Fatty acids as substrates for new catalytic transformations

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Abstract

Most of the hitherto realized reactions of unsaturated fatty acids deal with the double bond in its original position [1,2]. Mainly the "classical" olefin reactivity is used for additions, metathesis and oxidation reactions, leading to e.g. amines, dicarboxylates, hydroxy acids and epoxides. Our concept: Fast double bond migration followed by selective functionalization of the isomers, this substrate can be seen as an ultimate benchmark for tandem isomerization-functionalization processes.

Intramolecular isomerization-lactonization

Applying our new concept, we screened a broad range of catalysts for their ability to migrate the double bond of our model compound 10-undecenoic acid. Simple Brønsted acids (TOSOH, HBF4, F3CCOHH), Lewis acids (AuCl3, AuI, CuF2, AgBF4, FeCl2, FeCl3) and even ruthenium hydride complexes showed no activity. We finally discovered that the use of triflate counter-ions is crucial for visible catalytic turnover, and thus we obtained γ-undecalactone in up to 55% yield at 160 °C without solvent. [5] After optimization of conditions and catalyst system, we were able to isolate the product in 71% yield when using 10 mol% silver triflate in refluxing chlorobenzene.

The yields of known lactonization protocols starting from fatty acids are low and usually involve the use of large quantities of corrosive and hazardous mediators. [6] Our reaction methodology offers the catalytic use of non-toxic silver salt without the need for such reagents.

Oleic acid as the ultimate benchmark

We next approached the even more challenging transformation of oleic acid to γ-stearolactone. With its 33 possible double-bond isomers, this substrate can be seen as an ultimate benchmark for tandem isomerization-functionalization processes.

Established transformations of unsaturated fatty acids use the double bond in its original position

Under the optimized conditions we directly obtained this product in 33% yield. With a catalyst loading of 15 mol%, γ-stearolactone was isolated in a remarkable 51% yield.

The protocol could even be extended to other carboxylic acids and a broad variety of primary, secondary, aliphatic and aromatic amines [7].

Synthesis of lactams via isomerization

An extension of this ring-closing methodology would be the access to lactams via double bond migration-intramolecular addition of unsaturated long-chain amides.

Ongoing work on isomerizations

Recently, we discovered a superior rhodium-based isomerization catalyst, which is able to establish an extremely fast equilibrium of ethyl oleate isomers with a loading of just 0.5 mol%. Moreover, we are further investigating new types of tandem reactions comprising a double bond migration with subsequent derivatization, such as Michael additions of various nucleophiles.

The ultimate goal would be the application of this new methodology to naturally occurring polysaturated fatty acids or even triglycerides.

Literature and Further Reading


Our concept: Fast double bond migration followed by selective functionalization

We approach the development of new transformations by utilizing the mobility of the double bond within unsaturated fatty acids. In the presence of certain acids or transition metal complexes, it should be possible to move the double bond along the chain and establish a fast equilibrium of positional isomers (3). A suitable reaction could then be found to selectively trap one single isomer out of the mixture (2), e.g. via addition reactions. This way, new functionalized products of high value and useful properties are accessible (3). Only few examples of this in situ isomerization of fatty acids followed by direct functionalizations are described, but they suffer from low yields and tedious product purification [3,4].

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