration (Figure 2).<sup>15</sup> The stereochemistries of other mebroqualone derivatives **2b–h**, which have a large positive [ $\alpha$ ]<sub>D</sub> value as in **2a**, were also predicted to have the (*P*)-configuration.

We also attempted to convert mebroqualone **2a** to methaqualone **4a**. Miller et al. mentioned that Suzuki–Miyaura coupling of optically active mebroqualone analogue **VI** (Scheme 1) with organoboronic acid brings about a significant decrease in the ee in the coupling product.<sup>5</sup> After a detailed survey, they found the reaction conditions which proceed without a decrease in the original ee, while the reaction is limited to arylboronic acid and the reaction with alkyl boronic acid was not described. We investigated Suzuki–Miyaura coupling of optically active mebroqualone **2a** with methyl boronic acid in the presence of Pd(OAc)<sub>2</sub> and various phosphine ligands.<sup>16</sup> The reaction of (*P*)-**2a** (94% ee) with DPPP ligand gave 42% ee of methaqualone product (*P*)-**4a** in 40% yield (Scheme 3). Although reactions in the presence of other phosphine ligands [Ph<sub>3</sub>P, (*o*-Tol)<sub>3</sub>P, *t*-Bu<sub>3</sub>P, John-Phos] were also conducted, unfortunately, no better result than that of DPPP was obtained. Since the **2a** and **4a** have high rotational barriers (more than 31 kcal/mol), the significant decrease in the ee is most probably due to the lower rotational barrier around the chiral axis in aryl-Pd intermediates **2A** and **2A'**.

### Scheme 3. Conversion of **2a** to Methaqualone **4a**



In conclusion, we succeeded in the catalytic enantioselective synthesis of mebroqualone and its derivatives through chiral Pd-catalyzed reductive asymmetric desymmetrization of 3-(2,6-dibromoaryl)quinazolin-4-ones followed by kinetic resolution of the resulting monobromo products. Furthermore, the absolute stereochemistry of the mebroqualone product was determined to have the (*P*)-configuration.

### ■ ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02865.

Experimental details and spectroscopic data (PDF)

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#### Notes

The authors declare no competing financial interest.

### ■ ACKNOWLEDGMENTS

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(15) CCDC-1492721 (2a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.com.ac.uk/data\\_request/cif](http://www.ccdc.com.ac.uk/data_request/cif).

(16) We also attempted Suzuki–Miyaura coupling of (*P*)-2a (87% ee) with methyl boronic acid under Miller's conditions [10 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>, 20 mol % of *t*-Bu(*c*-hexyl)<sub>2</sub>P·HBF<sub>4</sub>, 4.0 equiv of K<sub>3</sub>PO<sub>4</sub> in THF–H<sub>2</sub>O (3:1) at 45 °C for 24 h]. Although 83% ee of 3a was obtained, the chemical yield was poor (10%).