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

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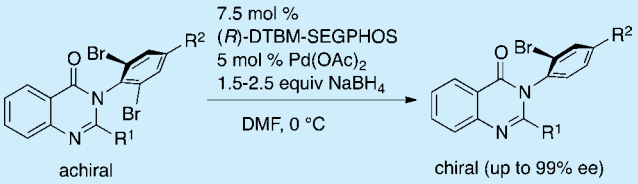
Supporting Information

ABSTRACT: In the presence of (*R*)-DTBM-SEGPHOS-Pd-$(OAc)_2$ catalyst, treatment of various 3-(2,6-dibromophenyl)-quinazolin-4-ones with $NaBH_4$ 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^2) at the C4′position, amount of $NaBH_4$, 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.[1] After that publication, catalytic asymmetric syntheses of various N−C axially chiral molecules were reported by many groups.[2,3] 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),[4] while there have been no reports to date on catalytic enantioselective synthesis of these bioactive quinazolinones.

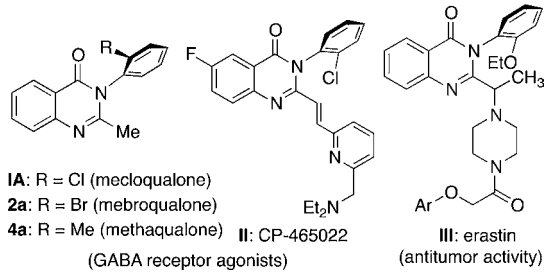
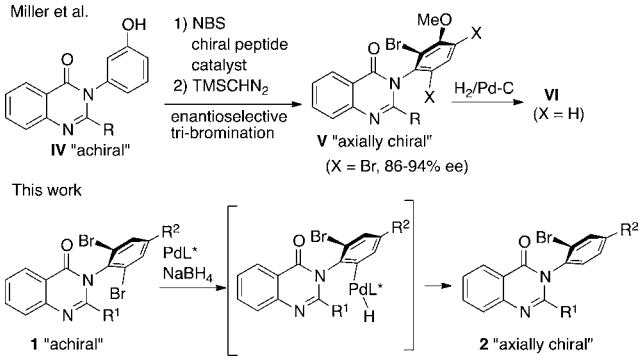


Figure 1. Various bioactive quinazolinone derivatives bearing an N−C axially chiral structure.

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).[5] 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)quinazoline-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)quinazoline-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_3.[6] 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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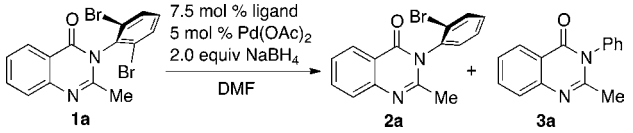
have already been reported by Hayashi et al.[7,8] However, the methodology with asymmetric cross-coupling did not give a good result for N−C axially chiral quinazolinone. In addition, since this methodology is not applicable to synthesis of mebroqualone **2a** and mecloqualone **IA**, we next tried asymmetric desymmetrization of **1** via chiral Pd-catalyzed hydrodebromination.[9]

In the presence of $Pd(OAc)_2$ catalyst (5.0 mol %) and $NaBH_4$ (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 found that the use of (*R*)-DTBM-SEGPHOS[10] 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 $NaBH_4$ 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).[11]

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

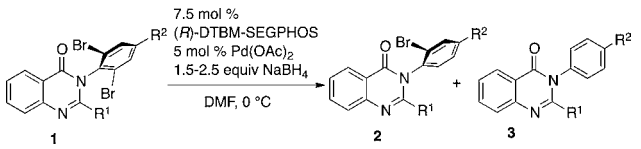


entry	chiral ligand	*t* (°C)	**2a** yield[a] (%)	**2a** ee[b] (%)	**3a** yield[a] (%)
1	(*R*)-DIFLUORO-PHOS	50	34	0	2
2	(*R*)-MOP	50	53	0	10
3	(*S,S*)-CHIRAPHOS	50	59	0	15
4	(*S,R*)-PPFA	50	61	0	26
5	(*R*)-SEGPHOS	50	53	9	7
6	(*R*)-BINAP	50	48	29	8
7	(*R*)-DTBM-SEGPHOS	50	49	39	20
8	(*R*)-DTBM-SEGPHOS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

[a]The yield was determined by ^{1}H NMR analysis of the mixture of **2a** and **3a**. [b]The ee was determined by HPLC analysis using a chiral AS-H column. [c]1.5 equiv of $NaBH_4$ was used.

Under the optimized conditions [7.5 mol % of (*R*)-DTBM-SEGPHOS, 5.0 mol % of $Pd(OAc)_2$, 1.5−2.5 equiv of $NaBH_4$ 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 $NaBH_4$ 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	**1**	R^1, R^2	$NaBH_4$[a]	**2**	**2** yield[b] (%)	**2** ee[c] (%)	**3**	**3** yield[b] (%)
1	**1a**	Me, H	1.5	**2a**	76	56	**3a**	7
2	**1a**	Me, H	2.0	**2a**	48	73	**3a**	27
3	**1b**	Et, H	1.5	**2b**	81	68	**3b**	11
4	**1b**	Et, H	2.0	**2b**	35	89	**3b**	45
5	**1c**	Me, Me	1.5	**2c**	83	77	**3c**	6
6	**1c**	Me, Me	2.0	**2c**	40	98	**3c**	40
7	**1d**	Et, Me	1.5	**2d**	90	77	**3d**	5
8	**1d**	Et, Me	2.0	**2d**	36	99	**3d**	58
9	**1e**	Me, *i*-Pr	1.5	**2e**	62	73	**3e**	3
10	**1e**	Me, *i*-Pr	2.0	**2e**	73	80	**3e**	13
11	**1e**	Me, *i*-Pr	2.5	**2e**	50	91	**3e**	32
12	**1f**	Et, *i*-Pr	2.0	**2f**	75	74	**3f**	12
13	**1f**	Et, *i*-Pr	2.5	**2f**	44	98	**3f**	40
14	**1g**	Me, OMe	1.5	**2g**	68[d]	29	**3g**	12[d]
15	**1g**	Me, OMe	2.0	**2g**	36[d]	59	**3g**	43[d]
16	**1h**	Me, Cl	1.5	**2h**	49[d]	28	**3h**	*e*

[a]Equivalents of $NaBH_4$. [b]The yield was determined by ^{1}H NMR analysis of the mixture of **2** and **3**. [c]The ee was determined by HPLC analysis using a chiral column. [d]Isolated yield. [e]The formation of several byproducts was observed, and these structures were not determined.

The enantioselectivity was significantly influenced by the R^2 (C4′) substituent on the N3-phenyl group to a greater extent than the R^1 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 $NaBH_4$ 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 $NaBH_4$ in comparison with other substrates was required. As shown in entries 11 and 13, the reactions with 2.5 equiv of $NaBH_4$ 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 $NaBH_4$ 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-

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nation) but also by kinetic resolution of the resulting **2** (the second hydrodebromination).[12]

Indeed, when racemic mebroqualone *rac*-**2a** was treated with 1.0 equiv of $NaBH_4$ in the presence of (*R*)-DTBM-SEGPHOS−$Pd(OAc)_2$ 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).[13,14] Subsequently, X-ray crystal structural

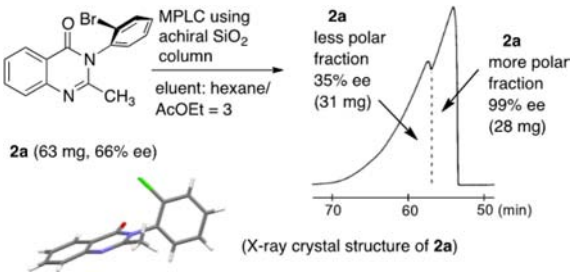
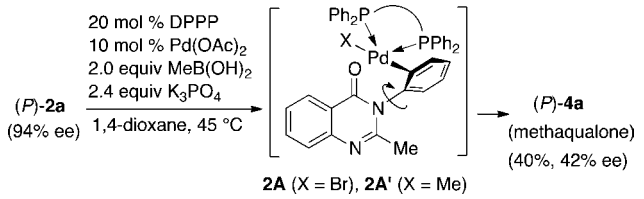


Figure 2. SDE observed in MPLC of **2a** (66% ee) and X-ray crystal structure of (+)-(*P*)-**2a**.

analysis of (+)-**2a** (99% ee) was performed, and the major enantiomer was determined to have the (*P*)-configuration (Figure 2).[15] The stereochemistries of other mebroqualone derivatives **2b**−**h**, which have a large positive $[\alpha]_D$ 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.[5] 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 $Pd(OAc)_2$ and various phosphine ligands.[16] 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_3P, $(o\text{-Tol})_3P$, $t\text{-Bu}_3P$, 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.

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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.
(16) We also attempted Suzuki−Miyaura coupling of (*P*)-**2a** (87% ee) with methyl boronic acid under Miller's conditions [10 mol % of $Pd_2(dba)_3$, 20 mol % of *t*-Bu(*c*-hexyl)$_2$P·HBF_4, 4.0 equiv of K_3PO_4 in THF−H_2O (3:1) at 45 °C for 24 h]. Although 83% ee of **3a** was obtained, the chemical yield was poor (10%).

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