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Asymmetric Synthesis of (+)-*anti*- and (–)-*syn*-Mefloquine Hydrochloride

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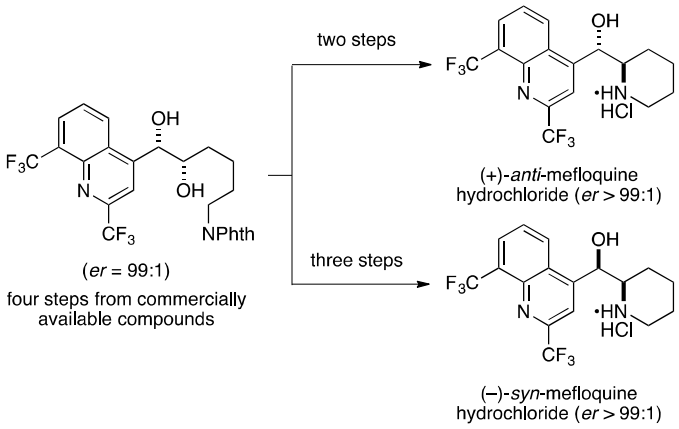


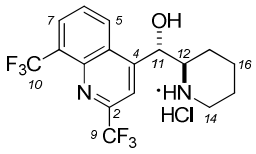
ABSTRACT

The asymmetric (*er* > 99:1) total synthesis of (+)-*anti*- and (–)-*syn*-mefloquine hydrochloride from a common intermediate is described. The Sharpless asymmetric dihydroxylation is the key asymmetric transformation used in the synthesis of this intermediate. It is carried out on an olefin that is accessed in three steps from commercially available materials, making the overall synthetic sequence very concise. The common diol intermediate derived from the Sharpless asymmetric dihydroxylation is

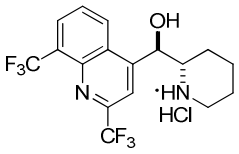
converted into either a *trans*- or *cis*-epoxide, and these are subsequently converted to (+)-*anti*- and (–)-*syn*-mefloquine, respectively. X-ray crystallographic analysis of derivatives of (+)-*anti*- and (–)-*syn*-mefloquine is used to lay to rest a 40 year argument regarding the absolute stereochemistry of the mefloquines. A formal asymmetric (*er* = 99:1) synthesis of (+)-*anti*-mefloquine hydrochloride is also presented that uses as a Sharpless asymmetric epoxidation as key step.

INTRODUCTION

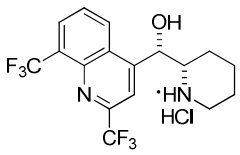
Malaria is the most lethal parasitic disease known. As of 2015, it was reported that 95 countries and territories have ongoing malaria transmission with approximately 214 million cases of malaria, leading to 438,000 deaths.[1] *Anti*-mefloquine hydrochloride[2] (**1**, Figure 1) is used for both treatment against malaria and prophylaxis. It is manufactured commercially by Hoffmann-LaRoche under the trade name Lariam[3] and is administered in racemic form. While extremely effective and widely used, *anti*-mefloquine hydrochloride has some limitations.[4,5] There are neurotoxic side effects that can be traced back to the difference in potencies of both enantiomers, with the (+)-enantiomer being at least 1.5 times more potent than the (–)-enantiomer.[6] Moreover, although distributed across many different types of tissue, evidence suggests that the (–)-enantiomer has a shorter *in vivo* half-life owing to higher blood plasma concentrations.[7] These issues have led to a growing interest in enantioselective syntheses of *anti*-mefloquine hydrochloride in order to further understand and potentially benefit from its use as a single enantiomer drug.



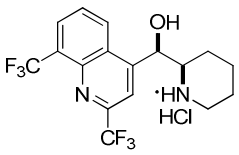
(+)-*anti*-mefloquine hydrochloride [(+)-**1**]



(–)-*anti*-mefloquine hydrochloride [(–)-**1**]



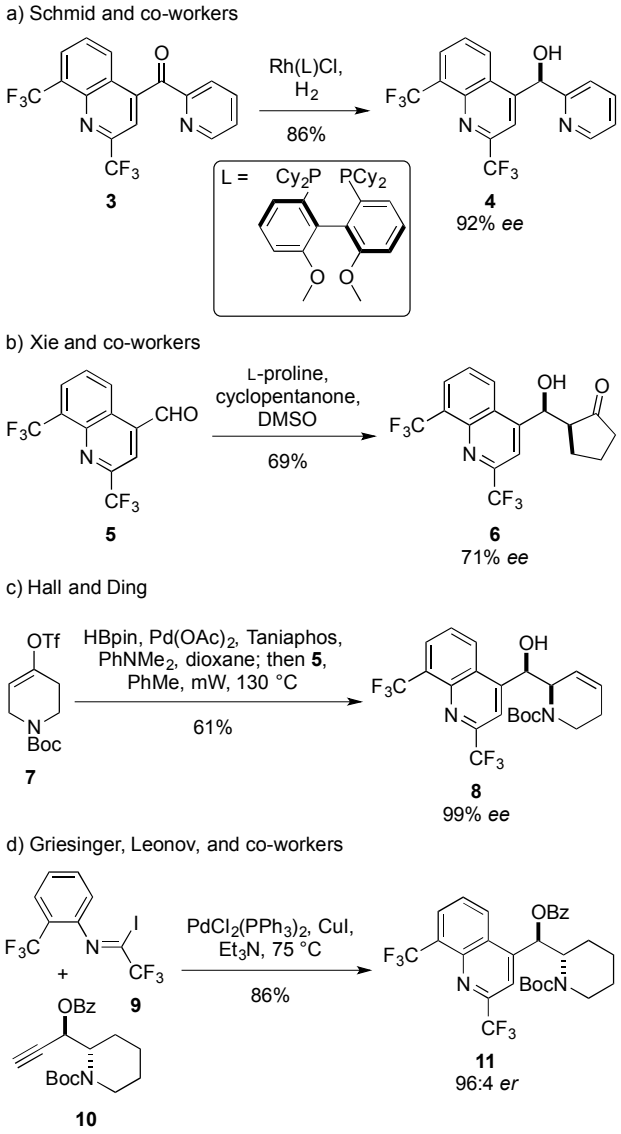
(+)-*syn*-mefloquine hydrochloride [(+)-**2**]



(–)-*syn*-mefloquine hydrochloride [(–)-**2**]

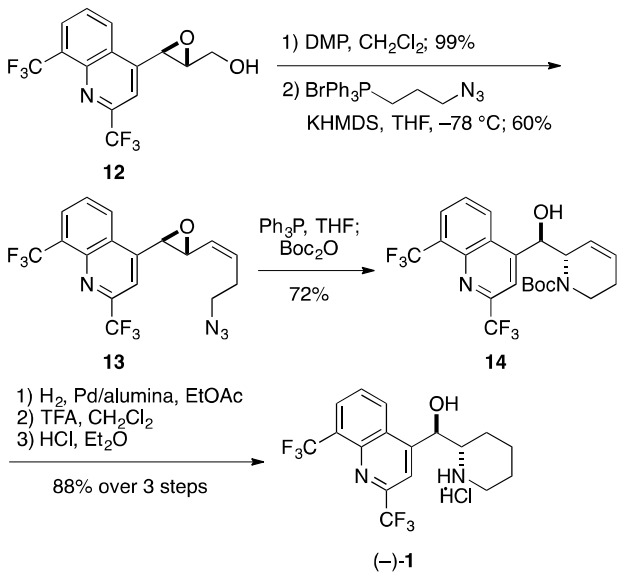
Figure 1. (+)- and (–)- *anti*-mefloquine hydrochloride and (+)- and (–)-*syn*-mefloquine hydrochloride salts.

Enantiomerically enriched (+)-*anti*-mefloquine has been synthesized on several occasions previously, including one instance in which it was generated by resolution of a racemate.[8] Asymmetric hydrogenation (86-96% *ee*)[9] has been employed to establish the C11 stereocenter in three separate approaches to enantiomerically enriched *anti*-mefloquine (Scheme 1). In order to set the C12 stereogenic center in these syntheses, a substrate controlled catalytic hydrogenation was conducted which gave an 85:15 ratio in favor of the desired diastereomer.[10] A different approach[11] to (–)-*anti* mefloquine relied on the use of an organocatalytic aldol reaction to set the C11 and C12 stereogenic centers, resulting in 71% ee. The enantiomeric excess was further increased from 71% to 95% as a result of subsequent synthetic operations. (+)-*anti* mefloquine has also been synthesized in an unspecified enantioselectivity[12] from (*S*)-(–)-1-*N*-Boc-2-piperidinecarboxylic acid. More recently, Hall[13] and Leonov[14] independently reported asymmetric syntheses of both *anti*- and *syn*-mefloquine hydrochloride, using approaches that led to the production of all four stereoisomers. An enantioselective allylboration reaction (99% ee) was used to produce a *syn* vicinal amino alcohol precursor in Hall's synthesis of *syn*-mefloquine hydrochloride.[15] This precursor was subsequently oxidized to the corresponding vicinal keto amine, which then underwent diastereoselective (10:1 *dr*) reduction to give an *anti*-vicinal amino alcohol, that was ultimately converted to *anti*-mefloquine hydrlochloride. Diastereoselctive (12:1 *dr*) addition of trimethylsilyl acetylide to an enantiomerically enriched aldehyde derived from pipecolinic acid served as the basis of Leonov's synthesis of both *anti*- and *syn*- mefloquine hydrochloride. The major diastereomer was used in a domino Sonogashira/6π electrocyclization to give *anti*-mefloquine as the major product, and *syn*-mefloquine as the minor product. The *syn*-mefloquine isomer was formed as a result of epimerization during the domino reaction. The *anti*- and *syn*-mefloquine products were separated chromatographically and the enantiomeric ratio was determined to be 93:7 and 96:4, respectively.



Scheme 1. Previous asymmetric syntheses of *anti* and *syn*-mefloquine.

In 2012, our lab reported an asymmetric total synthesis of (–)-*anti*-mefloquine hydrochloride[16] (>99:1 *er*) (Scheme 2). The synthesis was built around a cascading azide reduction/regioselective and stereospecific epoxide ring-opening reaction beginning with **13** that, following trapping of the 3,4-dehydropiperidine intermediate with Boc_2O, ultimately led to 3,4-dehydro-*N*-Boc-mefloquine (**14**) in a one-pot reaction. Reduction of the olefin, removal of the Boc protecting group, and HCl formation led to (–)-*anti*-mefloquine hydrochloride in excellent yield. A key intermediate in this synthesis was *trans*-epoxide **12**, which we had cause to prepare in enantiomerically enriched form via an asymmetric *N*-amino cyclic carbamate (ACC)-based[17] Darzens reaction.[16]



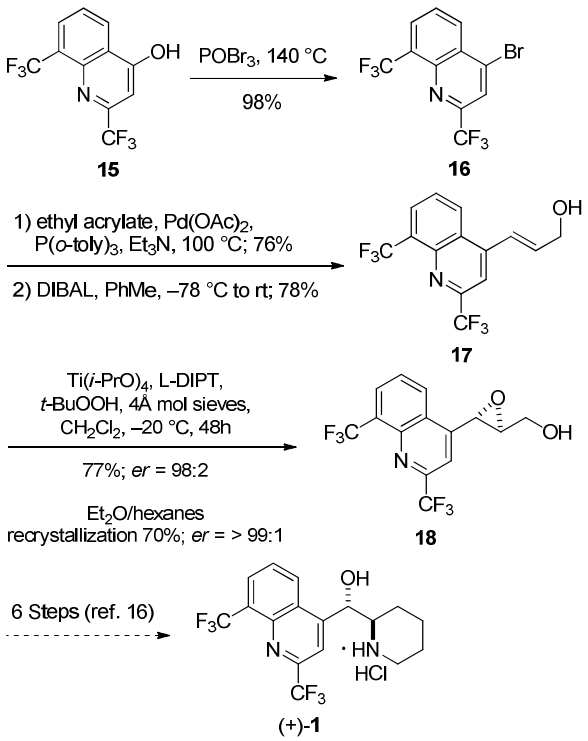
Scheme 2. Prior synthesis of (–)-*anti*-mefloquine hydrochloride.

While the annulative epoxide ring opening sequence used in the above synthesis was appealing to us, the route leading to **12** left room for improvement. After some effort, we were able to develop a new, concise, highly enantioselective (*er* > 99:1) synthesis of (–)-*anti*-mefloquine hydrochloride that maintained the annulative epoxide ring opening strategy.[18] The key asymmetric transformation in this case was a Sharpless asymmetric dihydroxylation of a structurally advanced olefin. As part of this work, we were also able to gain access to (–)-*syn*-mefloquine hydrochloride in an equally concise manner from the same Sharpless-derived diol. In what follows, we provide a full account of that work. In addition, we describe a new, more practically useful approach to the synthesis of the advanced olefin used for the Sharpless asymmetric dihydroxylation. We also present a formal asymmetric (*er* = 99:1) synthesis of (+)-*anti*-mefloquine hydrochloride that employs a Sharpless asymmetric epoxidation as key transformation.

RESULTS AND DISCUSSION

In our initial efforts to improve the efficiency of our first synthesis of (–)-*anti*-mefloquine hydrochloride (Scheme 2), we planned to pursue a different route to epoxide **12** that would take

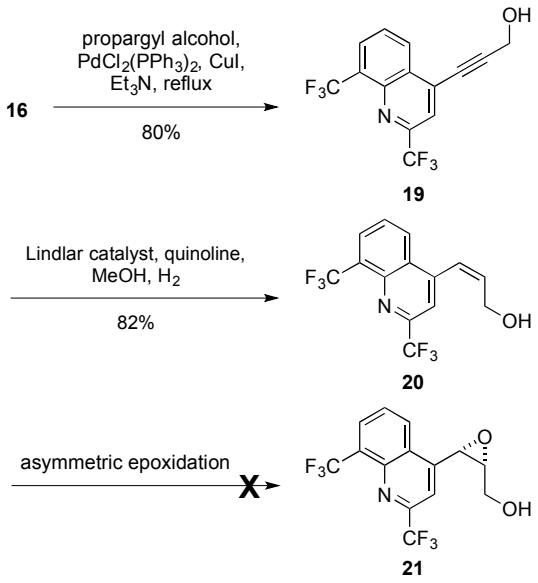
advantage of the Sharpless asymmetric epoxidation.[19] In the event, as a matter of convenience and economy, we prepared epoxide **18** (Scheme 3), the enantiomer of **12**, instead. The allylic alcohol (**17**) required for the epoxidation would be obtained from a Heck coupling between aryl bromide **16** and ethyl acrylate, followed by ester reduction. The synthesis of epoxide **18** began with the preparation of aryl bromide **16** from commercially available quinolinol **15**, according to a literature procedure[20] (Scheme 3). With the aryl bromide in hand, we were pleased to find that the proposed Heck coupling with ethyl acrylate proceeded in good yield under standard conditions. The resulting ester was then subjected to a DIBAL-mediated reduction to afford allylic alcohol **17**. As hoped, Sharpless asymmetric epoxidation of **17** furnished the desired epoxy alcohol (**18**) in good yield (77%) and with excellent enantioselectivity (*er* = 98:2). The enantiomeric purity of **18** was established by comparing it with a corresponding racemic sample[21] by HPLC analysis on a chiral, nonracemic stationary phase.[22] The enantiomeric purity of **18** was increased to >99:1 in a single and reasonably efficient (70% recovery) recrystallization using a mixture of Et_2O and hexanes. By analogy to what we have previously described for its enantiomer (**12**), epoxy alcohol **18** can be converted to (+)-*anti*-mefloquine hydrochloride in six steps, which constitutes a formal second generation synthesis that is considerably improved over our first effort. [16]



Scheme 3. Formal second generation synthesis of (+)-*anti*-mefloquine hydrochloride.

Having developed an effective synthesis of (+)-*anti*-mefloquine hydrochloride, we turned our attention to the synthesis of the *syn*-isomer. As was recently reported by Hall,[Error! Bookmark not defined.] (+)-*syn*-mefloquine hydrochloride also exhibits strong potency towards *Plasmodium falciparum*. In theory, access to (+)-*syn*-mefloquine hydrochloride could be gained using a similar strategy to that shown for the synthesis of (+)-**1** in Scheme 3, but by substituting *cis*-epoxide **21** in place of *trans*-epoxide **18**. Our attempt at preparing **21** began with a Sonogashira coupling between aryl bromide **16** and propargyl alcohol, which led to alkyne **19** in very good yield (Scheme 4). This was followed by careful reduction of the alkyne using Lindlar's catalyst to generate *cis*-allylic alcohol **20**. Unfortunately, all attempts at the Sharpless asymmetric epoxidation of **20** were unsuccessful, and showed no indication of epoxide formation. In each case, the starting material was recovered intact. We next attempted the epoxidation of **20** using the Shi conditions,[23] but once again the desired epoxide was not formed, and only **20** was recovered. Out of curiosity, we also tried to form a racemic epoxide from **20** by treatment with *m*-CPBA, but this also resulted in only recovered starting material. A similar result was obtained when

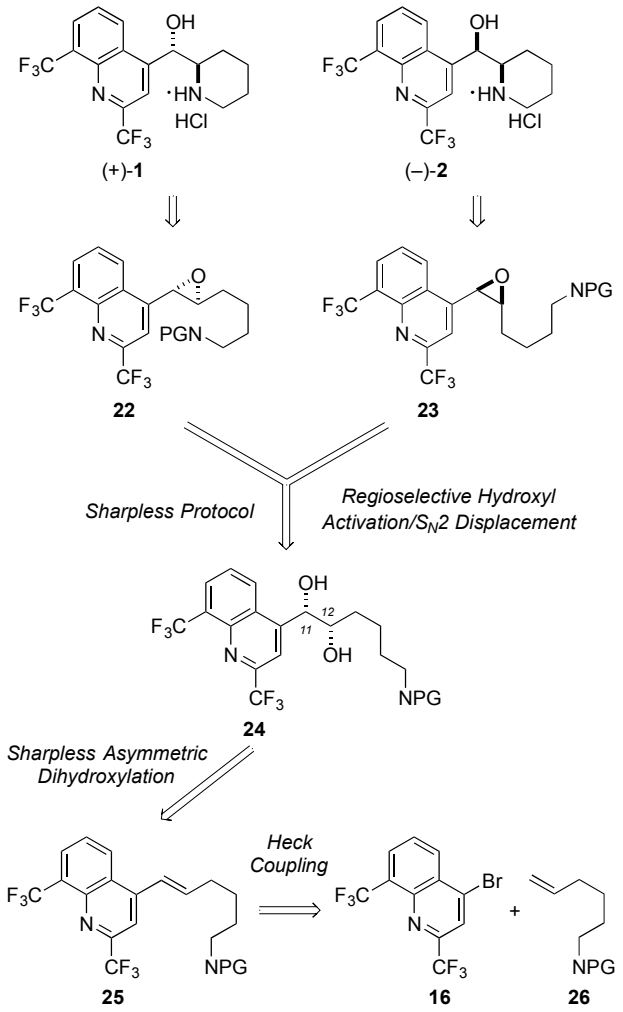
either DMDO or $Vo(acac)_2$ was used. Interestingly, the *cis*-form of the allylic alcohol (**20**) appears to be unreactive towards various modes of epoxidation, which is in contrast to the *trans*-isomer (**17**).



Scheme 4. Attempted formation of *cis*-epoxy alcohol **21**.

Frustrated by our inability to generate the desired *cis*-epoxide (**21**), we decided to modify our synthetic plan. Rather than rely on the asymmetric epoxidation of an allylic alcohol as a means of inducing asymmetry, we would generate a more structurally advanced olefin (**25**, Scheme 5) and attempt to conduct a Sharpless asymmetric dihydroxylation[24] on it. In principle, the required dihydroxylation substrate could still be accessed using a Heck reaction, but this time using an *N*-protected 1-aminohexene species of some type (**26**). Such an approach could potentially lead to an even more convergent and streamlined approach to the synthesis of the mefloquines than the formal synthesis shown above in Scheme 3. Significantly, the diol (**24**) obtained from the asymmetric dihydroxylation reaction would be leveraged to gain access to either *anti*- or *syn*-mefloquine. In one instance it would be converted to *trans*-epoxide **22** using the known Sharpless procedure.[25] Nitrogen deprotection followed by intramolecular epoxide ring opening would then give rise to a*nti*-mefloquine (**1**). In the second instance, the stereospecific formation of *cis*-epoxide **23** would require the regioselective conversion of one of the hydroxyl groups of diol **24** into a leaving group, with the other acting as a nucleophile in a S_N2 reaction. We reasoned that the C11 hydroxyl group should be considerably more

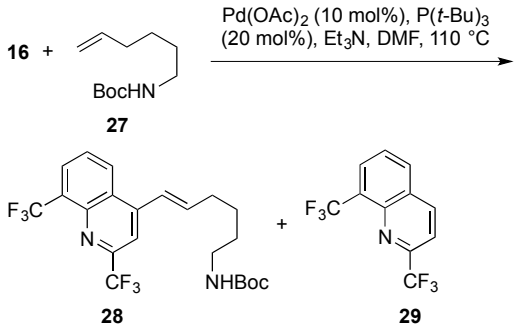
acidic than the C12 hydroxyl, due to the strongly electron-withdrawing nature of the aryl ring, and that this would allow for selective base-mediated functionalization of the C11 hydroxyl, ultimately leading to the required *cis*-epoxide.



Scheme 5. Retrosynthetic analysis towards both *anti*- and *syn*-mefloquine hydrochloride from a common diol intermediate.

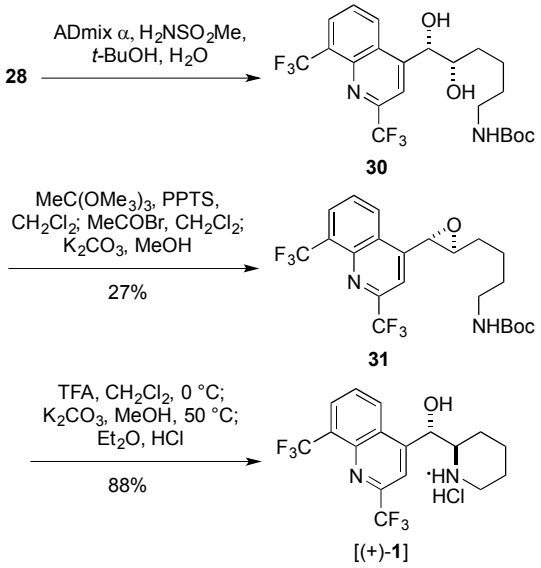
Work on the new synthetic strategy began with the preparation of the *N*-protected 1-aminohexene. We chose to mask the amine as something other than an azide, which we had done previously (see scheme 2), due to expected complications related to the use of phosphine ligands in the Heck coupling. In the event, we elected to protect the amine with a Boc group and, thus, prepared compound **27** (Scheme 6) according to a literature procedure.[26] Heck coupling between aryl bromide **16** and **27** did produce the desired product (**28**), however, in only a very low yield, with the major product

being **29**, the product of protodehalogenation of **16**. The use of a variety of different Pd sources and phosphine ligands did not led to any significant improvement in the outcome of the reaction. Moreover, the purification of **28** from the reaction mixture by column chromatography over silica gel was extremely difficult, and it could not be obtained in a highly pure form.



Scheme 6. Heck coupling of **16** and **27**.

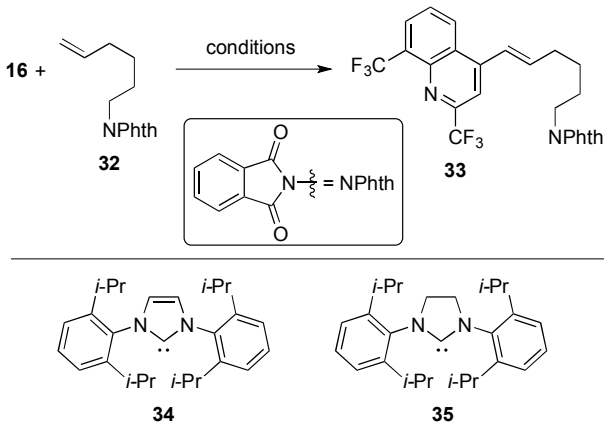
Despite the fact the Heck coupling was low yielding and the product obtained was difficult to purify, we were able to generate enough of it in semi-pure form to test the asymmetric Sharpless dihydroxylation.[24] We were pleased to find that the dihydroxylation proceeded smoothly (Scheme 7) and, conveniently, purification of the resulting diol (**30**) was very straightforward. A yield was not determined for the dihydroxylation reaction given the impure nature of olefin **28**. Transformation of **30** into *trans*-epoxide **31** proceeded smoothly using the Sharpless procedure,[25] but was also low yielding. Compound **31** was treated with TFA to remove the Boc protecting group. The resulting amine was combined with freshly ground K_2CO_3 in MeOH at 50 ºC, followed by HCl, which gave (+)-*anti*-mefloquine hydrochloride [(+)-**1**] in 88% yield for the one pot, three step reaction sequence. The enantiomeric purity of this material was not determined.



Scheme 7. Completion of synthesis of (+)-*anti*-mefloquine hydrochloride [(+)-**1**]

With the basis of our new strategy established as viable, we set out to improve on it. We began by trying the use of a different nitrogen protecting group for the 1-aminohexene-derived Heck coupling partner. Specifically, we chose the phthalimide protecting group. In this case, we would initiate the cascading deprotection/cyclization sequence (*cf*. **22** → **1**, Scheme 5) by treatment with hydrazine. The phthalimide protected amino alkene **32** was prepared according to a literature procedure,[27] and tried in the Heck coupling reaction with aryl bromide **16**. Upon screening different coupling conditions (Table 1), we found that the coupling of **32** and **16** could be carried out to a synthetically useful level using NHC ligand **34** (Table 1, entry 3). While protodehalogenation product **29** (see Scheme 6) was still observed, it was produced in a considerably reduced amount relative to the desired product. Once again, purification of the Heck product (**33**) proved difficult, so the yields shown in Table 1 correspond to material of approximately 95% purity, as judged by ^{1}H NMR.[28]

Table 1. Ligand screen for the Heck coupling of **16** and **32**.[a]



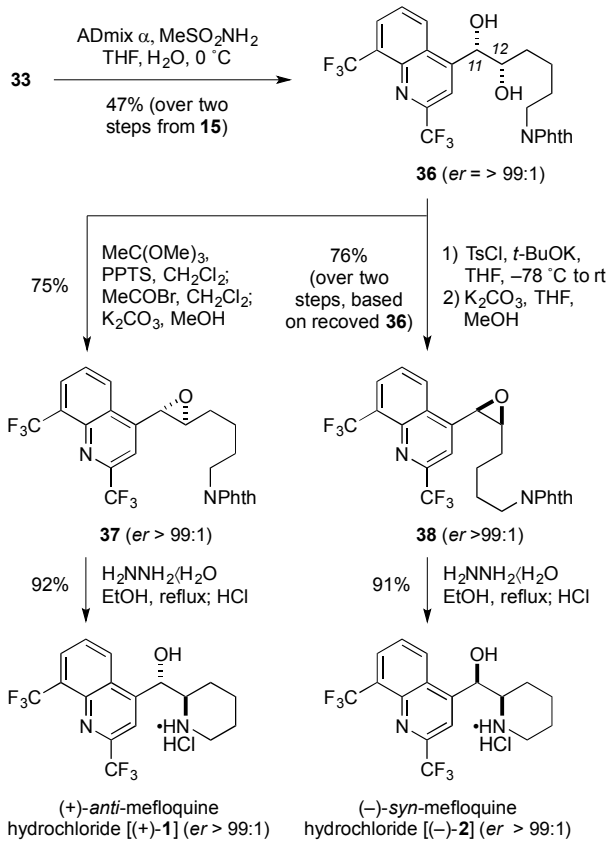
entry	Ligand	Yield (%)
1	P(*t*-Bu)$_3$	--
2	XPhos	48
3	**34**	68
4	**35**	65

[a]Reaction conditions: $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), Et_3N, DMF, 110 °C.

Asymmetric dihydroxylation of semi-purified olefin **33** produced the desired diol (**36**), which was then easily purified by silica gel chromatography (Scheme 8). The enantiomeric purity of **36** was determined by converting it into its corresponding acetonide, and comparing that with a racemic acetonide sample by HPLC analysis on a chiral, nonracemic stationary phase.[28] The *er* of the acetonide was established as 96:4, which is a likely a reasonable indication of the enantiomeric purity of the diol. The enantiomeric purity of the diol was easily increased to >99:1 by a single and efficient (92% recovery) recrystallization from acetonitrile.

With access to the diol secured, we converted it to *trans* epoxide **37** in very good yield via the Sharpless one-pot protocol (**36** → **37**).[25] To ensure that there was no loss of stereochemical integrity

during epoxide formation, it was compared to a corresponding racemic sample, by HPLC analysis on a chiral, nonracemic stationary phase.[28] The *er* of epoxide **37** was found to be >99:1. To complete the synthesis of *anti*-mefloquine hydrochloride, **37** was treated with hydrazine hydrate under reflux conditions, which served to remove the phthalimide protecting group and enable epoxide ring-opening. Subsequent acidification with HCl provided (+)-*anti*-mefloquine hydrochloride [(+)-**1**] in excellent yield. The enantiomeric purity of our synthetic material was established by HPLC analysis on a chiral, nonracemic stationary phase of the corresponding *N*-Boc derivative,[16] and was found to be >99:1 *er*. In addition, the optical rotation of the synthetic material was determined to be $[\alpha]_D^{20}$ = +26.0 (*c* = 0.45, MeOH), which corresponds to the reported value of $[\alpha]_D^{20}$ = +29.8 (*c* = 0.45, MeOH).**Error! Bookmark not defined.**



Scheme 8. Synthesis of (+)-**1** and (–)-**2**.

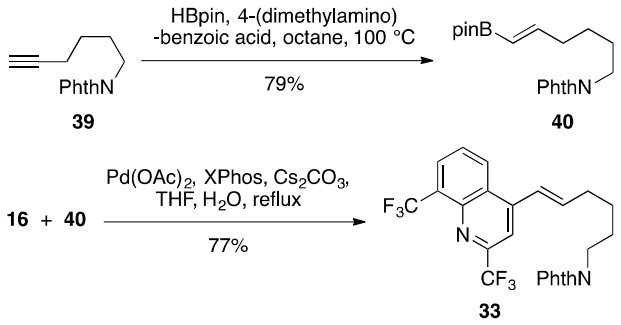
Having completed the synthesis of (+)-*anti*-mefloquine hydrochloride [(+)-**1**], we turned our attention to preparing *syn*-mefloquine hydrochloride [(–)-**2**]. As indicated above, in order to access this

compound from diol **36** we intended to take advantage of the predicted enhanced acidity of the C11 hydroxyl in order to regioselectively activate it, and then have it undergo a S_N2 displacement by the C12 hydroxyl group. After considerable experimentation, we found that this transformation was best executed as a one-pot procedure using 0.8 equiv. of *t*-BuOK and 1.0 equiv. of TsCl. This led to the conversion of the C11 hydroxyl into its corresponding tosylate, which then underwent base-mediated S_N2 displacement by the C12 hydroxyl group, giving the desired *cis*-epoxide in 76% yield (based on recovered starting material). The enantiomeric purity of **38** was established by comparison to the corresponding racemate by HPLC analysis on a chiral, nonracemic stationary phase, and was determined to be >99:1.[28]

To conclude the synthesis of *syn*-mefloquine hydrochloride, all that remained was removal of the phthalimide protecting group, intramolecular epoxide ring opening, and HCl salt formation. To achieve this, epoxide **38** was treated with hydrazine and the resulting mixture was acidified with HCl to afford (–)-**2** in excellent yield. Once again, the enantiomeric purity of our synthetic material was established by HPLC analysis on a chiral, nonracemic stationary phase on the corresponding *N*-Boc derivative,[16] and was found to be >99:1. The optical rotation of (–)-**2** was found to be $[\propto]_D^{20}$ = –41.4 (*c* = 0.91, MeOH), which is in agreement with the reported value of $[\propto]_D^{20}$ = –49.9 (*c* = 0.45, MeOH).**Error! Bookmark not defined.**

Although we had developed a concise synthesis of both (+)-*anti*- and (–)-*syn*-mefloquine from an advanced common intermediate (**36**), we were curious about the possibility of improving on the Heck coupling strategy that was used to access olefin **33**. As indicated above, when using the phthalimide alkene coupling partner, our best result gave a 68% yield (see Table 1, entry 3) of material having a purity of approximately 95%. In an effort to improve on this result, we investigated a modified synthetic strategy involving a Suzuki coupling between aryl bromide **16** and phthalimido containing boronic ester **40**. Compound **40** was easily prepared from commercially available acetylene **39** (Scheme 9).[29] After screening multiple Pd/ligand combinations, we found that $Pd(OAc)_2$/XPhos gave an

excellent outcome in the coupling of **40** and **16**, producing pure **33** in 77% yield, following silica gel chromatography. Notably, no proto-dehalogenation occurred in this instance and the purification of the product was straightforward.



Scheme 9. Suzuki coupling approach to olefin **33**.

To complete our studies, we set out to confirm the absolute stereochemistry of *anti*- and *syn*-mefloquine hydrochloride. Over the past 40 years there has been disagreement on the absolute stereochemistry of *anti*-mefloquine. The initial absolute stereochemical assignment by Carroll and Blackwell[8a] was completed on the basis of circular dichroism (CD) experiments, and (+)-*anti*- and (–)-*anti*- mefloquine were assigned the structures opposite to those shown in Figure 1. 28 years later, Karle and Karle contradicted the original assignment by using X-ray diffraction studies on *anti*-mefloquine hydrochloride and claimed the absolute stereochemistry of *anti*-mefloquine to be what is shown in Figure 1.6 An argument against the revised assignment was then made by Xie and co-workers during their total synthesis of (–)-*anti*-mefloquine hydrochloride.**Error! Bookmark not defined.** They employed a Mosher analysis that supported the absolute stereochemistry that Carroll and Blackwell originally assigned (*i.e.*, the opposite of that depicted in Figure 1). Recently, another argument regarding the absolute configuration of (+)- and (–)-*anti*-mefloquine was put forth.2 This analysis was based upon residual dipolar coupling (RDC) enhanced NMR spectroscopy in combination with optical rotatory dispersion (ORD) and CD spectroscopy. The result of this study recognized the absolute configuration given by Karle and Karle6 to be correct [*i.e.*, (+)-**1** and (–)-**1**, Figure 1]. In 2013, support

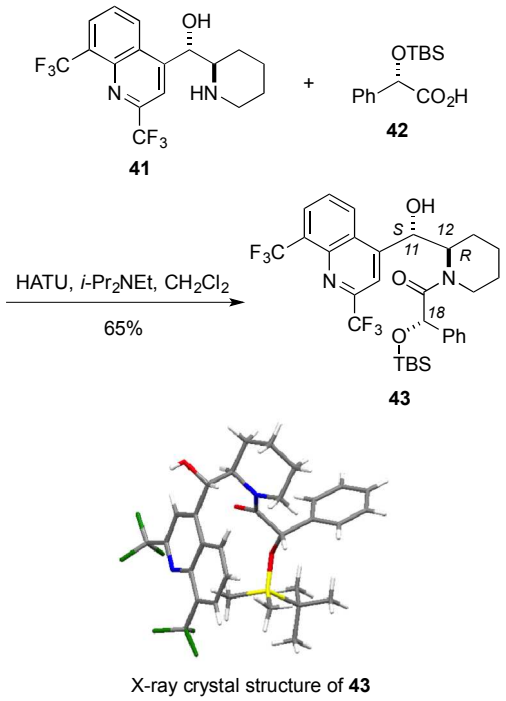
for the revised assignment was reported by Hall and Ding as part of a synthetic study.**Error! Bookmark not defined.**

While the above contributions towards the determination of the absolute stereochemistry of *anti*-mefloquine are important, we were surprised to find there were no studies reporting the derivatization of mefloquine with a known chiral, nonracemic compound, followed by X-ray crystallographic analysis. Thus, we set out to do this.

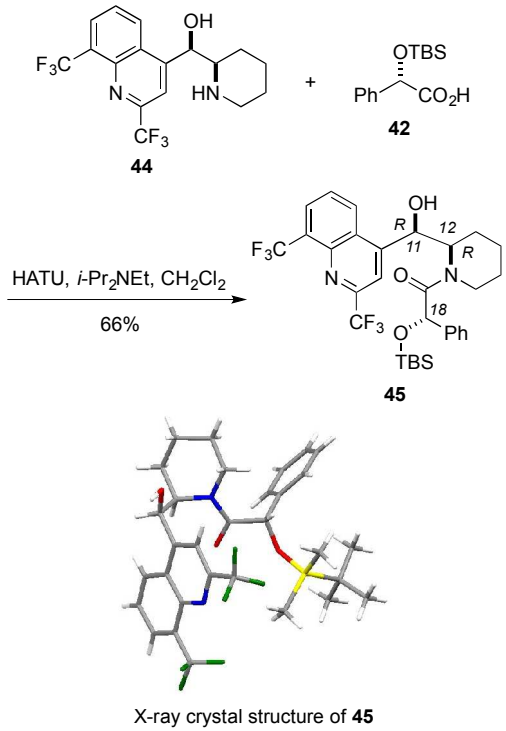
We initially attempted to achieve this by forming salt between (+)-*anti*-mefloquine (**41**) (Scheme 10) and a chiral, nonracemic acid. Compound **41** was prepared according to Scheme 8, but without the final HCl salt formation step that was used to prepare (+)-**1**. L-Tartaric acid, (+)-camphorsulfonic acid, and (+)-mandelic acid were each used attempts to make a crystalline salt of **41**, but with no success. Given that we were unable to form a suitable salt for X-ray analysis, we attempted to make a covalent derivative of **41** and obtain a crystal of that. To do so, compound **41** was coupled to (*S*)-(+)-mandelic acid *tert*-butyldimethylsilyl ether (**42**)[30] under non-epimerizing conditions to give **43** (Scheme 10). The optical rotation of the (*S*)-(+)-mandelic acid used to prepare **42** was measured as $[\propto]_D^{20}$ = +153.52 (*c* = 2.5, H_2O), which is consistent with the literature value $[\propto]_D^{20}$ = +149.0 (*c* = 2.5, H_2O).[31] By reference to the known *S*-configuration of the mandelic acid-derived stereogenic center, X-ray crystallography determined the absolute stereochemistry of C-11 and C-12 of **43** to be *S*, and *R*, respectively. This analysis confirms the absolute stereochemistry of (+)-*anti*-mefloquine to be that shown in Figure 1 [(+)-**1**], thus verifying the assignment by Karle and Karle.6

In an analogous manner, we carried out X-ray crystallographic analysis on our synthetic *syn*-melfoquine. Compound **44**, synthesized according to Scheme 8 but without the final HCl salt formation, was coupled to (*S*)-(+)-mandelic acid *tert*-butyldimethylsilyl ether (**42**) under non-epimerizing conditions to give **45** (Scheme 11). Again, using the known *S*-configuration of the mandelic acid-derived stereogenic center as a reference, X-ray crystallographic analysis established the absolute stereochemistry of C-11 and C-12 of **45** to be *R*, and *R*, respectively. On this basis we were

able to establish unambiguously, and for the first time, that the absolute stereochemistry of (–)-*syn*-mefloquine hydrochloride is that shown in Figure 1 [(–)-**2**].



Scheme 10. Synthesis and X-ray crystal structure of **43**.



Scheme 11. Synthesis and X-ray crystal structure of **45**.

CONCLUSION

In conclusion, we have developed a concise and highly enantioselective (*er* > 99:1) synthesis of both (+)-*anti*- and (–)-*syn*-mefloquine hydrochloride [(+)-**1** and (–)-**2**, respectively]. A key step in the synthesis of each compound is the enantioselective conversion of olefin **33** to diol **36**, the latter being converted into either a *trans*- or *cis*-epoxide, and ultimately to (+)-*anti*-mefloquine hydrochloride [(+)-**1**] and (–)-*syn*-mefloquine hydrochloride [(–)-**2**], respectively. Access to olefin **33** is achieved either via a Heck coupling or a Suzuki coupling, with the latter approach offering certain practical advantages. As a result of X-ray crystallographic and optical rotation studies on our synthetic material, the absolute stereochemistry for (+)-*anti*-mefloquine hydrochloride has been definitively confirmed as that reported by Karle and Karle [(+)-**1**, Figure 1].6 In addition, a similar analysis has established unambiguously, and for the first time, the absolute stereochemistry of (–)-*syn*-mefloquine hydrochloride [(–)-**2**, Figure 1]. Finally, we have also developed a formal synthesis of (+)-*anti*-mefloquine hydrochloride [(+)-**1**] that uses, as a key step, a Sharpless asymmetric epoxidation.

Experimental Section

General Considerations. Unless stated to the contrary, where applicable, the following considerations apply: reactions were carried out using dried solvents (see below) and under a slight static pressure of Ar (pre-purified quality) that had been passed through a column (5 x 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at

60 °C for at least 24 h prior to use and cooled in the same manner. Dry PhMe, CH_2Cl_2, and THF were obtained using asolvent purification system. All other dry solvents were of anhydrous quality purchased. Commercial grade solvents were used for routine purposes without further purification. Et_3N was distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded on a 600 MHz, 500, MHz or 400 MHz spectrometer at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS (7.26), ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). HRMS analyses were performed using a Q-ToF -MS instrument. HPLC analysis was performed using a 4.6 x 250 mm Chiralcel OD-H column. (+)-**1** has been previously characterized.[16] (–)-**2** has been previously characterized.**Error! Bookmark not defined.** The synthesis of **33**, **36**, **37**, **38**, **43**, and **45** have been previously described, as has their characterization.[18] Compounds **41** and **44** have been previously reported.**Error! Bookmark not defined.**

(E)-ethyl-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)acrylate (**46**). Aryl bromide **16** (1.22 g, 3.55 mmol), $Pd(OAc)_2$ (0.015 g, 0.071 mmol), and P-(*o*-toly)$_3$ (0.097 g, 0.319 mmol) were dissolved in ethyl acrylate/Et_3N (1:1 v/v, 2.5 mL/2.5 mL). The reaction was heated to reflux for 4 h and then cooled to rt and poured onto ice (25 mL). The mixture was partitioned between EtOAc and H_2O. The aqueous phase extracted with EtOAc (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography over silica gel (30:70 EtOAc-Hexanes) gave **46** as a light-yellow solid (0.927 g, 72%). mp 105–107 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.42-8.37 (m, 2 H), 8.21 (d, J = 8.0 Hz, 1 H), 7.93 (s, 1 H), 7.80 (t, J = 8.0 Hz, 1 H), 6.73 (d, J = 15.4 Hz, 1 H), 4.35 (q, J = 6.8 Hz, 2 H), 1.38 (t, J = 7.4 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.4, 148.3 (q, J_{C-F} = 35.6 Hz), 144.1, 142.9, 138.3, 137.2, 132.1, 129.5 (q, J_{C-F} = 6.1 Hz), 127.7, 127.1, 123.4 (q, J_{C-F} = 274 Hz), 121.1 (q, J_{C-F} = 275.6 Hz), 117.8, 114.8, 61.4, 14.2; **HRMS-ESI**: m/z calcd. for $C_{16}H_{11}F_6NO_2$ $[M+H]^+$ 364.0767, found 364.0767.

(E)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)prop-2-en-1-ol (**17**). Ester **46** was dissolved in PhMe (1.3 mL) and cooled to –78 °C. DIBAL (0.29 mL, 0.296 mmol, 1.0 M in hexane) was added dropwise over a period of ca. 2 min, and the resulting mixture was stirred at –78 °C for 10 min. before warming to 0 °C (ice-water bath). The mixture was stirred for 2 h at 0 °C then warmed to room temperature. Sat. aq. NH_4Cl (1.0 mL) was added, and the mixture was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2 (3 X 5 mL), and the combined organic extracts were washed with sat. NaCl (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography over silica gel (40:60 EtOAc-Hexanes) gave **17** as a white solid (0.034 g, 78%). mp 123–124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.2 Hz, 1 H), 8.16 (d, J = 7.3 Hz, 1 H), 7.85 (s, 1 H), 7.72 (t, J = 7.79 Hz, 1 H), 7.42 (dt, J = 16.0 Hz, 1.8 Hz, 1 H), 6.70 (dt, J = 15.5 Hz, 4.5 Hz, 1 H), 4.55-4.52 (m, 2 H), 1.73 (t, J = 5.9 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.3 (q, J_{C-F} = 35.2 Hz), 145.6, 144.1, 138.3, 129.3, 129.1 (q, J_{C-F} = 65.8 Hz), 128.0, 127.2, 127.0, 123.6 (q, J_{C-F} = 273.8 Hz), 123.2, 121.3 (q, J_{C-F} = 275.8 Hz),114.1, 62.9; **HRMS-ESI**: m/z calcd. for $C_{14}H_9F_6NO$ $[M+H]^+$ 322.0661, found 322.0664.

(2S,3S)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)methanol (**18**). A 25 mL round bottom was charged was crushed 4Å mol sieves (0.025 g), flamed dried under high vacuum, and then cooled to – 20 °C under an Ar atmosphere. To this flask was added CH_2Cl_2 (4 mL) and L-DIPT (0.027 g, 0.118 mmol). The mixture was stirred for 5 min, and Ti(O-*i*-Pr)$_4$ (0.031 mL, 0.105 mmol) was added drop-wise over a period of ca. 2 min. This mixture was stirred 10 min. *t*-BuOOH (0.21 mL, 1.05 mmol, 5.0 M in decane) was added drop-wise over a period of ca. 5 min, and the mixture stirred 30 min. Allylic alcohol **17** (0.085 g, 0.264 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and added to the reaction mixture drop-wise over a period of ca. 5 min. The reaction was stirred at –20 °C for 38 h. The reaction was quenched by addition of 30% NaOH in sat. NaCl (1.0 mL) and Et_2O (3 mL), followed by warming to rt. After stirring an additional 15 min, $MgSO_4$ and celite were added. Stirring was continued an additional 10 min before the reaction mixture was filtered over a tightly-packed pad of celite, followed

by concentration of the filtrate *in vacuo*. Flash chromatography over silica gel (60:40 EtOAc-Hexane) gave **18** as a white solid (0.068 g, 77%). Recrystallization from Et_2O/hexanes (70% recovery) led to an > 99:1 *er* [determined by HPLC, chiral OD-H column, 80:20 hexanes-*i*-PrOH, 0.35 mL/min, λ = 254 nm, t_R(major) = 20.6 min, t_R(minor) = 22.5 min]; mp 126–127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1 H), 8.20 (*J* = 7.4 Hz, 1 H), 7.81 (s, 1 H), 7.79 (t, *J* = 7.4 Hz, 1H), 4.67 (d, *J* = 1.7 Hz, 1 H), 4.19-4.16 (m, 1 H), 4.06-4.04 (m, 1 H), 3.23-3.22 (m, 1 H), 1.83 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.8 (q, J_{C-F} = 35.6 Hz), 146.2, 143.3, 129.5 (q, J_{C-F} = 30.7 Hz), 129.2 (q, J_{C-F} = 6.1 Hz), 127.7, 127.2, 127.1, 123.4 (q, J_{C-F} = 273.1 Hz), 121.1 (q, J_{C-F} = 275.6 Hz), 113.4, 62.5, 60.2, 51.8; **HRMS-ESI**: *m/z* calcd. for $C_{14}H_9F_6NO_2$ $[M+Na]^+$ 360.0430, found 360.0443.

(±)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)methanol [(±)-**18**]. Allylic alcohol **17** (0.092 g, 0.286 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0 °C. $NaHCO_3$ (0.024 g, 0.286 mmol) and *m*-CPBA (0.123 g, 0.716 mmol) were then added, and the reaction was warmed to rt and stirred for 14 h. The reaction was quenched with 1 M Na_2SO_3 (4 mL) and diluted with H_2O (5 mL). The layers were partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL), and sat. aq. NaCl (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography over silica gel (60:40 EtOAc-Hexanes) gave **(**±)-**18** as a white solid (0.084 g, 87%, and 50:50 *er* [determined by HPLC, chiral OD-H column, 80:20 hexanes-*i*-PrOH, 0.35 mL/min, λ = 254 nm, t_R = 21.4 min, t_R = 23.3 min]); spectral data was identical to that of **18**.

3-(2,8-bis(trifluoromethyl)quinolin-4-yl)prop-2-yn-1-ol (**19**). To a suspension of CuI (0.037 g, 0.198 mmol) in Et_3N (82 mL) was added propargylic alcohol (0.21 mL, 3.64 mmol), and the mixture was stirred for 5 min. Aryl bromide **16** (1.14 g, 3.31 mmol) and $PdCl_2(PPh_3)_2$ (0.092 g, 0.132 mmol) were added and the mixture was heated to reflux for 4 h and then cooled to rt. The reaction was filtered through a tightly-packed pad of Celite and rinsed with CH_2Cl_2 (75 mL). The filtrate was washed with sat. aq. NaCl (50 mL), dried over $MgSO_4$, filtered, and partially concentrated *in vacuo* until Et_3NH^+

precipitated out of solution. The suspension was filtered, washed with EtOAc (50 mL), and concentrated *in vacuo*. Flash chromatography over silica gel (40:60 EtOAc-Hexanes) gave **19** as an off-white solid (0.845 g, 80%). mp 106–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 7.3 Hz, 1 H), 8.18 (d, *J* = 6.8 Hz, 1 H), 7.89 (s, 1 H), 7.76 (t, *J* = 7.7 Hz, 1 H), 4.69 (d, *J* = 5.9 Hz, 2 H), 1.89 (t, *J* = 6.4 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.1 (q, J_{C-F} = 36.1 Hz), 143.6, 131.8, 130.2, 129.7 (q, J_{C-F} = 5.8 Hz), 129.1 (q, J_{C-F} = 30.3 Hz), 128.6, 127.9, 123.4 (q, J_{C-F} = 273.8 Hz), 121.0 (q, J_{C-F} = 275.8 Hz), 120.4, 99.3, 80.3, 51.6; **HRMS-ESI**: *m/z* calcd. for $C_{14}H_7F_6NO$ $[M+H]^+$ 320.0505, found 320.0511.

(Z)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)prop-2-en-1-ol (**20**). A 5 mL round bottom flask was charged with alkyne **19** (0.090 g, 0.282 mmol) and Lindlar's catalyst (0.020 g, 0.183 mmol). Anhydrous MeOH (1.2 mL) and quinoline (0.021 mL, 0.183 mmol) were added, and a balloon containing H_2 was attached to the flask. The reaction was stirred at rt for 17 h and subsequently filtered through a tightly-packed pad of celite. The mixture was concentrated *in vacuo*. Flash chromatography over silica gel (40:60 EtOAc-Hexanes) gave **20** as a white solid (0.074 g, 82%). mp 53–55 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.2 Hz, 1 H), 8.18 (d, *J* = 6.8 Hz, 1 H), 7.73 (t, *J* = 7.4 Hz, 1 H), 7.59 (s, 1 H), 7.02 (dd, *J* = 11.91 Hz, 0.9 Hz, 1 H), 6.39 (dt, *J* = 11.9 Hz, 6.4 Hz, 1 H), 4.28-4.25 (m, 2 H), 1.57 (brs, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.9 (q, J_{C-F} = 35.2 Hz), 145.0, 143.7, 137.0, 129.2 (q, J_{C-F} = 5.8 Hz), 129.0, 127.7, 128.6 (overlapped q), 127.3, 125.4, 123.6 (q, J_{C-F} = 272.9 Hz), 121.2 (q, J_{C-F} = 275.8 Hz), 117.4, 59.3; **HRMS-ESI**: *m/z* calcd. for $C_{14}H_9F_6NO$ $[M+H]^+$ 322.0661, found 322.0672.

tert-butyl-(5S,6S)-6-(2,8-bis(trifluoromethyl)quinolin-4-yl)-5,6-dihydroxyhexyl)carbamate (**30**). P(*t*-Bu)$_3$ (0.058 mL, 0.24 mmol), Et_3N (0.42 mL, 3.00 mmol), and DMF (2.4 mL) were added to a mixture of aryl bromide **16** (0.412 g, 1.2 mmol), alkene **27** (0.289 g, 1.45 mmol), and $Pd(OAc)_2$ (0.027 g, 0.12 mmol). The mixture was heated to 110 °C for 7 h. Upon cooling to rt, the reaction was quenched by addition of H_2O. The mixture was partitioned between Et_2O and H_2O, and the aqueous phase was extracted with Et_2O (3 X 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (30:70 EtOAc-

Hexanes) gave the semi-purified Heck product as an orange oil that was used directly in the subsequent transformation. To a solution of ADmix-α (0.273 g, 1.1g/mmol) and methansulfonamide (0.07 g, 0.744 mmol) in *t*-BuOH(1.2 mL) and H_2O (1.2 mL) at 0 °C was added semi-purified olefin (0.115 g, 0.248 mmol) dissolved in *t*-BuOH (1.0 mL, 0.5 mL wash). The reaction was stirred for 40 h at 0 °C. Sodium sulfite (0.320 g) was added and the reaction was allowed to warm to room temperature, and stirring was continued for an additional hour. The mixture was then partitioned between Et_2O and H_2O, and the aqueous phase extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with sat. aq. NaCl, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (30:70 to 80:20 EtOAc-Hexanes) yielded **30** as a white solid (0.04 g, 6.7 % over 2 steps). mp 127–128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (d, J = 7.79 Hz, 1 H), 8.16 (d, J = 7.33Hz, 1 H), 8.02 (s, 1 H) 7.72 (t, J = 7.79 Hz, 1 H), 5.35 (d, J = 4.12 Hz, 1 H), 4.61 (brs, 1 H), 3.82-3.804 (m, 1 H), 3.13 (brs, 2 H), 1.71-1.53 (m, 3 H), 1.50-1.39 (m, 12 H, apparent singlet at 1.41); **^{13}C NMR** (125 MHZ, $CDCl_3$): δ 156.8, 150.8, 148.1 (q, $J_{C\text{-}F}$ = 36.2 Hz), 143.8, 129.5 (q, $J_{C\text{-}F}$ = 30.6 Hz), 128.7 (q, $J_{C\text{-}F}$ = 4.8 Hz), 127.2, 127.1, 126.9, 123.5 (q, $J_{C\text{-}F}$ = 271.5 Hz), 121.3 (q, $J_{C\text{-}F}$ = 274 Hz), 115.9, 79.7, 74.6, 72.2, 39.6, 33.1, 29.9, 28.3, 22.4; **HRMS-ESI**: *m/z* calcd. for $C_{22}H_{26}F_6N_2O_4$ $[M+Na]^+$ 519.1689, found 519.1709.

Protodehalogenation product **29** (*2,8-bis(trifluoromethyl)quinoline*) was also isolated as an orange solid during the Heck coupling between **16** and **27**. mp 73–75 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ 8.41 (d, J = 8.25 Hz, 1 H), 8.16 (d, J = 7.56 Hz, 1 H), 8.09 (d, J = 8.25 Hz, 1 H), 7.82 (d, J = 8.25 Hz, 1 H), 7.22 (t, J = 7.56 Hz, 1 H); **^{13}C NMR** (150 MHZ, $CDCl_3$): δ 148.5 (q, $J_{C\text{-}F}$ = 35.4 Hz), 143.6, 138.3, 132.1, 129.2 (q, $J_{C\text{-}F}$ = 5.91 Hz), 129.1, 129.0 (q, $J_{C\text{-}F}$ = 31.0 Hz), 127.3, 123.5 (q, $J_{C\text{-}F}$ = 275.0 Hz), 121.2 (q, $J_{C\text{-}F}$ = 275.0 Hz), 117.8; **HRMS-ESI**: *m/z* calcd. for $C_{11}H_5F_6N$ $[M+Na]^+$ 288.0218, found 288.0217.

tert-butyl (4-(2S,3S)-3-(2,8-bis(trifluoromethyl)quinolin-4-yl)oxiran-2-yl)butyl)carbamate (**31**). Diol **30** (0.038 g, 0.076 mmol) was dissolved in CH_2Cl_2 (1.3 mL). Trimethylorthoacetate (0.03 mL, 0.229 mmol) and PPTS (0.003 g, 15 mol%) were added and the reaction mixture was stirred for 12 h and then concentrated *in vacuo*. The resulting yellow oil was dissolved in CH_2Cl_2 (1.3 mL) and cooled

to 0 °C. Acetyl bromide (0.017 mL, 0.229 mmol) was added dropwise drop-wise over a period of ca. 2 min, and the reaction was warmed to rt and stirred 6 h. The mixture was concentrated *in vacuo*, and the resulting orange residue was dissolved in MeOH (1.3 mL). K_2CO_3 (0.031 g, 0.229 mmol) was added and the heterogeneous mixture was stirred for 10 h. The mixture was then evaporated, dissolved in H_2O (5 mL), and extracted with Et_2O (3 X 10 mL). The combined organic extracts were washed with sat. aq. NaCl, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (35:65 EtOAc-Hexanes) yielded **31** as a white solid (0.01 g, 27 %). mp 93–95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.24 Hz, 1 H), 8.19 (d, J = 7.33 Hz, 1 H), 7.80-7.76 (m, 2 H), 4.57 (brs, 1 H), 4.30 (d, J = 1.83 Hz, 1 H), 3.18-3.17 (m, 2 H), 2.97 (tdd, J = 2.97 Hz, 5.04 Hz, 2.29 Hz, 1 H), 1.99-1.94 (m, 1 H), 1.87-1.80 (m, 1 H), 1.46-1.39 (m, 4 H), 1.47 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.1, 148.8 (q, $J_{C\text{-}F}$ = 35.2 Hz), 146.7, 143.3, 129.6 (q, $J_{C\text{-}F}$ = 30.3 Hz), 129.1 (q, $J_{C\text{-}F}$ = 4.8 Hz), 127.6, 127.4, 126.9, 123.5 (q, $J_{C\text{-}F}$ = 272.9 Hz), 121.1 (q, $J_{C\text{-}F}$ = 275.8 Hz), 113.3, 79.3, 63.3, 54.9, 40.2, 31.8, 30.0, 28.5, 23.2; **HRMS-ESI**: *m/z* calcd for $C_{22}H_{24}F_6N_2O_3$ $[M+Na]^+$ 501.1583, found 501.1603.

(R)-2-((S)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy)-methyl)piperidin-1-ium chloride [(+)-**1**]. A solution of **31** (0.004 g, 0.008 mmol) in CH_2Cl_2 (0.2 mL) was cooled to 0 °C (ice-water bath). TFA (3.3 µL, 0.043 mmol) was then added dropwise drop-wise over a period of ca. 2 min. The mixture was allowed to warm to rt and stirred for 30 min. It was then quenched by the addition of sat. aq. $NaHCO_3$ until pH = 7, followed by extraction of the aqueous phase with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting orange oil was dissolved in MeOH (0.5 mL). Freshly ground K_2CO_3 (0.002 g, 0.016 mmol) was added, and the reaction was heated at 50 °C for 3 h. The solution was filtered, washed with Et_2O (2 mL), and concentrated in *vacuo.* The resulting light-yellow solid was dissolved in Et_2O (2 mL) and cooled in an ice-water bath. Dry HCl gas was then bubbled through the solution until it was saturated. The resulting solid was filtered and dried under vacuum to afford [(+)-**1**] as a yellow solid (0.003 g, 88%). Spectral data was identical to that previously reported.[11]

(E)-2-(6-(4,4,5,5-tetramethyl-methyl-1,3,2-dioxaborolan-2-yl)hex-5-en-1-yl)isoindoline-1,3-dione (**40**). *N*-(5-hexynyl)phthalimide (0.15 g, 0.66 mmol), 4-(dimethylamino)benzoic acid (0.005 g, 5 mol%), and pinacol borane (0.28 mL, 1.98 mmol) were dissolved in octane (0.6 mL), and stirred at 100 °C for 12 h. The mixture was then cooled to rt and concentrated *in vacuo*. Flash chromatography over silica gel (0:100 to 30:70 EtOAc-Hexanes) gave **40** as a white solid (0.185 g, 79%). mp 51–53 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 2 H), 7.72-7.68 (m, 2 H), 6.57 (dt, *J* = 17.86 Hz, 6.87 Hz, 1 H), 5.41 (dt, *J* = 17.86Hz, 1.37 Hz, 1 H), 3.67 (t, *J* = 7.33 Hz, 2 H), 2.21-2.15 (m, 2 H), 1.71-1.64 (m, 2 H), 1.49-1.43 (m, 2 H), 1.24 (s, 12 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.3, 153.6, 133.8, 132.1, 123.1, 80.0, 37.8, 35.3, 28.2, 25.5, 24.8, 24.7; **HRMS-ESI**: *m/z* calcd. for $C_{20}H_{26}BNO_4$ $[M+Na]^+$ 378.1851, found 378.1868.

(E)-2-(6-(2,8-bis(trifluoromethyl)quinolin-4-yl)hex-5-en-1-yl)isoindoline-1,3-dione (**33**). Aryl bromide **16** (0.058 g, 0.168 mmol), pinacol boronate ester **40** (0.066 g, 0.185 mmol), $Pd(OAc)_2$ (0.0015 g, 4 mol%), XPhos (0.013 g, 8 mol%), and Cs_2CO_3 (0.164 g, 0.504 mmol) were dissolved in THF (2.0 mL) and H_2O (0.4 mL H_2O), and heated to reflux for 5 h. After cooling to rt the reaction was partitioned between Et_2O and H_2O. The aqueous phase was extracted with Et_2O (3 x 15 mL), and the combined organic extracts were washed with sat. aq. NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography over silica gel (30:70 EtOAc-Hexanes) gave **33** as a pale yellow solid (0.064 g, 77%). Spectral data was identical to that previously reported.[18]

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SUPPORTING INFORMATION

NMR spectra for all new compounds, selected HPLC chromatograms, and crystallographic data for compounds **43** and **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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