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Asymmetric Synthesis of Both Mirror Images of 3′-Fluorothalidomide by Enantiodivergent Fluorination Using a Single, Cinchona Alkaloid

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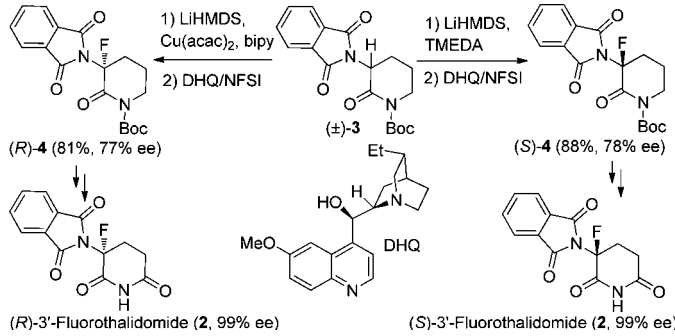
ABSTRACT



Enantiomerically pure 3′-fluorothalidomide (2) was successfully synthesized by enantiodivergent electrophilic fluorination using a combination of cinchona alkaloids and *N*-fluorobenzenesulfonimide (NFSI) as the key reaction. Importantly, a single chiral molecule, dihydroquinine (DHQ), allowed access to the mirror image form of 3′-fluorothalidimide by the choice of additives. While the use of TMEDA gave fluorinated (*S*)-4, the precursor of 2, with 78% ee, Cu(acac)$_2$/bipy, afforded the antipode, (*R*)-4, in 77% ee.

It is still indefinite whether thalidomide is stereospecifically teratogenic. Thalidomide was once used as a sleeping-pill tranquilizer and was popular among pregnant women in the late 1950s.[1] In the early 1960s, thalidomide was banned after it was found to cause malformation in children delivered from women who took it during pregnancy. However, a recent revival of thalidomide in the clinical field as an agent such as for the treatment of multiple myeloma has reactivated investigations of the molecular mechanism of its notorious teratogenicity.[1] Thalidomide (**1**) is a chiral molecule, and Blaschke and co-workers reported in 1979[2] that only (*S*)-thalidomide (**1**) was teratogenic; it was then believed that the thalidomide disaster could have been avoided if only the (*R*)-isomer of **1** had been marketed. However, in the 1990s, several groups disclosed that the strongly acidic hydrogen atom at the asymmetric center of **1** rapidly epimerizes under physiological conditions.[3] Hence, elucidating the differences in biological activity between thalidomide enantiomers

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previously reported is said to be difficult. To rationally answer the fundamental question in the opening sentence, nonracemizable, chiral analogues of thalidomide are strongly required.[4,5] Among various thalidomide analogues developed for this purpose, 3′-fluorothalidimide (**2**),[6,7] a fluorinated isostere of **1**, was developed by us in 1999[7a] and has been studied in depth by various investigators since this compound is able to mimic thalidomide itself with a high degree of structural accuracy (Figure 1).[6,7] Enantiomerically pure **2** is

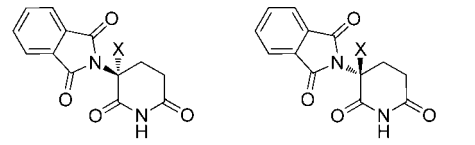

Figure 1. Structures of thalidomide (**1**) and its fluorinated isostere **2**.

now prepared via a chiral HPLC separation, and no asymmetric synthesis of **2** has been reported to date, which is thought to be a major impediment to the further tetragenic study of **2** *in vivo*. Additionally, both enantiomers of **2** are undoubtedly required for biological studies. As a part of our research in fluorine chemistry,[8] we herein report the first asymmetric synthesis of **2** by an enantiodivergent electrophilic fluorination reaction using cinchona alkaloids and a combination of fluorinating reagents as a key reaction. Importantly, dihydroquinine (DHQ) allows access to either mirror image form of fluorothalidomide precursor **4**, depending on the additives employed, including tetramethylethylenediamine (TMEDA) or $Cu(acac)_2$, and 2,2′-bipyridine (bipy). While the use of DHQ/TMEDA gave (*S*)-**4** in 88% yield with 78% ee, DHQ/$Cu(acac)_2$/bipy afforded (*R*)-**4** in 81% yield with 77% ee. Enantiopurities of (*S*)- and (*R*)-**4** can be easily improved to >99% ee by a single crystallization of **4**. As a consequence, the approach provides not only the first asymmetric synthesis of **2** but also one of the scarce examples of an enantiodivergent fluorination reaction. From a single, chiral, nonracemic cinchona alkaloid, either antipode of the final compound **2** can be obtained by appropriate selection of the additives at a practical level. Enantiodivergent synthesis is critically important in studies of thalidomide for selective formation of both enantiomers to answer the long-pending question.

Initial attempts to explore this sequence involved the use of a cinchona alkaloids/Selectfluor combination for the enantioselective electrophilic fluorination reaction as originally reported by us and others in 2000.[9,10] Thus, the fluorination of *N-tert*-butoxycarbonyl-3-phthalimidopiperidin-2-one (**3**) with lithium hexamethyldisilazide (LiHMDS) was carried out using various cinchona alkaloids/Selectfluor combinations. Namely, 3-phthalimidopiperidin-2-one **3**[7a] was deprotonated by LiHMDS (1.5 equiv) in THF at −20 °C for 30 min, followed by treatment with the cinchona alkaloids/Selectfluor (1.5 equiv) combination (prepared *in situ* in MeCN at rt) at −50 °C. While quinine (QN), cinchonidine (CD), and dihydroquinine (DHQ) provided the (*S*)-isomer of **4** in acceptable yields with moderate enantioselectivities of 49−65% ee's (Table 1, entries 1−3), quinidine (QD) and cinchonine (CN) gave (*R*)-**4** with low enantioselectivities (14−17% ees, entries 4−5). We next examined the fluorination using *bis*-cinchona alkaloids. Although the enantioselectivity was improved up to 72% ee (entries 6−9), a miserable yield was obtained (4%, entry 7).

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(6) The (*S*)-isomer of **2** is reported to be more active than both the (*R*)-**2** and **1** in lipopolysaccharide-induced TNF-α production enhancement produced from human peripheral blood lymphocytes cultivated in vitro (see ref 7a). On the other hand, any significant differences between the effects of enantiomers of **2** on the in vivo biological activity of 5,6-dimethylxanthenone-4-acetic acid in mice is reported (see ref 7c). Furthemore, the 4-amino analoge of **2** (racemate) is found to be 830-fold more potent that **1** as a TNF-α-inhibitor (see ref 7b).

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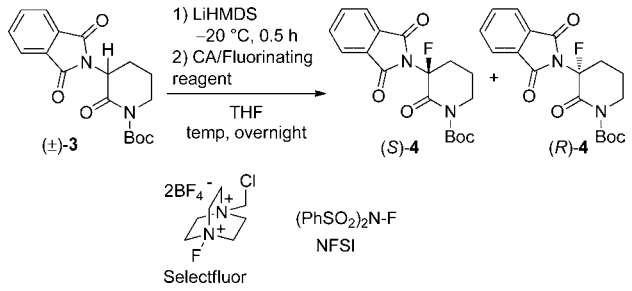
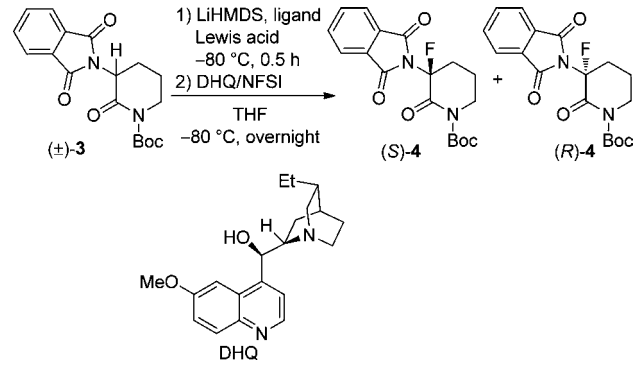
Table 1. Original Method: Enantioselective Fluorination by Cinchona Alkaloid/F-Reagent Combination



entry[a]	F-reagent	cinchona alkaloid (CA)	temp (°C)	yield (%)	ee (%)[b]
1	Selectfluor	QN	−50	43	49 (*S*)
2	Selectfluor	CD	−50	34	54 (*S*)
3	Selectfluor	DHQ	−50	45	65 (*S*)
4	Selectfluor	QD	−50	23	14 (*R*)
5	Selectfluor	CN	−50	42	17 (*R*)
6	Selectfluor	$(DHQ)_2PYR$	−50	15	22 (*R*)
7	Selectfluor	$(DHQD)_2PYR$	−50	4	72 (*R*)
8	Selectfluor	$(DHQ)_2AQN$	−50	21	64 (*R*)
9	Selectfluor	$(DHQD)_2AQN$	−50	56	38 (*R*)
10	NFSI	QN	−50	37	50 (*S*)
11	NFSI	QN	−80	28	74 (*S*)

[a] All reactions were performed on a 58 μmol scale of **3** with LiHMDS (1.5 equiv) and CA/Selectfluor or NFSI combination (1.5 equiv) in THF. The CA/Selectfluor combination was prepared *in situ* in MeCN at rt. CA/NFSI combination was prepared *in situ* in THF at rt. [b] Ee was determined by HPLC using a CHIRALCEL OJ-H with ethanol as elute.

Table 2. New Method: Enantiodivergent Fluorination by DHQ/NFSI/Additive System



entry[a]	ligand	Lewis acid	yield (%)	ee (%)[b]
1	bipy	−	82	69 (*S*)
2	dmbipy	−	23	16 (*S*)
3	phen	−	51	58 (*S*)
4	dppe	−	57	28 (*S*)
5	HMPA	−	49	20 (*S*)
6	12-crown-4	−	79	60 (*S*)
7	TMEDA	−	88	78 (99)[c] (*S*)
8	TMEDA	$CuBr_2$	14	60 (*R*)
9	TMEDA	$CuCl_2$	40	19 (*R*)
10	TMEDA	$Cu(OAc)_2$	52	30 (*R*)
11	TMEDA	$Cu(acac)_2$	80	71 (*R*)
12	phen	$Cu(acac)_2$	46	75 (*R*)
13	12-crown-4	$Cu(acac)_2$	80	74 (*R*)
14	bipy	$Cu(acac)_2$	81	77 (99)[c] (*R*)

[a] All reactions were performed on a 58 μmol scale of **3** with LiHMDS (1.5 equiv), ligand (1.5 equiv), Lewis acid (1.0 equiv), and DHQ/NFSI combination (1.5 equiv) in THF. The DHQ/NFSI combination was prepared *in situ* in THF at rt. [b] Ee was determined by HPLC using a CHIRALCEL OJ-H with ethanol as elute. [c] After single-recrystallization from ethanol.

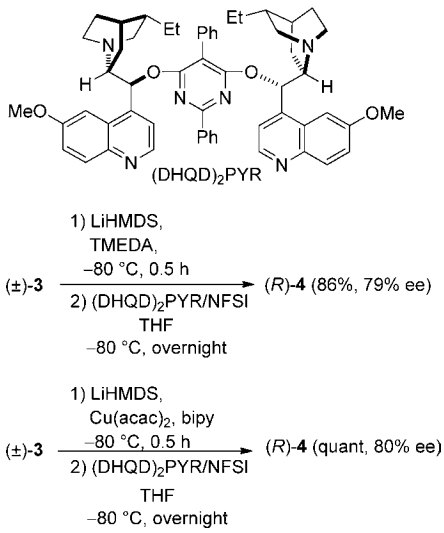
The enantioselectivity of product **4** was not affected by the nature of the fluorinating reagent (F-reagent) employed, Selectfluor or *N*-fluorobenzenesulfonimide (NFSI) (entries 1 vs 10). Enantioselectivity was improved to 74% ee at −80 °C, although the chemical yield decreased to 28% (entry 11).

In an attempt to improve both the chemical yield and enantioselectivity of **4** to a practical level, we next required novel conditions suitable for an enantioselective fluorination reaction of **3**. First, various ligands were added to our original DHQ/NFSI combination system (Table 2). When bipy was added as a ligand of the lithium enolate of **3**, a high yield of (*S*)-**4** with acceptable enantioselectivity was obtained (82%, 69% ee, entry 1). The success of this preliminary study encouraged us to explore the use ligands in the fluorination reaction. Optimization of ligands including 2,2′-bipicoline (dmbipy), phenanthroline (phen), 1,2-bis(diphenylphosphino)ethane (dppe), hexamethylphosphoric triamide (HMPA), and 12-crown-4 (entries 2−6) indicated that both the yield and enantioselectivity of (*S*)-**4** were further improved to 88% with 78% ee in the presence of TMEDA at −80 °C (entry 7). Next, Lewis acids were added together with TMEDA. We were surprised to learn that, when electrophilic fluorination was performed in the presence of $CuBr_2$, the fluorinated product **4** obtained was the reversed (*R*)-configuration with 60% ee, despite using the same chiral source, DHQ (entry 8). The (*R*)-isomer **4** with 19−30% ee's was again obtained using the DHQ/NFSI combination with copper(II) chloride or acetate (entries 9 and 10). In the presence of $Cu(acac)_2$, both the yield and ee of (*R*)-**4** were significantly improved to 80% and 71% ee (entry 11). Further optimization of the conditions (entries 12−14) afforded the best result, 81% with 77% ee of (*R*)-**4** in the presence of bipy and $Cu(acac)_2$ (entry 14). Enantiomerically pure (*S*)- and (*R*)-**4** (>99% ee) were easily obtained by single recrystallization from ethanol (entries 2 and 6). Although an antipode of fluorinated product could be accessed by the choice of pseudo enantiomer of cinchona alkaloids in the original cinchona alkaloid/F-reagent combination, this is the first example of enantiodivergent fluorination using a single cinchona alkaloid as a chiral source.[11,12]

It is interesting to note that this enantiodivergent fluorination was not observed for the fluorination of **3** using the *bis*-cinchona alkaloid, $(DHQD)_2PYR$/NFSI combination. When $(DHQD)_2PYR$ was used as the combination partner of NFSI instead of DHQ, the fluorinated compound (*R*)-**4** was obtained in high yields with high enantioselectivity, independent of whether Lewis acid was used or not (Scheme 1),

(11) Enantiodivergent fluorination of β-ketoesters using Box-Ph/Metal(II) catalysis was reported by us. Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703.

Scheme 1. Enantioselective Fluorination of (±)-**3** Using $(DHQD)_2PYR$/NFSI/Additive System

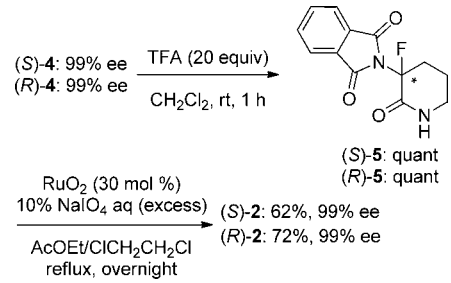


although both yield and enantioselectivity were improved compared to those from the original method (see entry 5 in Table 1).

Finally, synthesis of enantiomerically pure **2** was completed from **4** in two steps by removal of the Boc-protecting group and Ru-catalyzed oxidation (Scheme 2). Namely, enantiomerically pure (*S*)- and (*R*)-**4** were deprotected by trifluoroacetic acid treatment at rt to furnish (*S*)- and (*R*)-**5** in quantitative yields. Next, oxidation of the 6′-position of **5** with a catalytic amount of RuO_2 in the presence of excess $NaIO_4$ in a two-phase system furnished target enantiomers of (*S*)- and (*R*)-**2** (Scheme 2). Enantiopurities of (*S*)- and (*R*)-**2** were determined to be >99% ee by HPLC analysis. Absolute configurations of them were determined by comparison of $[\alpha]_D$ values with those in the literature.[7a] ((*S*)-**2**: $[\alpha]_{25}^{D}$ −253 (*c* 1.18, DMF), lit. $[\alpha]_{27}^{D}$ −263 (*c* 1.18, DMF); (*R*)-**2**: $[\alpha]_{25}^{D}$ +255 (*c* 1.52, DMF), lit. $[\alpha]_{27}^{D}$ +257 (*c* 1.11, DMF)).

In summary, we have established the first asymmetric synthesis of 3′-fluorothalidomide (**2**), an isosteric analogue

Scheme 2. Synthesis of Enantiomerically Pure (*S*)- and (*R*)-3′-Fluorothalidomide (**2**)



of thalidomide (**1**), using electrophilic enantiodivergent fluorination by a DHQ/NFSI combination with ligands and Lewis acids. Thus, the DHQ/NFSI combination with $Cu(acac)_2$ and bipy provides the fluorinated product **4** with an (*R*)-configuration, which is opposite to the product obtained when the DHQ/NFSI combination is used with TMEDA in practical levels of enantioselectivity. Synthesis of enantiomerically pure (*S*)- and (*R*)-3′-fluorothalidomide (**2**) was accomplished from **4** in two steps. Although the key fluorination step requires a stoichiometric amount of cinchona alkaloids, this is the first example of an asymmetric synthesis of **2**, which is a promising candidate alternative to thalidomide. Controlling the enantio-flexibility of fluorination using cinchona alkaloids as the sole chiral source by the use of additives is also the first example in this field,[12] although the reaction mechanism is very uncertain.[13] The catalytic asymmetric synthesis of **2** and teratogenicity of enantiomerically pure (*S*)- and (*R*)-**2** are under investigation.

Acknowledgment. This study was financially supported in part by Kakenhi (21390030, 22106515).

Supporting Information Available: Experimental procedures, spectra data for all new compounds, and HPLC charts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Chelation and nonchelation model transition states between the enolate of **3** and N-fluorinated DHQ could be involved in this enantio-flexible fluorination reaction, since the fluorination using the *bis*-cinchona alkaloid, $(DHQD)_2PYR$, leads to the same (*R*)-stereochemistry of the product, **4**. Hence, the hydroxyl group of DHQ should play an important role in these phenomena, and the absolute stereochemistry of **4** depends on the metal species, lithium or copper, on the enolate. The enantioselection itself is indeed independent of the ligands and their structures according to the results in Tables 1 and 2; thus the role of ligand appears to enhance the chemical yield and enantioselectivity. Although there should be several possible transition states that can be written for this reaction, two of them are shown as TS-I and TS-II in Figure S1 in the Supporting Information to provide (*S*)-**4** and (*R*)-**4**, which were depicted from the X-ray crystallographic structure of *N*-fluorinated DHQ in our previous paper.[9b]