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A Practical Synthesis of Renin Inhibitor MK-1597 (ACT-178882) via Catalytic Enantioselective Hydrogenation and Epimerization of Piperidine Intermediate

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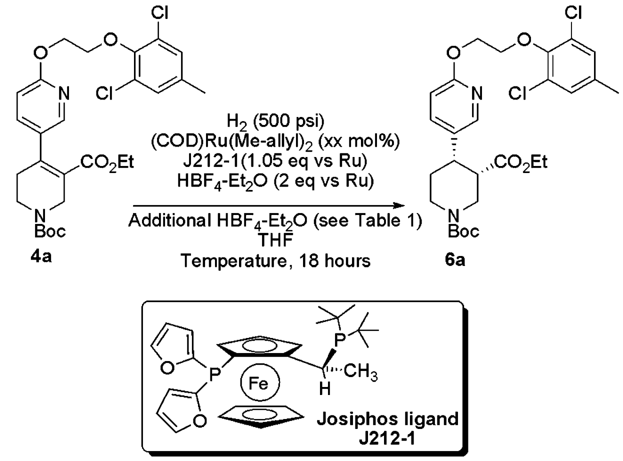
Corrected scheme for Table 1:



Procedure for microscale screening reactions in Table 1: A 1.5 mg/mL stock solution of (COD)Ru(Me-allyl)$_2$ was prepared in 1,2-dicholoroethane and then pipetted into a 1 mL glass vial containing the desired phosphine ligand (0.42 mmol, 1.05 equiv). The solution was agitated, and 2.0 equiv (relative to Ru) of $HBF_4{\cdot}OEt_2$ (20 mM in 1,2-dichloroethane) was added. The resultant solutions were agitated for 30 min and evaporated to dryness. A stock solution of the ene ester **4a** and $HBF_4{\cdot}OEt_2$ (at a ratio as determined in Table 1) was prepared in the appropriate screening solvent. The concentration of this stock solution was determined on the basis of achieving the desired substrate to catalyst ratio as given in Table 1 and a fixed addition of 150 μL to the 1 mL glass vial containing dried catalyst. Hydrogenations were carried out at 500 psig of H_2 and for a duration of 18 h. **Note:** For entries 1−7 in Table 1, the amount of $HBF_4{\cdot}OEt_2$ is the molar amount relative to substrate **4a** and does not include acid added during catalyst preparation.

For previous work on precatalysts and catalysts in this area, see: (a) Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131. (c) Currao, A.; Feiken, N; Macchioni, A; R. Nesper, R.; Pregosin, P. S.; Trabesinger, G. G. *Helv. Chim. Acta* **1996**, *79*, 1587. (d) Wiles, J. A.; Lee, C. E.; McDonald, R.; Bergens, S. H. *Organometallics* **1996**, *15*, 3782. (e) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genet, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992. (f) Wiles, J. A.; Bergens, S. H.; Vanhessche, K. P. M.; Dobbs, D. A.; Rautenstrauch, V. *Angew. Chem., Int. Ed.* **2001**, *40*, 914. (g) Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 331. (h) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. Reviews: (i) Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908. (j) Shultz, S. C.; Krska, S. K. *Acc. Chem. Res.* **2007**, *12*, 1320. (k) Inter alia: Blaser, H. U.; Spindler, F.; Thommen, M. Industrial Applications. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: New York, 2007; pp 1279−1324.

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