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Authors: Ahmad Altiti, Yousef Al-Abed, Kai Fan Cheng, and Mingzhu He

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β-Hydroxy-tetrahydroquinolines from quinolines using chloroborane: Synthesis of the peptidomimetic FISLE-412

Ahmad S. Altiti* [a], Kai Fan Cheng [a], Mingzhu He [a], and Yousef Al-Abed*[a]

Dedication ((We Dedicate this work to Professor Wolfgang Voelter on his 80th birthday))

Abstract: A new synthetic protocol provides a simple and direct method to generate functionalized β-hydroxy-tetrahydroquinolines (THQs). Hydroboration of quinolines using chloroboranes followed by oxidation led to the formation of functionalized β-hydroxy-tetrahydroquinolines. High *regio* and diastereoselectivities were observed in α or γ substituted quinolines and the *trans* diastereomer of β-hydroxy-THQ was the major isostere. This new protocol was utilized to build the novel antibody-targeted lupus peptidomimetic **FISLE-412**.

1,2,3,4-tetrahydroquinolines (THQ) are abundant scaffolds in many biologically active natural molecules and pharmaceutical drugs. Particularly, β-functionalized-THQs play a vital role in various biologically active compounds (Figure 1).[1] These compounds are synthetically challenging, they are usually made through multistep synthesis.[1a,2] Wide varieties of reducing agents have been used extensively to make THQ,[3] however, very limited reduction approaches were synchronized with significant functionalization.[4] Stereoselective silylative reduction of quinolines using $B(C_6F_5)_3$ and Et_2SiH_2 is a good example to access β-silylated THQs,[4a] which can be used as precursors for wide range of transformations including β-hydroxy-THQs. Yet, this reduction system might suffer from undesired reductive-deoxygenation products.[5]

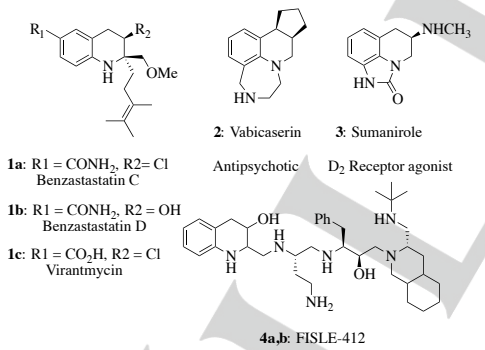

Figure 1. Important β-functionalized tetrahydroquinolines

Furthermore, activated quinoline systems react readily with borane reagents to give the 1,2-dihydroquinolines or the 1,2,3,4-THQs.[1a,6] During the preparation of this report, Ito and co-workers disclosed a *regio*- and *enantio*-enriched borylation of *N*-acetylated 1,2-dihydroquinolines using Cu(I) salts and $B_2(Pin)_2$.[6b,6c] Earlier, the reaction of quinoline with BH_3.THF or its salts was limited to the reduction of the pyridine ring in the quinoline system upon protonolysis.[7] On the other side, Brown and co-workers demonstrated that chloroboranes are superior to BH_3.THF in terms of reactivity and *regio*-selectivity.[8] Vedejs and co-workers also reported the activation of the amine-borane complexes with halides to improve their reactivity and regioselectivity; they demonstrated that halide could act as a good leaving group and facilitate the hydroboration through S_N2 like pathway.[9] In the light of these findings, we considered the use of chloroborane to reduce the quinoline ring with concomitant borylation of the β-position, which can be readily oxidized to give the corresponding β–hydroxy THQ. Quinoline is a polarized heterocyclic moiety where the pyridine ring is susceptible to hydride nucleuphilic attacks at α or γ positions.[10] Formation of the quinolinium-borane complex is expected to facilitate such reduction leaving the resulting dihydroquinoline prone to further hydroboration under thermodynamic conditions. Herein, we wish to report that β-functionalized THQ and especially β-hydroxy THQ could be accessed directly in a one-step operation using chloroborane reagents followed by appropriate work up.

In an early pursuit of optimal hydroborating agents, we settled on borane (BH_3.THF) and mono-chloroborane (BH_2Cl.THF) reagents as promising leads (*see supporting information*). A 1:3 mixture of BCl_3/BH_3 (4mmol) was capable of converting the quinoline moiety (1mmol) into β-borylated THQ after stirring at rt for 48 h; the reaction progress was monitored by TLC upon simple oxidation of the reaction mixture with $NaBO_3$. The corresponding hydroxylated product was isolated in 44% yield in addition to the 1,2,3,4-THQ. The commercially available $Me_2S{\cdot}BH_2Cl$ was also effective in obtaining the β-hydroxy THQ in similar yield under similar conditions. Unlike mono-chloroboranes, BH_3.THF reacted with quinoline sluggishly at rt and gave much lower yield and slower conversion rate (7 days).[7a] These results are not in a full agreement with the theoretical calculations that predicted BH_3 and BH_2Cl to have similar reactivity as Lewis acids.[11] Hence, we explored the potential of this reaction as a synthetic tool to access β-functionalized THQ. In order to cut the reaction time, we considered repeating the reaction under high temperature. Interestingly, 1 equiv of $Me_2S{\cdot}BH_2Cl$ was enough to induce the reaction when refluxed at 65 °C for 4 h; however, the reaction did not go to completion. The borane transfer process to the β-carbon under stoichiometric condition indicates that this process might involve a dissociation event of the B-N bond in the borane-dihydroquinolinium complex **II** (eq.1 Scheme 1) especially at high temperature.[12] We reasoned that such a process could be facilitated by enamine-imine tautomerism eq.1, Scheme 1).[7e] When 2 equiv $Me_2S{\cdot}BH_2Cl$ were used, a complete conversion of

[a] Center for Molecular Innovation, The Feinstein Institute for Medical Research, 350 Commuinty Drive, Manhasset, New York 11030, United States
Dr. Ahmad Altiti, Dr. Kai Fan Cheng, Dr. Mingzhu He, Professor. Dr. Yousef Al-abed.
E-mail: aaltiti@northwell.edu, Yalabed@northwell.edu

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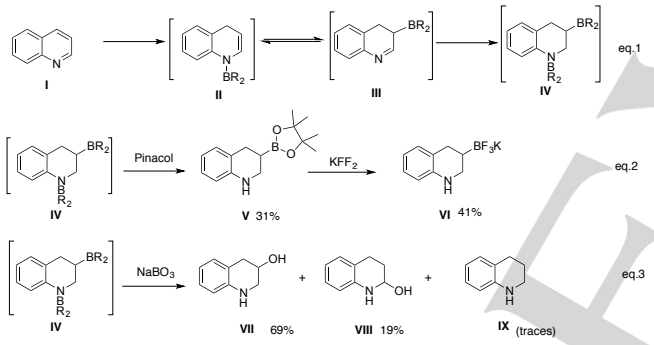
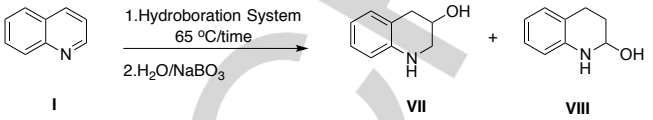
the quinoline into products took place in less than 2 h at 65 °C. The borylated intermediate was isolated as a pinacolate ester **V** (eq.2, Scheme 1) upon treatment with pinacol, which was isolated in 31% after purification over basic alumina. Due to the instability of the pinacol ester under the standard extraction and purification procedure, we treated **V** with KHF_2 and isolated the borylated intermediate as trifluorborate salt **VI** in 41 % from quinoline, **VI** was purified by trituration with ether in order to get rid of the pinacol and the 1,4-butane-diol, a side product that results from opening the THF ring. Besides the borylated intermediate, we isolated the 1,2,3,4-THQ **IX**, which theoretically might be produced from protonlysis of **IV**. [7a] We were unable to isolate any borylated intermediate at the *α*-position. However, when the borylated intermediate **IV** was treated with ice-cold water and $NaBO_3$, *β*-hydroxy THQ **VII** and *α*-hydroxy THQ **VIII** were isolated as major products with ratio of 7:2 respectively in addition to traces of **IX** (eq.3, Scheme 1). When the isolated trifluoroborate compound **VI** was treated with $NaBO_3$ under the same work up conditions previously used, only the *β*-hydroxy THQ **VII** was observed. This indicates that the two hydroxylated products might be formed independently through different pathways. Next, we subjected the quinoline to various sources of chloroboranes in an effort to understand the factors that might affect the ratio of *β*-hydroxy THQ **VII** and *α*-hydroxy THQ **VIII** (Table 1).



Scheme 1. Hydroboration of the quinoline system using $Me_2S.BH_2Cl$.

Treatment of quinoline **I** with excess BH_3.THF (8 equiv) resulted in a complete conversion of the starting material into products after 16 h reflux at 65 °C. The products were characterized after oxidative work up as **VII** and **VIII** with 1:1 ratio. $Me_2S{\cdot}BH_2Cl$ (8 equiv) gave **VII** in 61% (Entry5) in shorter time (2h). Decreasing the amount of $Me_2S.BH_2Cl$ to 4 equiv gave similar results (Entry4), to avoid the malodorous effect of the Me_2S, we considered the preparation of mono-chloroborane following Brown's protocol[8c] by simply mixing 1 equiv of 1M BCl_3/hexane with 2 equiv of 1M of BH_3.THF. Brown's chloroborane mixture (3 equiv) was effective in reducing the quinoline system, where the *β*-hydroxy THQ **VII** was isolated in 54% yield. However, the use of 8 equiv of 1:7 mixture of BCl_3/BH_3 gave **VII** in 70% isolated yield (Entry 8). Increasing the stoichiometriy of BCl_3 did not improve the selectivity or the yield (Entry 7). We also considered the use of trichloroisocyanuric acid TCCA as a chlorininating agent (Entry 9).[13] Similarly, **VII** and **VIII** were collected with ratios comparable to the previous chloroboranes systems. As we see form the results in Table1, monochloroborane indeed favors the formation of the *β*-hydroxy THQ **VII** compare to BH_3. All the examined monochloroboranes had similar effect on the quinoline in terms of reactivity and selectivity, a slight increase in reaction rate was observed when higher concentrations were applied (Entries 2 and 3). Controlling the reaction concentration was only possible when $Me_2S{\cdot}BH_2Cl$ was used because it is supplied as a neat reagent.

Table 1. Hydroboration-oxidation of quinoline using mono-chloroborane



Entry	Hydroboration System	Conc. (M)	Time (h)	VII%	VIII%
1	BH_3.THF (8 equiv)	0.13	16	48	49
2	$Me_2S.BH_2Cl$ (2 equiv)	1.0	1.0	65	18
3	$Me_2S.BH_2Cl$ (2 equiv)	0.5	1.5	69	19
4	$Me_2S.BH_2Cl$ (4 equiv)	0.13	2	64	32
5	$Me_2S.BH_2Cl$ (8 equiv)	0.13	2	61	33
6	BCl_3/BH_3 (1equiv+2equiv)	0.33	4	54	33
7	BCl_3/BH_3 (2equiv+6equiv)	0.13	4	59	31
8	BCl_3/BH_3 (1equiv+7equiv)	0.13	4	70	23
9	TCCA/BH_3 (0.5equiv/8 equiv)	0.13	4	63	29

In order to account for the substituents effect on the quinoline system and to avoid the malodorous effect of Me_2S, we settled on the procedure used in entry 8 (Table 1) to test the scope of this reaction. Using excess borane reagent should not be a burden at this stage, especially as our target is to access the *β*-hydroxy THQ and the oxidative work up is mild and inexpensive.

We first explored the scope of quinoline derivatives bearing substituents at the benzene ring (Table 2). The BCl_3/BH_3 hydroboration system tolerated quinolines with halide substituents on the benzene ring (Entry 6), however, halides on the pyridine ring were susceptible to reduction.[7a] When 2-chloroquinoline was treated with this reduction system, the *β*-hydroxy-THQ **VII** was isolated as the major product accompanied with traces of **VIII** (*results not shown*), the methoxy substituent (Entry 5) also survived the BCl_3/BH_3 reduction system; the corresponding *β*-hydroxy-THQ was isolated in 54% yield. The methyl-substituted quinolines (Entries 3 and 4) gave good yields of the corresponding *β*-hydroxy-THQ, on the other hand carboxylic acid moieties suffered from expected partial reduction only and gave the corresponding primary alcohols (Entries 2 and 7); these functionalities can be retained with simple oxidations after appropriate functional group manipulation. Interestingly, the unprotected 8-amino quinoline (Entry 8) gave the corresponding *β*-hydroxy-THQ in 74% isolated yield; the borylated intermediate of this quinoline can be elaborated easily to give the racemic version of Sumanirole (Figure 1).[6c] Regardless of the modest regioselectivity of some of the quinolines presented here, we believe this protocol has a superior synthetic value compared to the traditionally used protocols to access such substrates using multistep synthesis [2] (*vide infra*).

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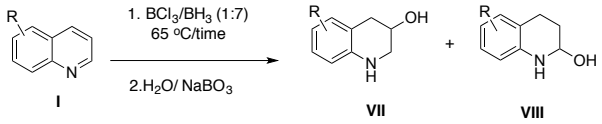
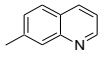
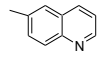
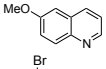
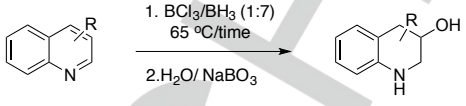
Table2. Hydroboration-oxidation of quinolines bearing substituents at the benzene ring



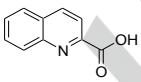
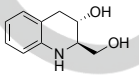
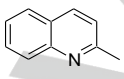
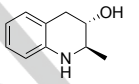
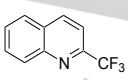
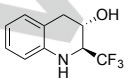
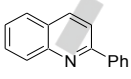
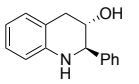
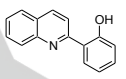
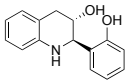
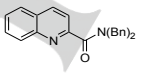
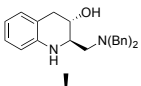
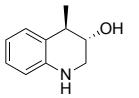
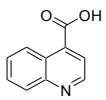
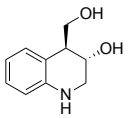
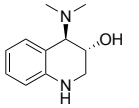
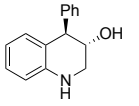
Entry	Substrates	Time (h)	**VII** %	**VIII**%
1		4	70	21
2		3	38	45
3		8	73	13
4		7	68	24
5		6	54	13
6		6	44	48
7		6	47	38
8		8	74	17

Satisfied with the performance of the BCl_3/BH_3 hydroboration system in Table 2, we decided to investigate the role of this system on quinolines bearing varied substituents on the pyridine ring (Table 3). In general the BCl_3/BH_3 hydroboration system gave greater yields and better *regio*- and diasteroselectivities for quinolines with substituents on the pyridine ring. The diastereoselectivity was confirmed by nOe analysis (*see supporting information*). As expected, quinolines with available chelating arm at the α position (Entries 1 and 5) exhibited faster reactions and higher yields; this behavior can be attributed to an alcohol directed hydroboration effect, the formation of the alkoxy-borane complex facilitates the borylation of the *β*-position through an intramolecular process.[14] The α-methyl, α-trifluoromethyl, and α-phenyl-quinolines performed well and gave good *trans*-diastereoselectivity (Entries 2, 3, and 4), however, longer reaction time was required. For example, the α-phenyl quinoline was very sluggish under the BH_3.THF reduction system (*result not shown*). After 2 days of reflux, the hydroxylated products were collected in poor selectivity (1:1 *cis/trans*) in addition to the recovery of some starting material, however, when subjected to the BCl_3/BH_3 reduction system, the reaction proceeded smoothly and the corresponding *β*-hydroxy-THQ was generated with 9:91 *cis/trans* selectivity. The γ-substituted quinolines exhibited similar behavior to α-substited quinolines and gave the *β*-hydroxy-THQs in good yields and good *trans* diastereoselectivity. Though, these compounds required longer reaction time to achieve full conversion. Interestingly, the *α*-hydroxy-THQ was not observed as a side product in the case of the γ-substituted quinolines. Instead, the fully reduced 1,2,3,4-THQ was isolated; this indicates that γ-substituted quinolines might undergo a different reduction pathway as a rate-limiting step.[4b] Further, the electron rich γ-dimethylamino quinoline (Entry9) was expected to form a strong Lewis acid-Lewis base complex and resist the borane reduction. Indeed, the corresponding *β*-hydroxy-THQ was isolated in 6% yield after 16 h at 65 °C beside the recovered starting material.

Table3. Hydroboration of quinolines bearing substituents at the pyridine ring.



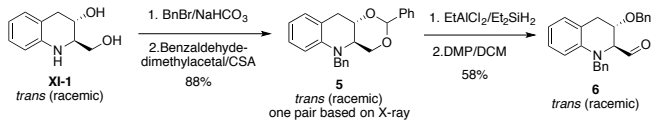
X **XI** *trans*-(racemic)

Entry	Substrates	Products*	Time (h)	Isolated yield%	Diastereos elctivity (*cis/trans*)
1			1	94	9:91
2			6	65	11:89
3			16	55	11:89
4			8	82	9:91
5			0.5	84	> 98 *trans*
6			16	70	> 98 *trans*
7			16	91	> 98 *trans*
8			16	46	> 98 *trans*
9			24	6	> 98 *trans*
10			4	72	> 98 *trans*

* The depicted structural formulas do not reflect the absolute stereochemistry

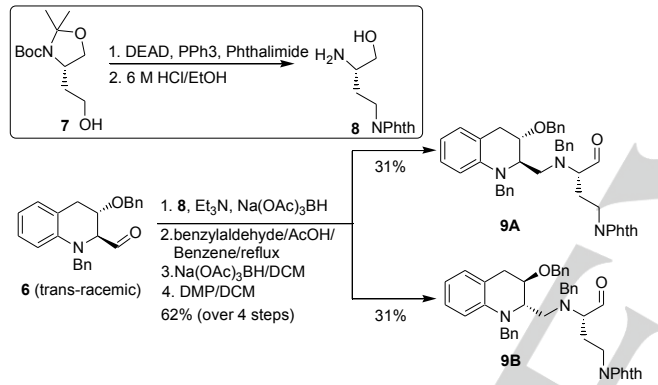
Next, we turned our attention to explore the utility of this protocol in asymmetric synthesis by building the novel peptidomimetic **FISLE-412**; a potent polyamine-alcohol neutralizes *anti*-dsDNA/NMDAR lupus autoantibodies and prevents their pathogenic interaction with tissue antigens.[1l, 1m] This poly amine is very challenging in terms of synthesis, resolution and purification, the only access to this molecule was through global reduction of the corresponding peptide "Saquinavir", this reduction process was very tedious and gave an inseparable mixture of **FISLE-412** with very low yield after multiple purifications.[1l] We envisaged the synthesis of the complex polyamine **FISLE-412** through the resolution of the *β*-hydroxy THQ moiety **XI-1** (Entry 1, Table 3), which could be later integrated in the synthesis of **FISLE-412** through benign

reductive-amination steps after simple protecting groups handling.



Scheme 2. Synthesis of the racemic aldehyde **6**

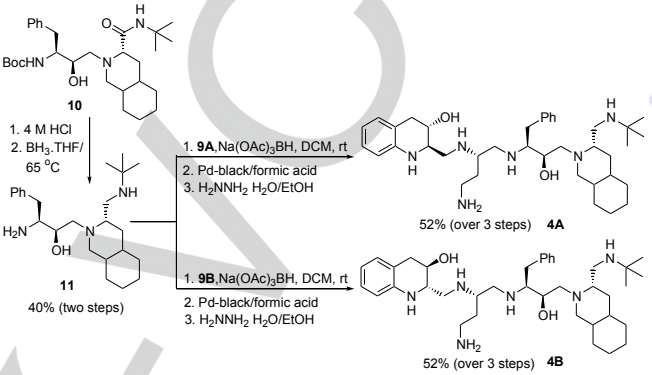
Accordingly, the *trans* diol **XI-1** was treated with stoichiometric amount of BnBr in aq $NaHCO_3$ to give the *N*-Bn derivative, which was then treated with benzyladehyde dimethylacetal and camphorsulphonic acid (CSA) to give only one pair of the racemic acetal **5** in 88% yield over two steps. The stereochemistry was confirmed to be *trans* based on X-ray analysis of **5** (*see supporting information*), which was isolated as white-needled shaped crystals. Regioselective reductive opening of the acetal **5** using $Et_3SiH/EtAlCl_2$ gave exclusively the primary alcohol,[15] which was oxidized using Dess Martin periodinane (DMP) to give the corresponding racemic aldehyde **6** in 58% yield over two steps (Scheme 2).



Scheme3. Synthesis and resolution of Aldehydes **9A** & **9B**

Next, we sought a chiral fragment that could resolve the racemic aldehyde and integrate the THQ moieties in the synthesis of the complex peptidomimetics **FISLE-412**. We chose the homologue of Garner's alcohol **7** because it could be converted into the 2,4-diaminobutanol with orthogonal protection of the distal nitrogen. Alcohol **7** was treated with DEAD, Ph_3P, and phthalimide followed by acidic hydrolysis of the Boc and the isopropylidene groups using 6 M HCl to give amino alcohol **8** in 89% yield over two steps. Reductive amination on **6** and amino alcohol **8** followed by selective protection of the nitrogen with Benzyl group through reductive amination using PhCHO/AcOH and $Na(OAc)_3BH$ afforded two separable alcohols by conventional chromatography. The resulting diasteromeric alcohols were oxidized respectively using DMP to give aldehydes **9A/9B** in roughly 60% total yield over 4 steps (yield is averaged for both diastereomers because the absolute stereochemistry is not assigned yet) (Scheme 3).

Amino-alcohol **11** was accessed from the known decahydroisoquinoline (DIQ) fragment **10**,[16] which was reduced with BH_3.THF upon the deprotection of the Boc group to furnish **11** in 40% yield. Reductive-amination on the amino-alcohol **11** and either aldehyde **9A** or **9B** gave the protected **FISLE-412** in 69% for each (the yield is averaged for both isomers). After exhausting several attempts to cleave the benzyl groups safely, we found that the Pd black-formic acid combination under reflux condition in 75% aqueous EtOH cleaved all benzyl groups orthogonally [17] without affecting the phthalimide group, which was cleaved with hydrazine $NH_2NH_2 \cdot H_2O$ under reflux condition to afford **FISLE-412A** and **FISLE-412B** (Scheme4). Both isomers were isolated as TFA salts after C18 column purification with approximately 50% yield of each over 3 steps (averaged yield), the purity of these compounds was confirmed by HPLC analysis (*see supporting information*).



Scheme4. Synthesis of the FISLE-412 compounds **4A** and **4B**

In summary, we have successfully developed a rapid and inexpensive protocol to access *β*-hydroxy-THQs. The new procedure features a hydroboration-oxidation reaction using chloroboranes. High *regio*- and *trans* diastereoselectivies were observed for the *α*- and *γ*-substituted quinolines. This methodology was used to build an interesting library of *β*-hydroxy-1,2,3,4-tetrahydroquinolines. We assert that this protocol has a superior synthetic value compared with other synthetic approaches used to build *β*-hydroxy-1,2,3,4-THQ scaffolds. We are currently investigating the utility of this method in the synthesis of other biologically relevant alkaloids of interest

Supporting Information

The Supporting Information is available free of charge. Procedures for reactions and characterization of isolated products, NMR spectra and X-Ray analysis are available in PDF format files.

AUTHOR INFORMATION

Corresponding Authors
* E-mail: aaltiti@northwell.edu; yalabed@northwell.edu

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Keywords: Quinoline • β-hydroxy-1,2,3,4 tetrahydroquinoline • Hydroboration of quinolines •Monochloroborane• β-borylated tetrahydro quinolines.

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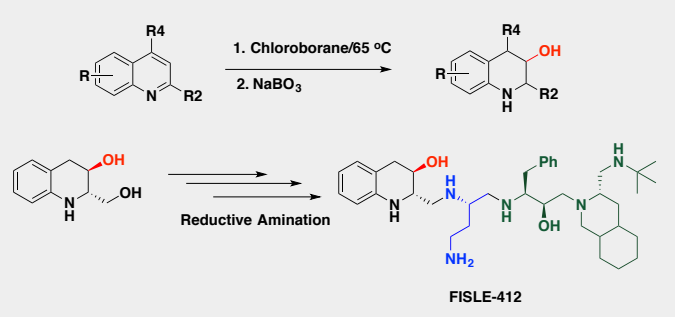

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