

CATALYTIC HYDROGENATION

An old reagent becomes a new precatalyst

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The archetypal reductant in organic chemistry is undeniably LiAlH_4 , which most often finds use in stoichiometric conversions of polar unsaturated substrates into saturated species. This methodology remains widespread despite its poor atom efficiency — the net addition of H_2 to a substrate first requires delivery of H^- from LiAlH_4 and then H^+ from a protic solvent. The environmental and economic consequences of this poor efficiency beg the question: can LiAlH_4 also serve as a catalyst for the addition of H_2 to organic molecules? LiAlH_4 catalytically hydrogenates alkynes and 1,3-dienes to their corresponding alkenes, but does so only under forcing conditions. More recent work has shown that LiAlH_4 is also a catalyst for the hydroboration of alkenes, ketones and aldehydes. Imines are of intermediate polarity, and a group led by Sjoerd Harder now describes in *Angewandte Chemie International Edition* a disarmingly mild methodology for their catalytic hydrogenation using LiAlH_4 .

The catalytic reduction of imines is typically the domain of precious metal catalysts, which can oxidatively add H_2 and transfer it to a substrate. Such H_2 homolysis contrasts the H_2 heterolysis that takes place between imines and the Lewis acid $\text{B}(\text{C}_6\text{F}_5)_3$, with the former first accepting H^+ and then H^- before becoming an amine. However, the search for another non-transition-metal hydrogenation catalyst continued because $\text{B}(\text{C}_6\text{F}_5)_3$ is neither cheap nor compatible with many nucleophiles. Amido hydrides $\text{MH}[\text{N}(\text{SiMe}_3)_2]$ ($\text{M}=\text{Mg}, \text{Ca}, \text{Sr}, \text{Ba}$) are catalysts for imine hydrogenation, so it seemed conceivable that LiAlH_4 — long known as a stoichiometric imine reductant — may also be a useful precatalyst. Harder's team found that catalytic amounts of LiAlH_4 , under merely 1 bar of H_2 pressure, convert neat aldimine substrates $\text{Ar}(\text{H})\text{C}=\text{NR}$ into the amines $\text{Ar}(\text{H})_2\text{C}-\text{NHR}$.

The team monitored reaction mixtures and performed independent syntheses of putative intermediates to support their proposed catalytic mechanism. “It is likely that two imine insertions into LiAlH_4 afford $\text{Li}(\mu\text{-H})_2\text{Al}[\text{Ar}(\text{H})_2\text{CNR}]_2$, an active species belonging to a well-studied class of diamido dihydrides,” notes Harder. The Lewis acidic Li can bind the N atom of an imine substrate, with concomitant attack of a bridging hydride ligand on the imine C atom resulting in a six-membered transition state. The resulting triamido hydride $\text{Li}(\mu\text{-H})\text{Al}[\text{Ar}(\text{H})_2\text{CNR}]_3$ is thought to heterolyze H_2 through a frustrated Lewis pair mechanism. In this key step, H_2 binds both the Lewis

acidic Li centre and the lone pair of an amido ligand, after which σ -bond metathesis liberates the amine product $\text{Ar}(\text{H})_2\text{C}-\text{NHR}$ and regenerates the diamido dihydride.

Of the substrates tested, it was $\text{Ph}(\text{H})\text{C}=\text{N}^t\text{Bu}$ that underwent hydrogenation the most smoothly, with Harder and colleagues using just 2.5 mol% LiAlH_4 to achieve >99% conversion in 2 h at 85 °C. Replacing Ph with electron-rich or electron-deficient aryls (or a bulky electron-releasing ^tBu group) resulted in lower yields. Similarly, the aliphatic ^tBu N-substituent proved crucial, and its replacement with Ph caused the reaction to be much slower because the amido ligands in the triamido hydride $\text{Li}(\mu\text{-H})\text{Al}[\text{Ar}(\text{H})_2\text{CNR}]_3$ are insufficiently basic to deprotonate H_2 and effect σ -bond metathesis. The methodology is presently limited to N-alkyl aldimines, with preliminary testing on alkene substrates being unsuccessful. Likewise, Harder admits that the conditions are unlikely to work for ketones because alkoxy intermediates are unlikely to deprotonate H_2 . Far from being discouraged, the team is conducting further *in silico* studies to unravel details of the imine hydrogenation. The cooperativity between one metal and a proximal metal amido might be generalizable. “A heterobimetallic mechanism for LiAlH_4 catalysis would be exciting in that the matrix for catalyst optimization could be enormous,” says Harder.

David Schilter

ORIGINAL ARTICLE Elsen, H. et al. LiAlH_4 : from stoichiometric reduction to imine hydrogenation catalysis. *Angew. Chem. Int. Ed.* <https://doi.org/10.1002/anie.201803804> (2018)

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