Ligand-Based Proton and Electron Transfer Facilitated Electrocatalytic Hydrogenation of a Terminal Alkyne for the Synthesis of Alectinib

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The final reaction in Oki and coworkers' total synthesis of the Alectinib free base is the hydrogenation of its terminal alkyne. This is accomplished via the use of Pd/C and H_2, with a THF and MeOH solvent system. Only a 25% product yield was reported, which may be improved for production via the use of a replacement reaction.

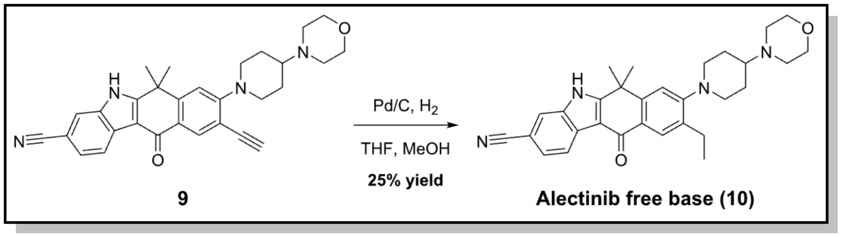

Fig 1: Oki and coworkers' synthesis of the Alectinib free base via use of a Pd/C and H_2 catalytic system.

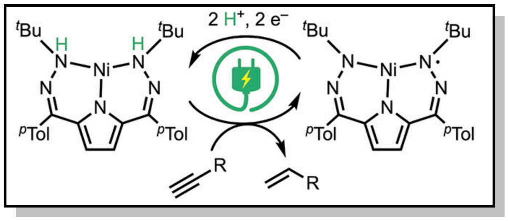

Fig 2: Czaikowski and coworkers' electrocatalytic system for the semihydrogenation of alkynes.

Because Oki and coworkers' Pd/C system only obtains yields of 25%, examining alternative catalytic systems may assist with the scaled-up production of the target compound. A potential system for this replacement is a modified version of Czaikowski and coworkers' electrocatalytic semihydrogenation via the use of a dihydrazonopyrrole Ni complex. This system is an interesting candidate for implementation due to its high selectivity for terminal alkynes over other functional groups and its electrocatalytic nature. Additionally, no evidence of oligomerization was found in the study of reactions using this catalyst.

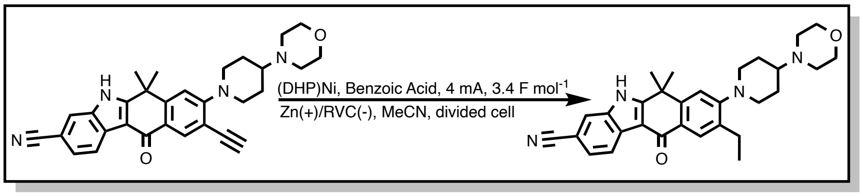

Fig 4: Proposed reaction scheme for the synthesis of the Alectinib free base using Oki and coworkers' electrocatalytic system.

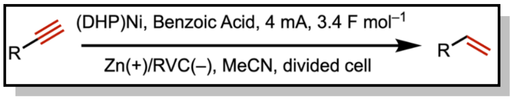

Fig 3: Czaikowski and coworkers' catalytic reaction scheme.

Electrocatalytic Semihydrogenation of Terminal Alkynes Using Ligand-Based Transfer of Protons and Electrons
Maia E. Czaikowski, Sophie W. Anferov, Alex P. Tascher, and John S. Anderson
Journal of the American Chemical Society 2024 146 (1), 476-486
DOI: 10.1021/jacs.3c09885

While Czaikowski and coworkers' electrocatalytic system is selective for terminal alkynes, the reaction conducts a semihydrogenation instead of a complete hydrogenation to an alkane. This reaction may be pushed in favor of a full hydrogenation by increasing the current density, increasing the quantity of the proton source (benzoic acid), increasing the residence time, and decreasing the concentration of the substrate. These changes, in addition to using a proton-exchange membrane (PEM), have been suggested by Askikari and coworkers as a means of facilitating the over-reduction of a semihydrogenation reaction.

Potential obstacles for the scale-up of this replacement reaction include the acquisition of the catalyst. Unlike Pd/C with H_2, the (DHP)Ni complex must first be synthesized as it is not a commercially available product. The cost of synthesizing the catalyst could be offset by avoiding consuming hydrogen gas and by using renewable energy to power the electrochemical process. Czaikowski and coworkers did not specify an isolation technique, however this replacement step does not incur additional purification risks. The Alectinib free base should be crystallized from solution and purified via column chromatography. Additionally, the modification of the semihydrogenation reaction into a full hydrogenation provides additional concerns for scalability. Despite the ability to over-reduce the substrate, the semihydrogenated alkene will remain a major product which must be separated via column. The vastly extended residence time to ensure full conversion alongside the required lower concentration provides additional obstacles for scaling, which leads to the conclusion that **this reaction is not suitable for process scale**. With optimization some improvements may be made, however this reaction will likely provide few additional advantages.

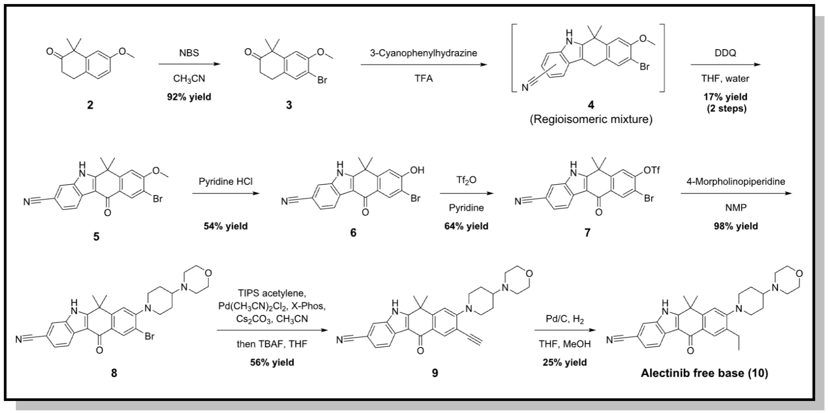

Fig 5: Total Synthesis of Alectinib as reported by Oki and coworkers.

Investigation of Parameter Control for Electrocatalytic Semihydrogenation in a Proton-Exchange Membrane Reactor Utilizing Bayesian Optimization.
Ashikari Y, Tamaki T, Takahashi Y, Yao Y, Atobe M and Nagaki A (2022)
Front. Chem. Eng. 3:819752. doi: 10.3389/fceng.2021.819752

Development of a Scalable Manufacturing Process for Alectinib with a Concise Preparation of the Indole-Containing Tetracyclic Core
Tomohiro Oki, Masao Tsukazaki, Junichi Shiina, Hiroshi Fukuda, Minoru Yamawaki, Yasushi Kito, Takenori Ishizawa, Kazutomo Kinoshita, Sosuke Hara, Noriyuki Furuichi, Hatsuo Kawada, Toshiya Ito, Kota Tanaka, Noriaki Maruyama, Daisuke Tamaru, Takahiro Ichige, Masatoshi Koizumi, Yosuke Hosoya, Masahiro Kimura, Mami Yamaguchi, Shigeki Sato, Yuta Miyazaki, Azusa Toya, Hiroshi Iwamura, and Kenji Maeda
Organic Process Research & Development Article ASAP, 2024
DOI: 10.1021/acs.oprd.4c00376