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Diastereoselective α-Alkylation of Metallo Enamines Generated from N−C Axially Chiral Mebroqualone Derivatives

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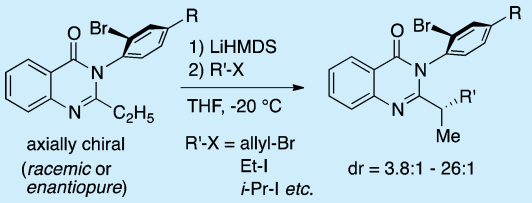
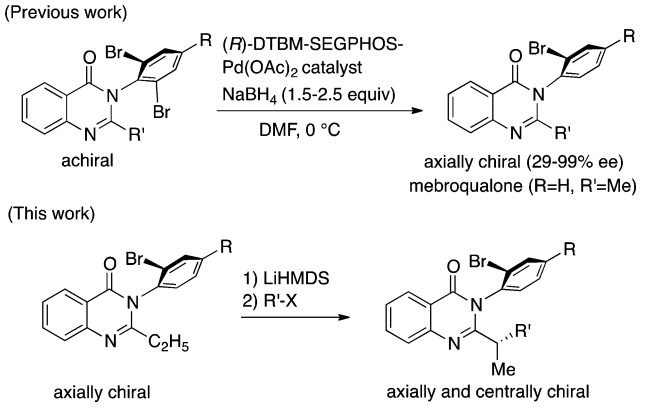
Supporting Information

ABSTRACT: The reactions of various alkyl halides with the metallo enamines generated from racemic and optically pure N−C axially chiral mebroqualone derivatives were found to proceed with a synthetically attractive stereochemical outcome (up to 99% yield and up to dr = 26:1) allowing preparation of a structurally new type of pharmaceutically interesting compounds possessing elements of axial and central chirality.



Chiral phenomena, generated by the rotational restriction of an N−C single bond, have recently attracted considerable attention.[1] Catalytic asymmetric syntheses of various N−C axially chiral compounds and their applications to asymmetric transformations have been reported by many groups.[2,3] It has also been well-known that quinazolinone derivatives, bearing an *ortho*-substituted phenyl group at N3 position, are configurationally stable N−C axially chiral compounds possessing various bioactivities such as anticonvulsant, sedative hypnotic, and antitumor actions.[4] Quite recently, we succeeded in the enantioselective synthesis of mebroqualone (GABA agonist) and its derivatives via chiral Pd-catalyzed reductive asymmetric desymmetrization (Scheme 1).[5] The reported method represents the first catalytic asymmetric synthesis of bioactive N−C axially chiral quinazolinone derivatives.[6]

Scheme 1. Catalytic asymmetric synthesis of N−C axially chiral quinazolinones and their application



From the viewpoint of synthetic application of N−C axially chiral quinazolinone to asymmetric transformations, as well as a part of our continuing interest in N−C axially chiral compounds, we were excited with the unexplored methodological potential of chiral metallo enamines generated from optically active mebroqualone derivatives. In particular, we envisioned that the reaction of mebroqualone enamines with alkyl halides would afford the corresponding α-alkylation products representing a virtually unknown type of biologically interesting compounds (Scheme 1). To the best of our knowledge, only two previous literature reports can be related to this topic.[7] Thus, one example of the reaction with bromine and another with aldehyde were conducted with racemic quinazolinone substrates bearing an *ortho*-chlorophenyl or (*ortho*-ethoxycarbonyl)phenyl group at the N3 position. However, the diastereoselectivity in these reactions was not high (dr = 1.5/1 and 3/1). Moreover, the stereochemical assignment of the diastereomers was not described, leaving the issue of the nature of stereocontrol in the reactions completely unanswered.

Thus, the reactions of electrophiles with metallo enamines generated from N−C axially quinazolinones still remain an unexplored area of research. In addition, the configurational stability of the N−C chiral axis in the quinazolinone enamines is an open question, as the reaction of optically active derivatives has never been investigated.

In this Letter, we report diastereoselective α-alkylation of the chiral metallo enamines generated from racemic and optically pure N−C axially chiral mebroqualone derivatives (Scheme 1). The disclosed data, including the stereochemical assignment of the α-alkylation products, the origin of the diastereoselectivity,

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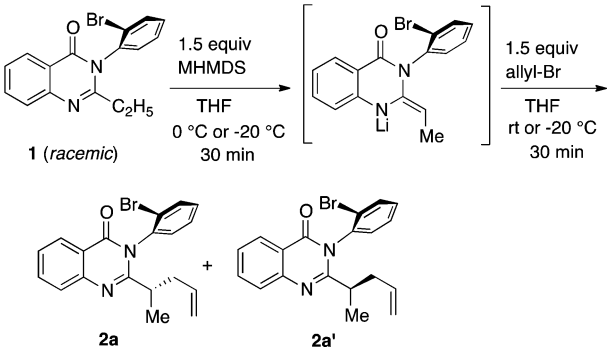
and stability of the axial chirality in the mebroqualone enamines, constitute a significant advance in this area providing a reliable access to a new structural type of biologically interesting compounds.

Initially, we optimized the reaction conditions of α-alkylation through the reaction of allyl bromide with the metallo enamines prepared from racemic mebroqualone derivative **1** (Table 1).

Table 1. Optimization of Reaction Conditions for α-Allylation Reaction with Mebroqualone Enamine



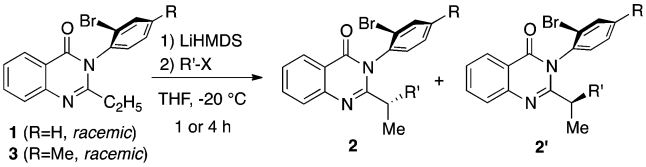
entry	M-HMDS	temp	solvent	2a,2a′yield (%)[a]	2a/2a′[b]
1	LiHMDS	0 °C−rt	THF	87	7.5
2	LiHMDS	0 °C−rt	*i*-Pr_2O	82	7.2
3	LiHMDS	0 °C−rt	1,4-dioxane	83	5.1
4	NaHMDS	0 °C−rt	THF	quant	5.5
5	LiHMDS	−20 °C	THF	85	7.5

[a]Isolated yield. [b]The ratio of **2a** and **2a′** was determined by ^{1}H NMR analysis.

When 1.5 equiv of LiHMDS [LiN(TMS)$_2$] was added to **1** in THF at 0 °C, the colorless solution was changed to a wine red colored solution, indicating successful formation of the desired quinazolinone enamine. The addition of 1.5 equiv of allyl bromide to the solution at rt led to the formation of an α-allyation product along with the disappearance of the wine red color. In this case, diastereomeric products **2a** and **2a′** were obtained in good yield (87%) and in a ratio of 7.5:1 (entry 1). The reaction in di-isopropyl ether also afforded **2a** and **2a′** in a similar yield and diastereoselectivity (entry 2), while the reaction in 1,4-dioxane and the use of NaHMDS [NaN(TMS)$_2$] as a base resulted in a slight decrease in the diastereoselectivity (entries 3 and 4). The enamine formation and α-allyation proceeded smoothly at −20 °C to give **2a** and **2a′** in almost the same yield and diastereoselectivity as those at rt (entries 1 and 5).

Under the optimized conditions (1.5 equiv of LiHMDS, 1.5 equiv of alkyl halide in THF at −20 °C), the reactions with various alkyl halides were further investigated (Table 2). The reaction with reactive alkyl halides such as benzyl bromide, methallyl bromide, and *para*-methoxybenzyl chloride gave α-alkylation products **2b−d** and **2b′−d′** in good yields (81−99%, entries 2−4). Importantly, the present reaction can be applied to the less reactive alkyl halides. That is, with ethyl iodide and isopropyl iodide, products **2e−f** and **2e′−f′** were also obtained in good yields (90% and 86%, entries 5 and 6). Especially, it is noteworthy that the α-isopropylation proceeds at −20 °C (entry 6), while a longer reaction time (5 h) was required in comparison with the reaction of entries 1−5 (1 h).

Table 2. α-Alkylation of Mebroqualone Derivatives 1 and 3 with Various Alkyl Halides



entry	1 or 3	R′−X	2, 2′	yield (%)[a]	2/2′[b]
1[c]	1	allyl-Br	**2a**, **2a′**	85	7.5
2[c]	1	$PhCH_2$-Br	**2b**, **2b′**	99	13.0
3[c]	1	methallyl-Br	**2c**, **2c′**	81	13.1
4[c]	1	PMB-Cl	**2d**, **2d′**	88	15.1
5[c]	1	C_2H_5-I	**2e**, **2e′**	90	3.8
6[d]	1	Me_2CH-I	**2f**, **2f′**	86	25.6
7[c]	3	allyl-Br	**2g**, **2g′**	93	7.6
8[c]	3	PMB-Cl	**2h**, **2h′**	88	15.8

[a]Isolated yield. [b]The ratio was determined by ^{1}H NMR analysis of the mixture of **2** and **2′**. [c]The reaction completed within 1 h. [d]The reaction completed within 5 h.

The diastereoselectivity was found to strongly depend on the alkyl halides and showed increasing values as the bulkiness increased. Although the diastereoselectivity of the reaction with ethyl iodide was not high (**2e**/**2e′** = 3.8, entry 5), in the reaction with allyl bromide, an increase in the selectivity was observed (**2a**/**2a′** = 7.5, entry 1). The reaction with more bulky benzyl, methallyl, and *para*-methoxybenzyl halides afforded the products with synthetically attractive diastereoselectivities (**2b−d**/**2b′-d′** = 13.0−15.1, entries 2−4). The best selectivity was observed in the reaction with isopropyl iodide. In this case, the product was obtained in a ratio of **2f**/**2f′** = 25.6 (entry 6). The allylation and *para*-methoxybenzylation with another mebroqualone derivative **3** (racemate) bearing a 2-bromo-4-methylphenyl group at the N3 position were also examined. In these reactions, similar reactivity and selectivity to those with **1** were observed (entries 7 and 8).

The relative configuration of the major diastereomer in the present α-alkylation was determined to be (*P**,*S**) by the X-ray crystal structure of allylation product **2a** (Figure 1).[8] The configurations of the other major diastereomers **2b−h** were also assigned as (*P**,*S**) on the basis of the chemical shifts of the Me group in ^{1}H NMR. That is, the Me group in minor diastereomer **2a′** appeared at higher magnetic field than that in major diastereomer **2a** (Figure 1). Such a higher field shift of the Me group in the minor diastereomer was also observed in the cases of all other compounds **2b′−h′**. These differences in chemical shifts can be rationally explained as follows. In both diastereomers **2** and **2′**, conformers **II** (**2-II** and **2′-II**) show direct exposure of the Me group to the anisotropy effect of the bromophenyl group and the Me group appears at higher magnetic field with increasing the contribution (proportion) of the conformers **II**. Since **2-II** in major diastereomer **2** is disfavored in comparison with **2′-II** in minor diastereomer **2′** by the repulsion between R′ and *ortho*-bromo groups, the contribution of conformer **II** increases in minor diastereomer **2′** more than in major diastereomer **2** to bring about a higher field shift of the Me group in **2′**.

On the basis of the stereochemical assignment, the origin of the diastereoselectivity should be rationalized as follows. The *E*-enamine is preferentially formed through the reaction of **1** and **3** with LiHMDS (the *Z*-enamine is rendered much less

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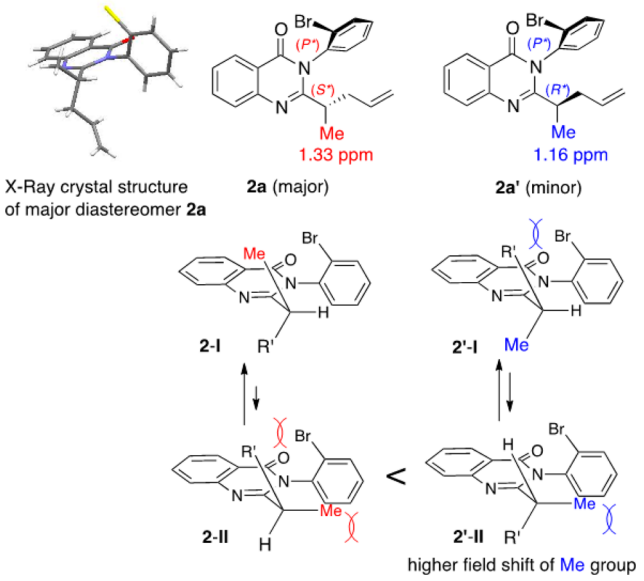


Figure 1. Stereochemical assignment of diastereomers **2** and **2′**.

favorable because of the obvious steric repulsion between the Me and the bromophenyl groups), and an alkyl halide selectively attacks from the opposite site of the *ortho*-bromo group in the *E*-enamine to give (*P**,*S**)-products **2** as a major diastereomer (Figure 2).

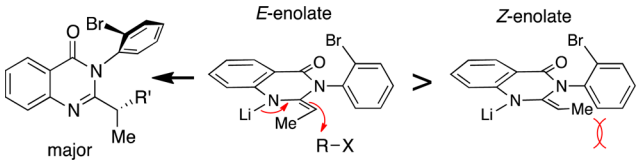
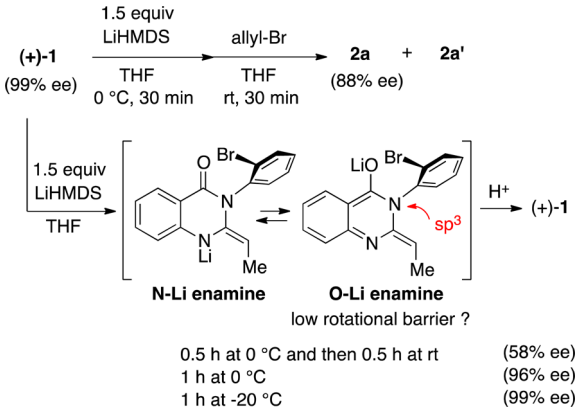


Figure 2. Origin of the diastereoselectivity.

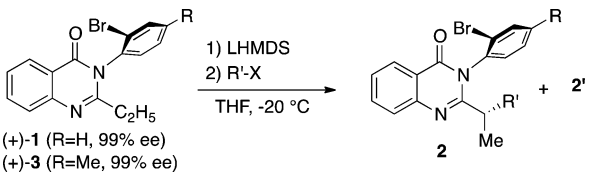
With these results in hand we were in position to investigate the asymmetric α-alkylation using optically pure mebroqualone derivatives (+)-**1** and (+)-**3**.[9] After forming the enamine from (+)-**1** (99% ee) at 0 °C (30 min), ally bromide was added and then the mixture was stirred for 30 min at rt. Although the products **2a** and **2a′** were obtained with diastereoselectivity similar to that for allylation with racemic **1**, quite unexpectedly, the ee of major diastereomer **2a** was noticeably lowered (88% ee, Scheme 2). The observed decrease in the ee of **2a** was found to be due to the low rotational barrier of the mebroqualone enamine. That is, when the enamine from (+)-**1** (99% ee) was protonated after standing for 30 min at 0 °C and 30 min at rt, the ee of (+)-**1** decreased to 58% (Scheme 2). The significantly lower rotational barrier of the enamine may be caused by the preferential formation of the corresponding O−Li intermediate rather than the expected N−Li intermediate. The wine red color in the enamine solution may indicate the existence of the O−Li intermediate possessing a 1,2-quinoid skeleton. In the O−Li intermediate bearing a nitrogen atom (N3) of sp^3 character,[10] the steric repulsion during the N−C bond rotation is remarkably alleviated in comparison with mebroqualone derivatives **1** and **3** bearing an sp^2 nitrogen (N3).[11] As a result, the rotational barrier of the mebroqualone enamine is significantly decreased. We should emphasize that the observed preferences for the enamine structure were unexpected and contribute to the newly gained knowledge from this research.

Scheme 2. Enamine Prepared from Optically Pure Mebroqualone Derivative (+)-1



On the other hand, we were fortunate to discover that the racemization of the enamine does not take place at −20 °C (Scheme 2). Following this finding the formation of the enamine and the reaction with alkyl halides were conducted at −20 °C. The results are shown in Table 3. The allylation of

Table 3. Asymmetric α-Alkylation with Optically Pure Mebroqualones 1 or 3



entry	1 or 3	R′−X	2, 2′	yield (%)[a]	2/2′[b]	% ee of 2[c]
1[d]	1	allyl-Br	**2a**, **2a′**	80	7.3	99
2[d]	1	Me_2CH-I	**2f**, **2f′**	74	26.4	99
3[d]	3	allyl-Br	**2g**, **2g′**	96	8.4	99
4[e]	3	PMB-Cl	**2h**, **2h′**	79	14.5	99

[a]Isolated yield. [b]The ratio was determined by ^{1}H NMR analysis of the mixture of **2** and **2′**. [c]The ee was determined by HPLC analysis using chiral column. [d]The reaction completed within 1 h. [e]The reaction completed within 5 h.

(+)-**1** (99% ee) at −20 °C proceeded without any racemization to afford the product **2a** of 99% ee (entry 1). In the reaction with less reactive isopropyl iodide, although a longer reaction time was required (5 h), the product **2f** was obtained without any decrease in the ee (entry 2). In the allylation and *para*-methoxybenzylation of (+)-**3** (99% ee), also no racemization was observed (entries 3 and 4). Thus, the alkylation at −20 °C was found to proceed without racemization.

In conclusion, we successfully developed a new approach for the diastereoselective α-alkylation process using the metallo enamine prepared from N−C axially chiral mebroqualone derivatives. The mebroqualone enamines have high reactivity, and the α-alkylation with various alkyl halides proceeded with a synthetically attractive stereochemical outcome. It was also found that the diastereoselectivity was strongly influenced by the bulkiness of alky halides favoring the major diastereomers possessing the (*P*,*S*)-configuration. Furthermore, the application of these asymmetric reactions with optically pure mebroqualone derivatives allowed us to discover the formation and configurational instability of the corresponding O−Li enamine. This problem was solved by the enamine formation

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and the alkylation conducted at −20 °C. In this case, the α-alkylation products were obtained without any decrease in the original ee. These results show unique stereocontrol exerted by the N−C axial chirality and provide a new methodology for the stereoselective synthesis of optically active quinazolinone derivatives bearing various carbon side chains.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00998.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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