

A Concise and Highly Enantioselective Total Synthesis of (+)-*anti*- and (-)-*syn*-Mefloquine Hydrochloride: Definitive Absolute Stereochemical Assignment of the Mefloquines

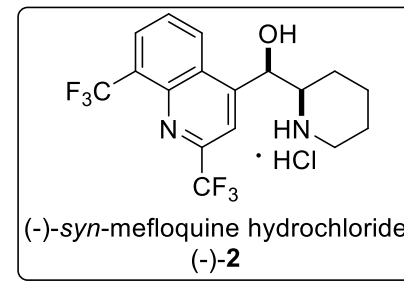
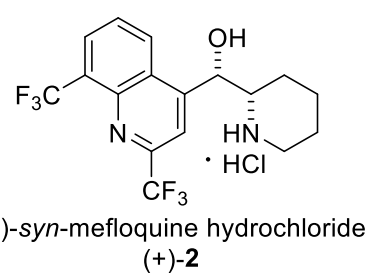
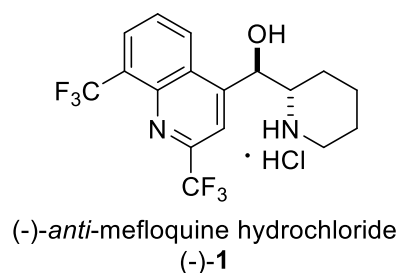
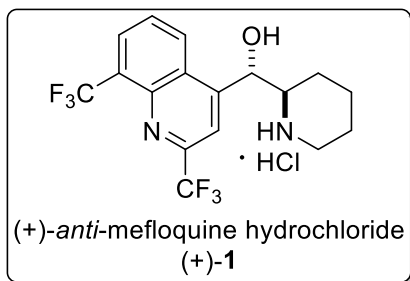
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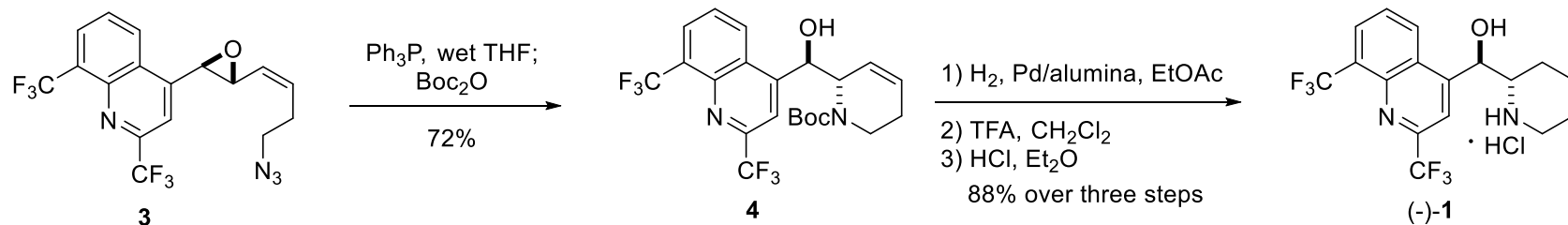
Presented by Hyelee Lee, Liu Research Group, Boston College

I. Introduction

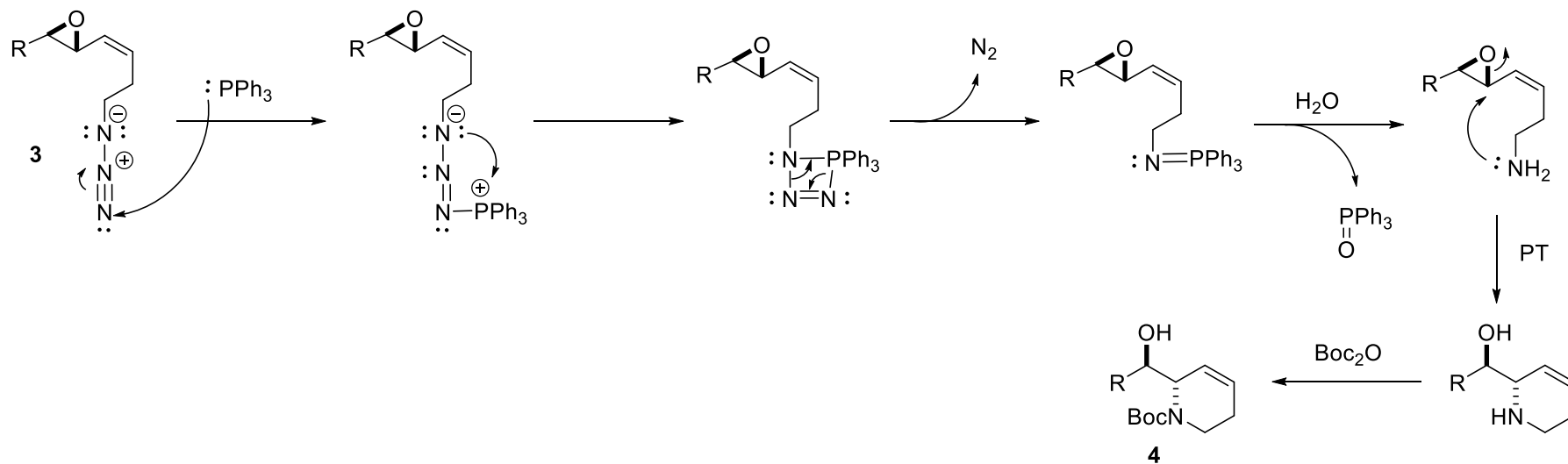


- *anti*-Mefloquine hydrochloride (**±1**) has been used both for treatment of malaria and prophylaxis.
- The drug is administered in racemic form, and is marketed under the name Lariam.
- (+)-**1** is at least 1.5 times more active than the (-)-**1**. ((-)-**1** has a shorter in vivo half-life)
- Side effect: psychiatric effects (anxiety, hallucinations, depression, unusual behavior, and suicidal ideations), neurologic effects (dizziness, loss of balance, and tinnitus), and cardiac effects (abnormalities with heart rhythms).
- Both *anti*- and *syn*-mefloquine hydrochloride were previously synthesized by Hall¹⁾ and Leonov²⁾ groups in 2013 .
- The group reported an asymmetric total synthesis of (-)-**1** in 2011³⁾.

Previous synthesis of (-)-**1**³⁾

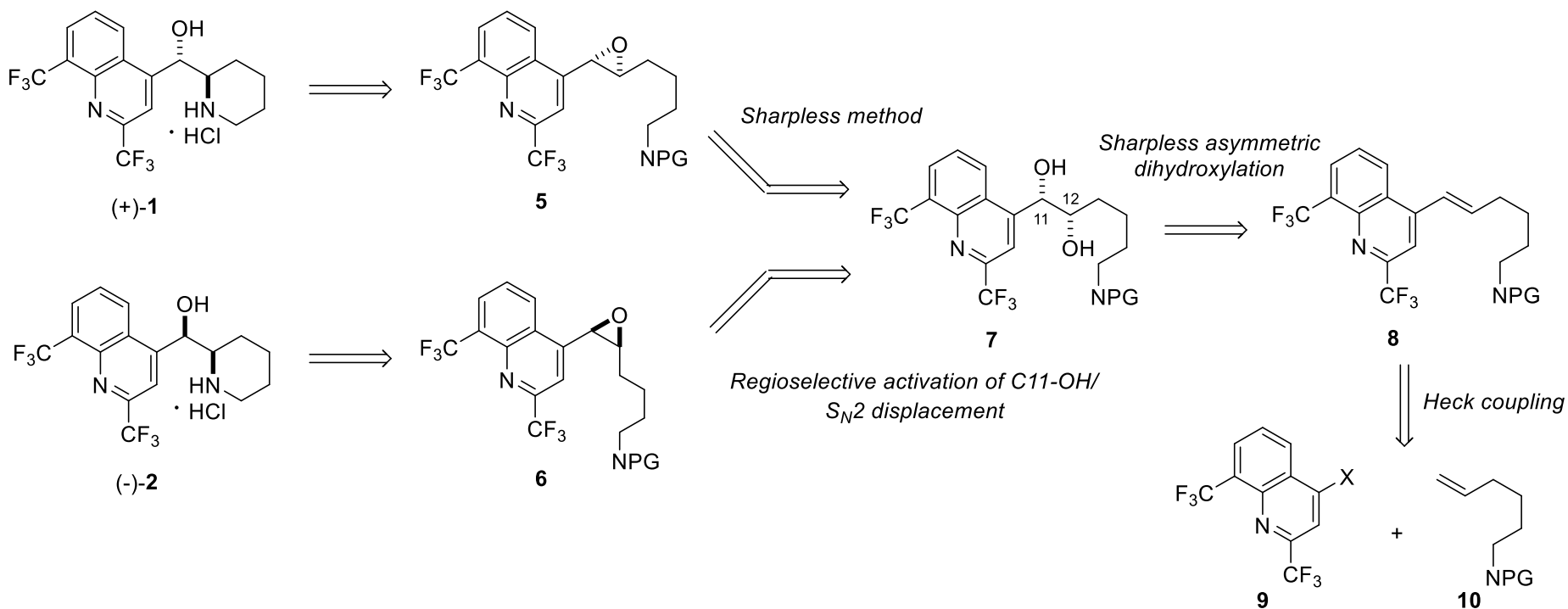


3 to 4 (azide reduction (Staudinger reaction) - epoxide opening cascade reaction)



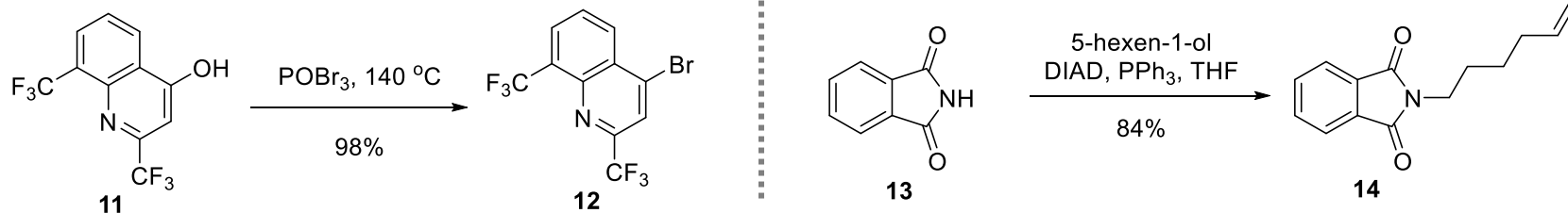
- A key step: a cascade azide reduction to amine/ epoxide ring-opening in one-pot reaction.
- Total 11 steps synthesis.

II. Retrosynthesis

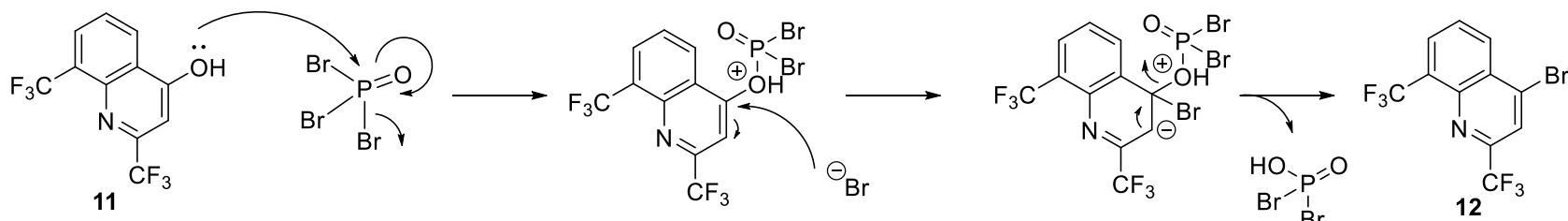


- Cyclization of **5** to (+)-**1** and **6** to (-)-**2**.
- A common diol intermediate **7** to divergent synthesis to *trans*-epoxide **5** and *cis*-epoxide **6**.
- Asymmetric Sharpless dihydroxylation of olefin **8** to **7**.
- Selective base-mediated functionalization of C11-OH by the enhanced acidity towards synthesis of **6**.
- Heck coupling between **9** and **10**.

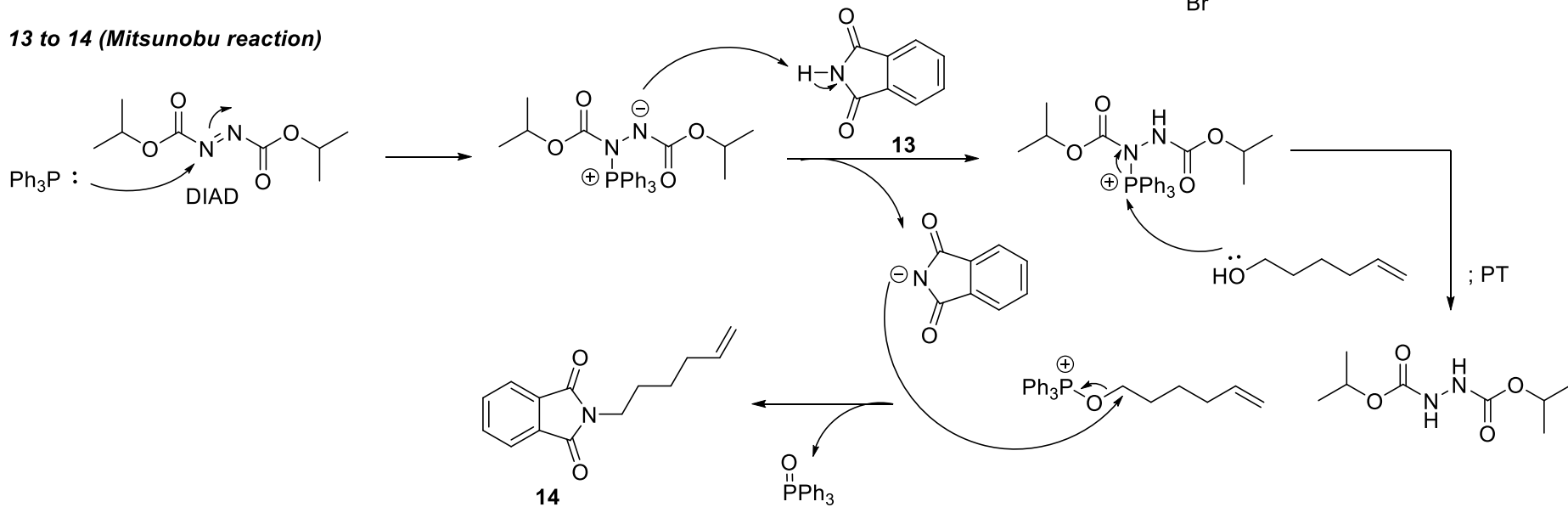
III. Forward synthesis

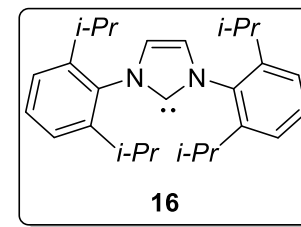
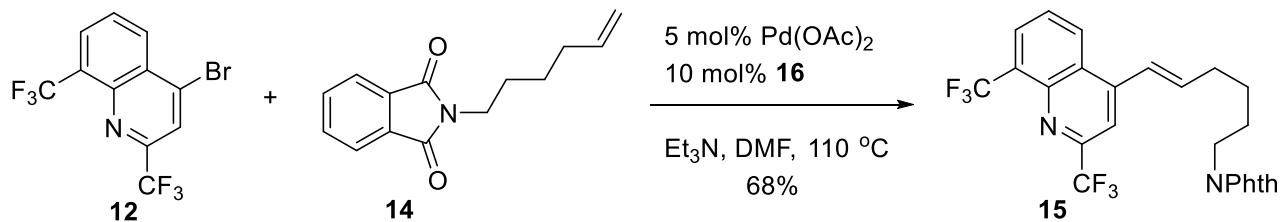


11 to 12 (Bromination)



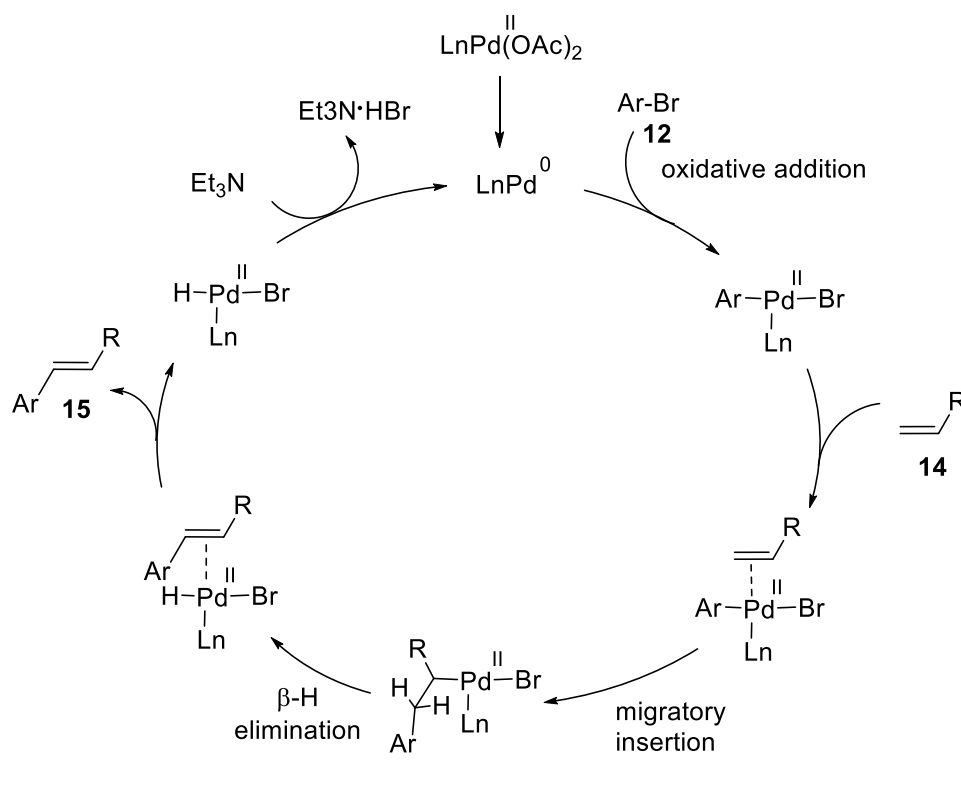
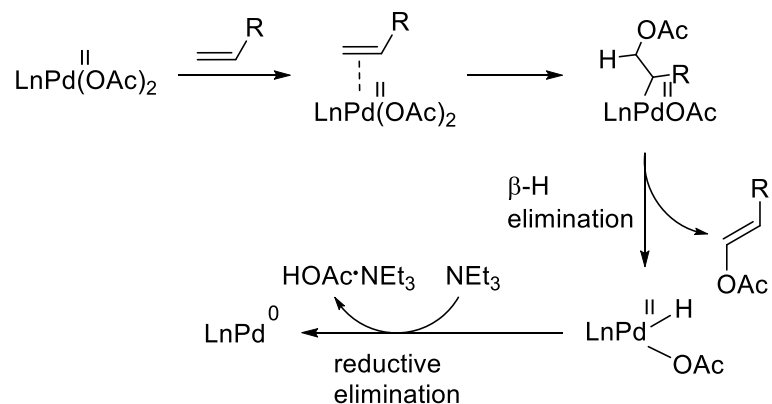
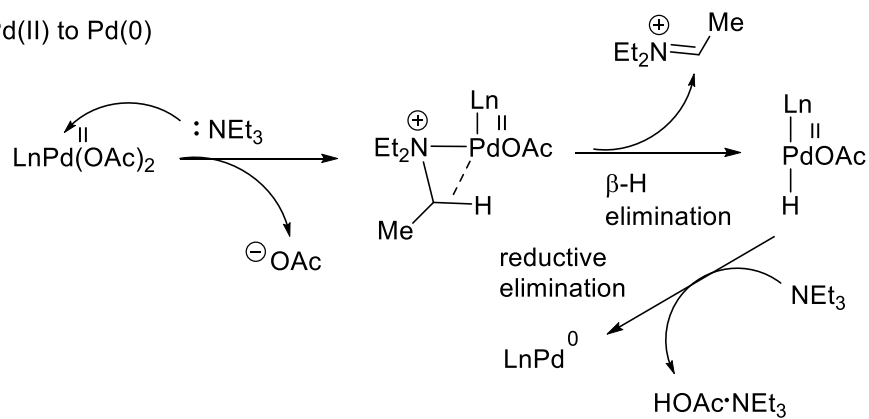
13 to 14 (Mitsunobu reaction)

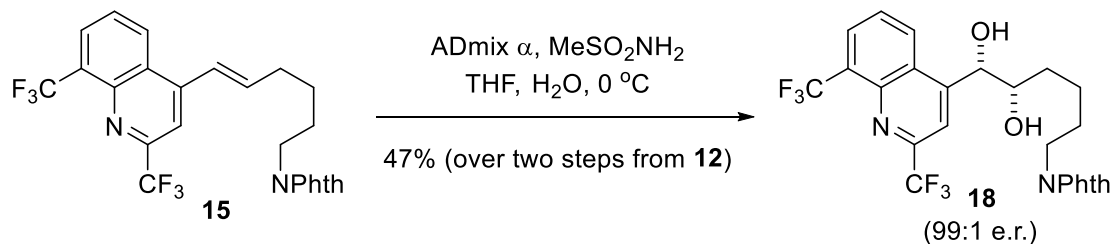




Heck coupling reaction

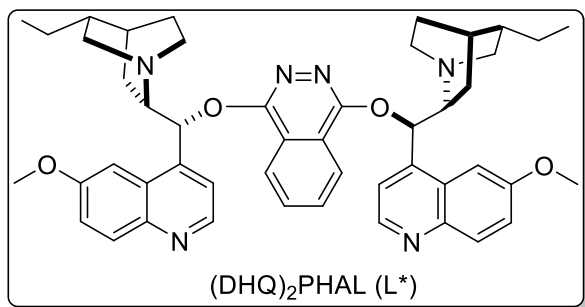
Pd(II) to Pd(0)



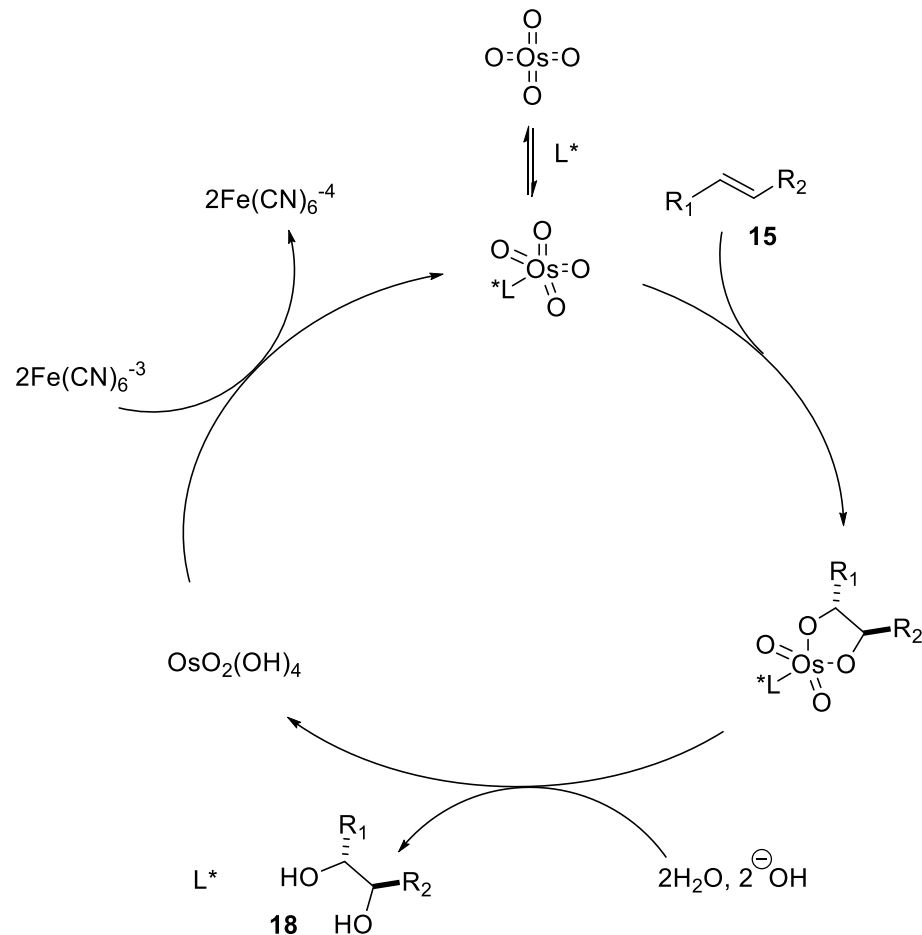
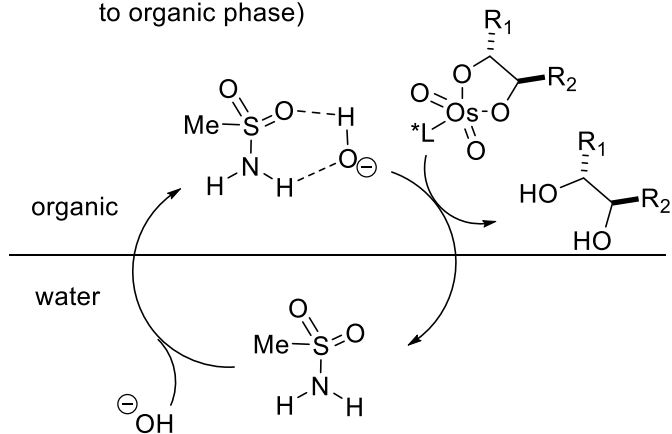


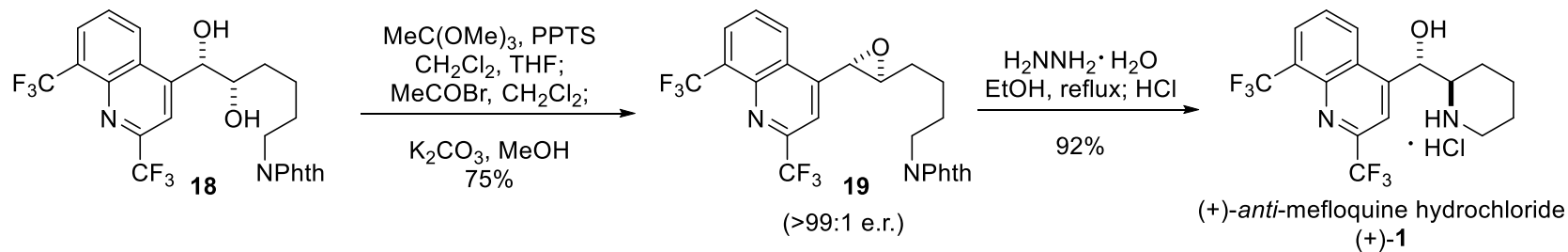
Sharpless asymmetric dihydroxylation

ADMIX α = K₂OsO₂(OH)₄, K₂CO₃, K₃Fe(CN)₆, (DHQ)₂PHAL

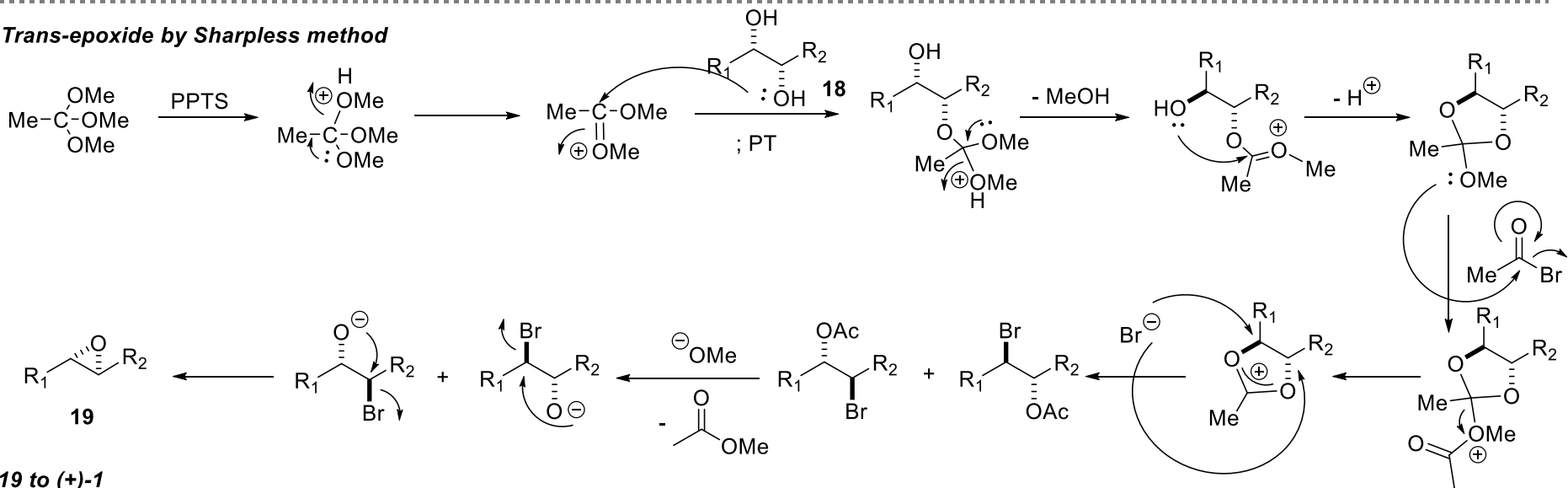


MeSO₂NH⁴): cosolvent and general acid catalyst
 (helps in the transfer of OH[⊖] from water phase to organic phase)

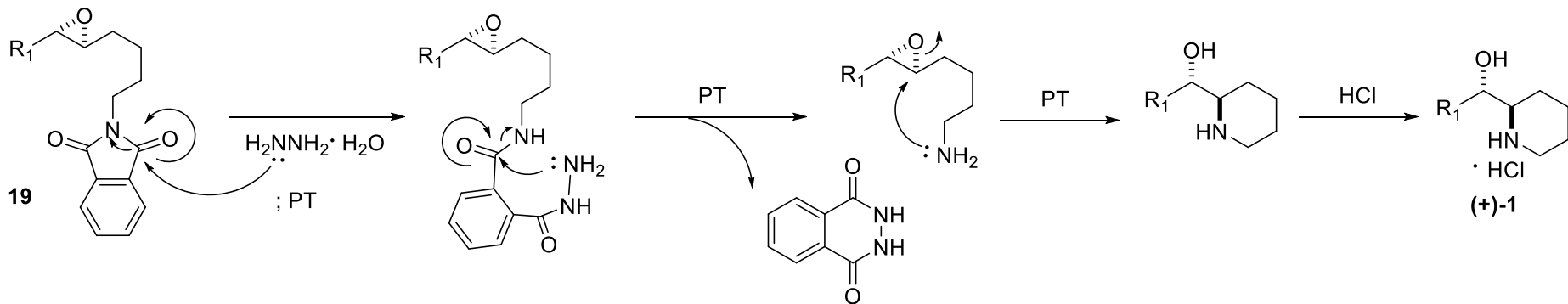


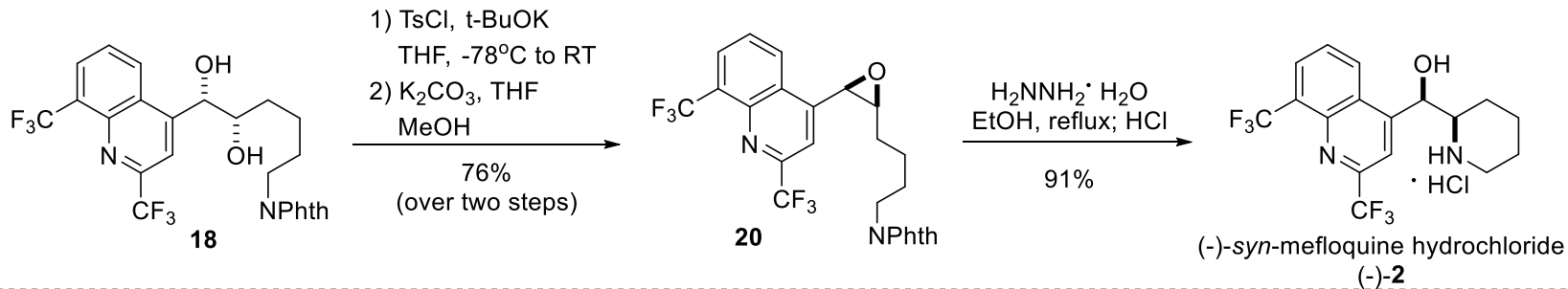


Trans-epoxide by Sharpless method

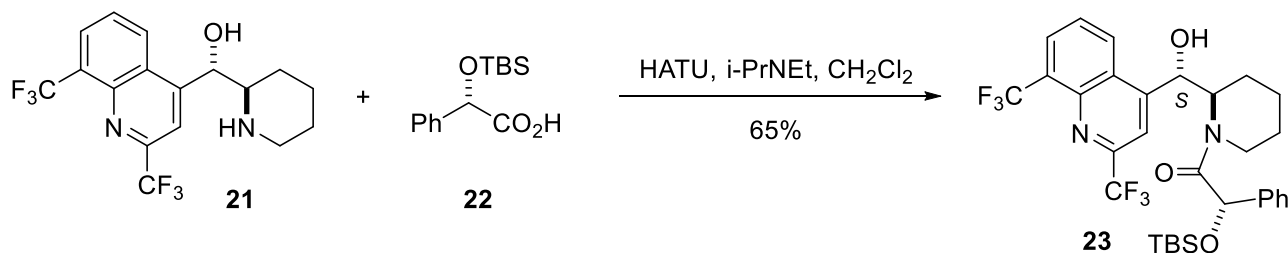
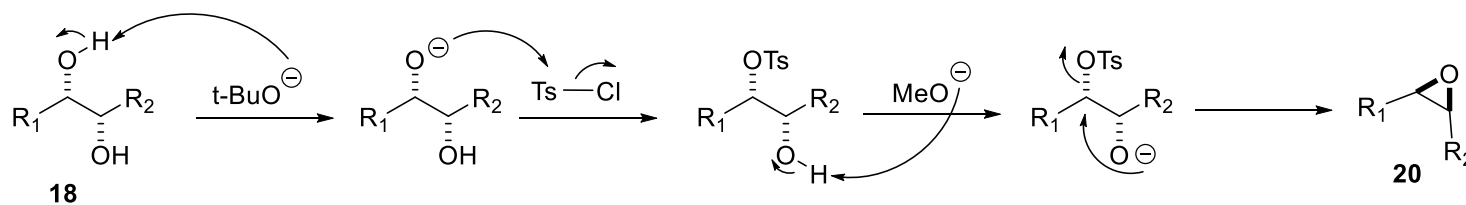


19 to (+)-1





Regioselective activation of C11-OH/ S_N2 displacement



Amide coupling for determination of the absolute configuration of (+)-1

