

Reversible interconversion between alkenes and nitriles without using HCN

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The structure of a nitrile: the functional group is highlighted blue. Credit: Wikipedia

Researchers from Max Planck Institute have devised a synthetic strategy that opens the door to many medically important molecules. Their strategy is a reversible reaction that converts alkenes to alkyl nitriles without using or producing noxious HCN gas. Their work appears in the recent issue of *Science*.

Alkyl nitriles are excellent reagents for many types of reactions. The nitrile group (-CN) is electron withdrawing, thus activating the neighboring atoms for various transformations. However, to add a nitrile group to a molecule typically requires a reaction with an alkene and HCN. Because HCN is highly toxic, corrosive, and explosive, it is impractical for the laboratory setting.

Xianjie Fang, Peng Yu, and Bill Morandi of Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr decided to explore the synthetic possibilities of a reversible hydrocyanation reaction by devising a scheme that is analogous to H₂-free transfer hydrogenation. In a hydrogenation reaction, a metal catalyst promotes the stereoselective addition of hydrogen to an alkene or carbonyl.

For this experiment, Fang, et al. used a nickel catalyst because nickel is known to be highly reactive in traditional hydrocyanation reactions using HCN, and nickel complexes are often used for the oxidative addition of polar bonds. After testing various catalysts and catalyst combinations, they found that a [nickel catalyst](#) generated in situ from Ni(COD)₂ and DPEphos along with an aluminum co-catalyst, AlMe₂Cl, worked best for their reaction plan. Notably Fang, et al. found that less flammable AlCl₃ could also serve as a co-catalyst.

They then selected model reagents to investigate how to thermodynamically control the forward and reverse reactions. Producing a gaseous product and releasing ring strain are two typical ways to drive the equilibrium of reaction forward. They used isovaleronitrile as their test reagent for producing a gas and norbornadiene as their test reagent for releasing ring strain. They found that these factors, plus the level of substitution on the hydrocyanation by-product, adequately drove the reaction forward. They also found that the product from the isovaleronitrile reaction could be used to test the reverse reaction.

In order to test the scope of the hydrocyanation reaction, they tested several styrene derivatives and found that products showed anti-Markovnikov regioselectivity. Typically, addition across an alkene will demonstrate Markovnikov regioselectivity in which the hydrogen adds to the least substituted carbon. Since the reverse is observed here, it is reasonable to assume that this is a reversible reaction in which the thermodynamic product is favored. Additional studies found that a wide

range of reagent types tolerated this reaction, including several heterocycles, non-activated linear alkenes, allylic alcohols, cycloalkanes, norbornenes, some alkynes, and several types of functional groups.

The retro-hydrocyanation reaction also has a broad range of reagents that are compatible with its test conditions. They were able to transform primary, secondary, and tertiary nitriles using various styrene derivatives. Additionally, Fang et al. combined their retro-hydrocyanation reaction with known organic mechanisms, demonstrating that their mechanism has practical advantages to current laboratory processes.

Mechanism studies with deuterium confirm that there is, indeed, a transfer between a hydrogen and the (-CN) group among the reagents. Furthermore, they confirmed that the reaction is reversible and reaches equilibrium under the reaction conditions.

"We believe that the current [reaction](#) is directly useful to research laboratories in both academia and industry and might find applications in fine chemicals synthesis," says principle investigator, Dr. Bill Morandi. The next step in their research, according to Dr. Morandi, involves refining their method for large scale applications, "There are a few aspects that need to be further developed, such as minimizing the amount of catalyst and recycling the alkene by-product."

Overall, the hydrocyanation mechanism is safer than traditional methods, reversible and thermodynamically controllable, exhibits specific regiochemistry, and works for a wide range of starting materials. This work has much potential for application in many organic syntheses including medicinal chemistry.

More information: X. Fang et al. Catalytic reversible alkene-nitrile interconversion through controllable transfer hydrocyanation, *Science*

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