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Use of an Iridium-Catalyzed Redox-Neutral Alcohol–Amine Coupling on Kilogram Scale for the Synthesis of a GlyT1 Inhibitor

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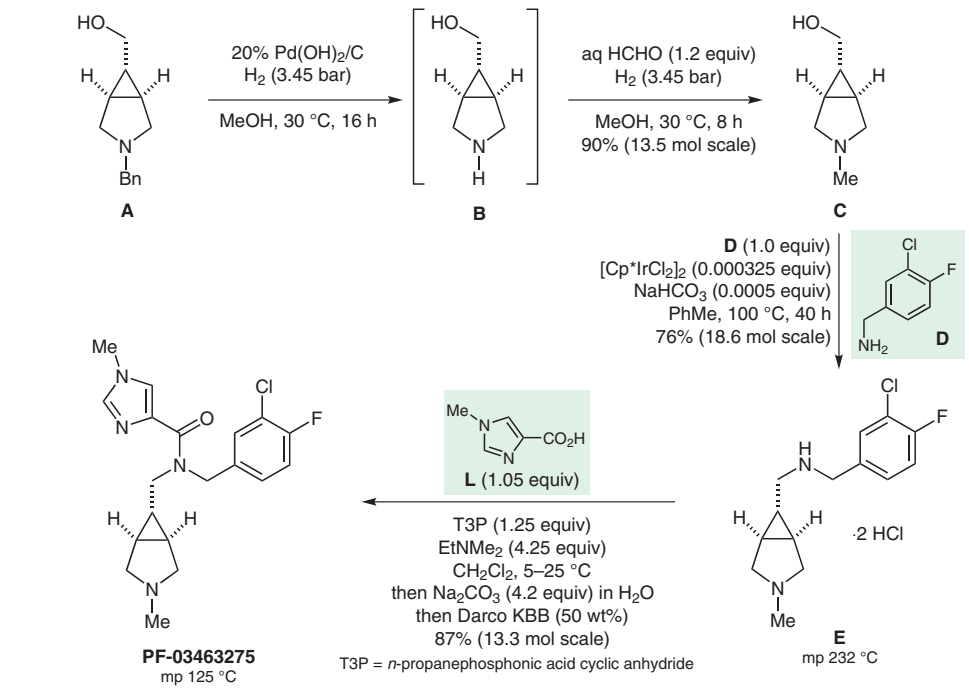
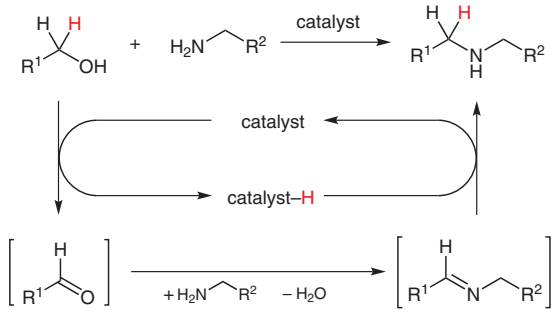
Synthesis of PF-03463275



Schematic representation of metal-catalyzed hydrogen borrowing:



Significance: PF-03463275 is a glycine transporter type 1 (GlyT1) inhibitor that has potential for the treatment of schizophrenia. The synthesis depicted features the first kilogram-scale application of iridium-catalyzed hydrogen borrowing to achieve the operational equivalent of reductive amination in the union of **C** and **D** to give **E**. The only byproduct of the reaction is water.

Comment: An extensive optimization study achieved a S/C of ≥2000 (i.e. lower than 0.05 mol% of catalyst), but the reaction tended to stall thereby requiring a second charge of catalyst. After this work was complete the authors discovered that water and a tertiary amine are essential for high catalyst activity resulting in high rates and complete conversion on a single charge.

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