Enantioselective Total Synthesis of (—)-Himalensine A via a Palladium and 4-Hydroxyproline Co-catalyzed Desymmetrization of Vinyl-bromide-tethered Cyclohexanones.

Kučera, R.; Ellis, S. R.; Yamazakl, K.; Cook, J. H.; Chekshin, N.; Christensen, K. E.; Hamlin, T. A.; Dixon D. J.

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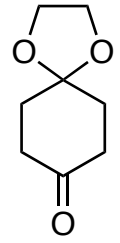
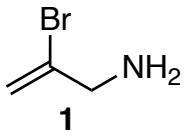


1-4

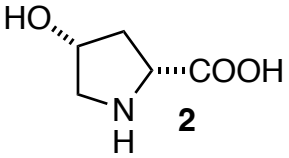
A

5-12

B



1



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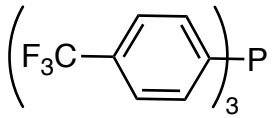
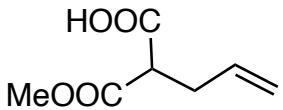


3

1) **1**, $NaBH(OAc)_3$
2) 3 M HCl, THF
3) TsCl, NEt_3, DMAP, DCM
4) **2** (20 mol%), **3** (15 mol%), $Pd(OAc)_2$ (5 mol%), K_2HPO_4, MeOH, 85 ˚C

5) Crabtree's catalyst (1.5 mol%), H_2 (58 bar)
6) $Pd(TFA)_2$, O_2, DMSO, AcOH, 80 ˚C
7) MeLi, CuI, THF *then* TMSCl, NEt_3
8) NBS, $NaHCO_3$, THF, -78 ˚C
9) Li_2CO_3, LiBr, DMF, 155 ˚C
10) NaHMDS, THF, 0 ˚C *then* Na-Nap
11) **4**, EDC•HCl, DMAP
12) K_2CO_3, MeCN, Δ



4

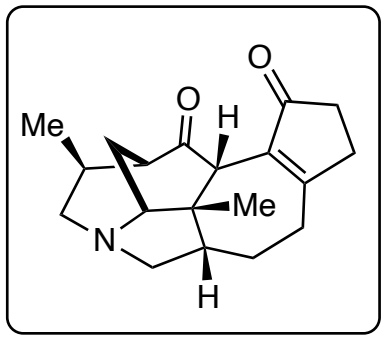
How would you make **1**?

4) Propose a mechanism. *Hint*: Similar to Heck reaction but double bond at which migratory insertion takes place is generated *in situ*.

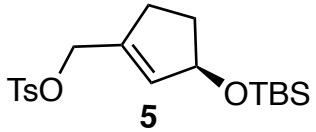
5) structure of Crabtree's catalyst?

6) Who developed these conditions?

13-18



Himalensine A



5

13) KHMDS, **5**, 18-crown-6, THF, -78 ˚C
14) mesitylene, 200 ˚C *then* HG-II (2.5 mol%), PhMe, 125 ˚C
15) LiCl, DMSO, H_2O, 170 ˚C
16) KF, 4 M H_2SO_4, acetone
17) AZADO, PIDA
18) Vaska's catalyst, TMDS, PhMe *then* HCOOH, MeOH, 60 ˚C

14) An epimerization occurs during the second part of this step. What is the intermediate following heating in mesitylene?