

Well connected through amides

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Linking molecular components through amide bonds is one of the most important reactions in research and the chemical industry. In the journal *Angewandte Chemie*, scientists have now introduced a new type of reaction for making amide bonds. Called an ASHA ligation, this reaction is fast, efficient, works under mild aqueous conditions, and is broadly

applicable.

Amide bonds are the [bond](#) between a carbonyl carbon ($\text{C}=\text{O}$) and an organic nitrogen atom. It is [amide bonds](#) that link individual amino acids together into proteins and bind monomers into polyamide plastics like perlon and nylon. Many life-saving medicines such as taxol, lipitor and penicillin, as well as agrochemicals, biological conjugates, natural substances, and other products contain amide bonds. In addition to the classical method of production—the reaction of an acid group ($-\text{COOH}$) with an amino group ($-\text{NH}_2$)—a variety of different reactions have been developed for the formation of amide bonds. However, many of them are not broadly applicable due to a lack of chemoselectivity. They also require specialized coupling agents. New types of reactions are in demand.

A team led by Rajavel Srinivasan at Tianjin University (China) was searching for an efficient, sustainable method that starts with easily accessible materials and works fast. They chose a reaction between acylsilanes and hydroxylamines (a class of organic nitrogen compounds with an $-\text{N}-\text{O}-$ linkage). Acylsilanes are a class of organic silicon compounds with a general structural formula of $\text{R}(\text{CO})-\text{SiR}_3$. Their reactivity often differs completely from that of the related ketones. Although their chemistry is well known, they have previously rarely been used in the field of biomedical chemistry.

Based on their first letters, the reaction of acylsilanes with hydroxylamines is called an ASHA ligation. The [driving force](#) appears to be intramolecular migration of a silyl group from a carbon atom to an oxygen atom (Brook rearrangement), in which a strong $\text{Si}-\text{O}$ bond is formed.

The researchers successfully tested the ligation with a broad palette of different molecular building blocks, including pharmaceutical agents,

peptides, natural products, and other biologically active compounds. The reaction is chemoselective and works under mild conditions in an aqueous milieu. It produces [high yields](#) in the majority of cases and is tolerant toward most functional groups. New variants of ASHA ligation are in development for peptide synthesis as it did not work well.

However the simplicity and efficiency of the ASHA ligation should open pathways to new approaches in [medicinal chemistry](#) and [chemical biology](#), such as fragment-based drug development, in which active substances are built up successively from small fragments.

More information: Xingwang Deng et al, Chemoselective Amide-Forming Ligation Between Acylsilanes and Hydroxylamines Under Aqueous Conditions, *Angewandte Chemie International Edition* (2020). [DOI: 10.1002/anie.202012459](https://doi.org/10.1002/anie.202012459)

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