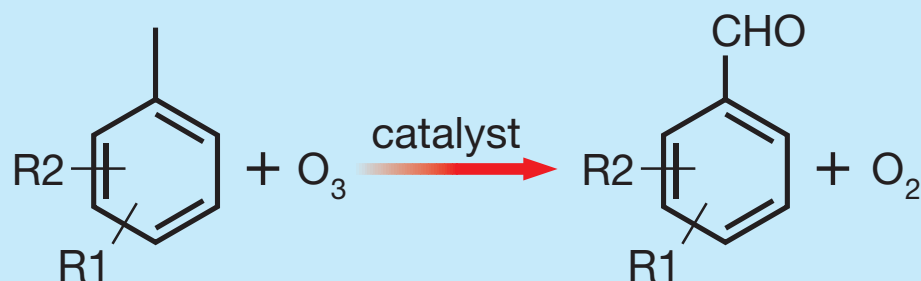


Transition Metal Catalysed Benzylic Oxidations with Ozone

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Oxidative transformations are basic to organic chemistry, and they are extensively used in the synthesis of fine chemicals. The majority of the processes employed industrially involve catalysis by metal complexes, and an increasing variety of catalytic processes has been developed for laboratory synthesis. Catalytic processes enjoy the advantages over their non-catalytic counterparts of proceeding efficiently under mild conditions, thus leading to more energy efficient processes. Furthermore, catalytic processes are generally more selective and instrumental for optimal utilization of raw materials. Unlike the stoichiometric oxidations with traditional oxidants such as permanganate or dichromate, the catalytic processes do not produce vast amounts

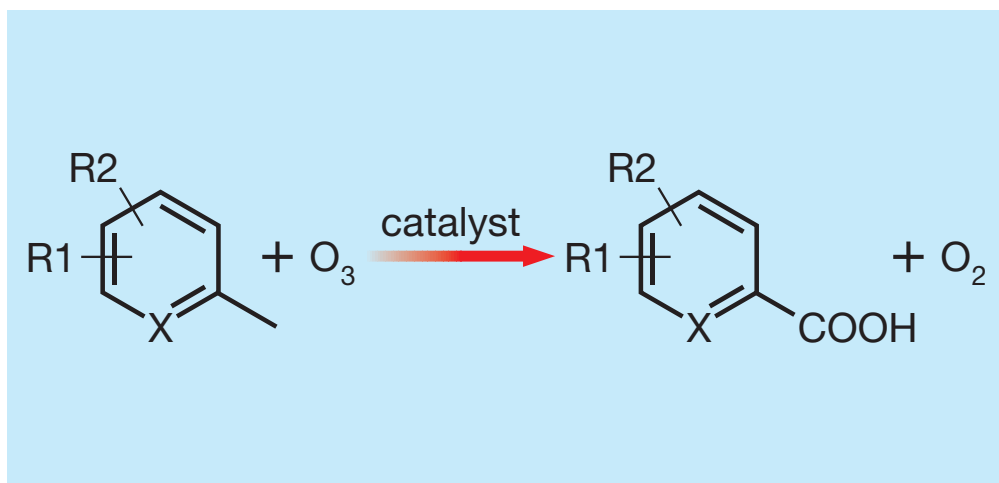
of inorganic effluents, which are difficult to dispose. As a result, the development of new, improved catalytic processes is a target for fine chemicals industry. Oxidative transformations involving ozone have been known for a long time, but only a limited number of different transformations, mainly the selective cleavage of double bonds, have been applied. Ozonisation in combination with catalysts is generally used in the wastewater treatment. We investigated the use of ozone in the presence of various catalysts and found that the combined use of a transition metals and ozone results in an industrially attractive and very powerful process for the oxidation of benzylic groups. In its simplest application, substituted toluenes are converted into the corresponding benzaldehydes.



Substrate	catalyst	conversion	yield	by-product
R1 = Br R2 = H	Mn(II)acetate	99 % (GC)	80 % (isolated)	8 % monoacetate
R1 = tert-butyl R2 = H	Mn(III)acetate	99 % (GC)	78 % (isolated)	9 % monoacetate
R1 = Br R2 = F	Mn(II)acetate	98 % (GC)	75 % (isolated)	8 % monoacetate

If the carboxylic acid is the desired product, acetic acid or aqueous mineral acids are used as solvents. For reactions in aqueous media, the starting material and product have to be soluble, e.g. salt formation.

For instance, we have converted 4-bromotoluene, 4-tert-butyltoluene, 4-bromo-2-fluoro-toluene or 2-methylpicoline into the corresponding acids.



After the solvent was distilled the desired acids were obtained by extraction. Losses of the product in the extractive work up are not optimised.

This process is environmentally friendly, because water can be used as the solvent, a manganese based non-toxic catalyst was used and oxygen is the only off gas of this process, which can easily be used in further ozone generation.

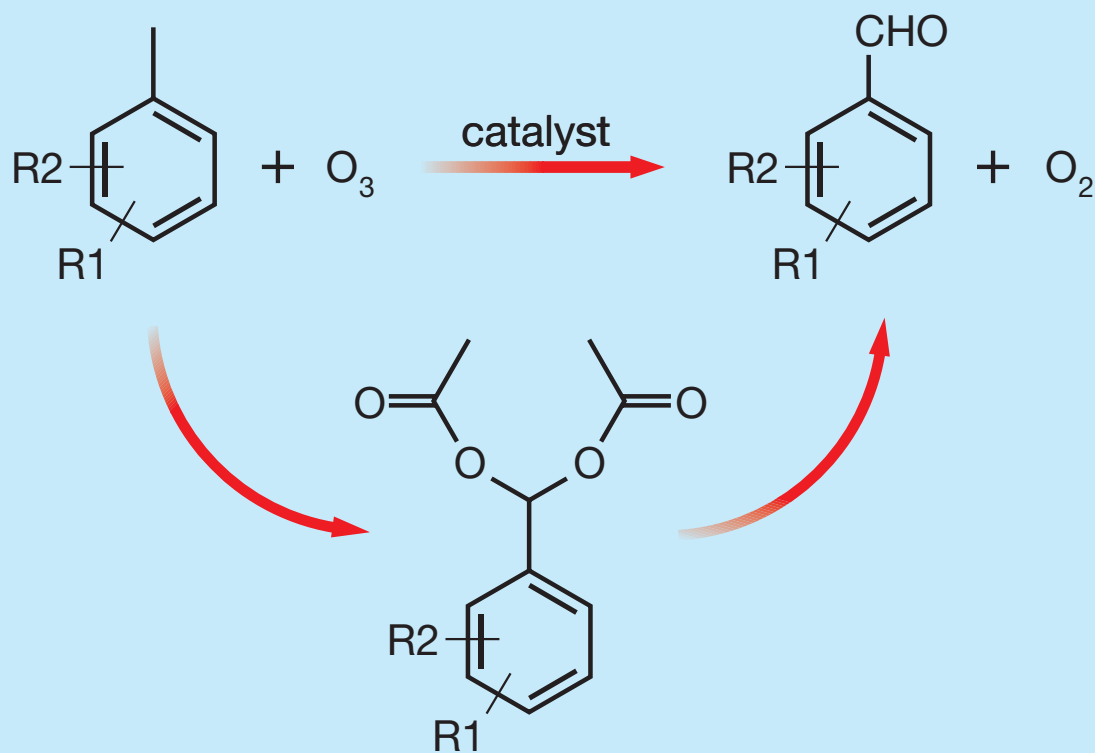
Substrate	catalyst	conversion	yield	solvent
R1 = Br R2 = H X = C	Mn(II)acetate	99 % (GC)	92 % (isolated)	acetic acid
R1 = tert-butyl R2 = H X = C	Mn(III)acetate	99 % (GC)	90 % (isolated)	acetic acid
R1 = Br R2 = F X = C	Mn(II)acetate	98 % (GC)	91 % (isolated)	acetic acid
R1; R2 = H X = N	Mn(III)acetate	30 % (HPLC)	not isolated	acetic acid or acetic acid water mixtures

The transformation avoids toxic off-gas emission related to similar oxidation methods, such as HNO_3 oxidations.

The oxidation of toluene derivatives can be directed either towards the aldehyde or the carboxylic acid as the main product, by a proper choice of the reaction conditions and selection of different solvents.

If the aldehyde is the desired product, the reaction is performed in acetic anhydride and primarily yields the acylal, which can be subsequently hydrolysed to the free aldehyde. Thus any over-oxidation is avoided!

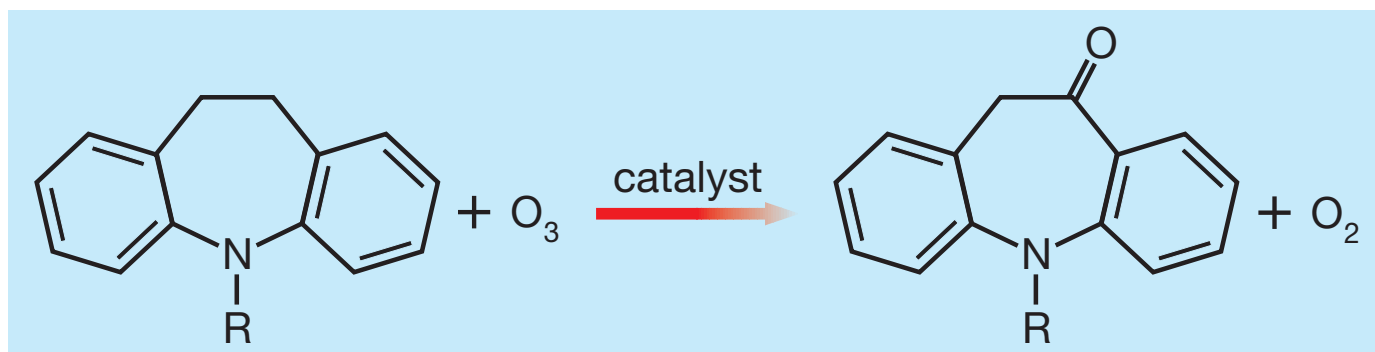
The desired aldehyde can be isolated via extraction or preferably via steam distillation. The only by-product, the mono acetate, which is stable under acidic conditions, remains in the mother liquid.



The method is furthermore suitable for the oxidation of some classes of toluene derivatives or other substrates with benzylic positions which are otherwise difficult to oxidize: Especially substrates containing 2 or more benzylic positions, which tend to over-oxidation were oxidised with this method in high selectivity and conversion.

A key feature of a new method in industrial fine chemical synthesis is its quick and general applicability to a relevant substrate. In order to study the usefulness of this novel industrial method, we selected the oxidation of benzazepine-derivatives as one of our model reactions.

These examples show that the transition metal catalysed oxidation with ozone fulfils the requirements to be called a sustainable oxidation process:



Starting with our “standard reaction” conditions using acetic anhydride as solvent, 10 mol % catalyst and 16°C reaction temperature only small amounts of the desired product was detected. Changing the reaction conditions by

- varying the reaction temperatures
- varying solvents (acetic acid, acetic anhydride or mixtures of it, varying concentration of aqueous H₂SO₄)
- varying the concentration of the catalyst, the

- It avoids toxic waste.
- The process off-gas is pure oxygen.
- Water can be used as the solvent, if not all other solvents can be recycled.
- The used catalyst is not toxic.
- It can be adapted to a variety of substrates within a short development time.
- And, in contrast to normal ozonolysis, no dangerous peroxide solutions are formed, which makes the process very safe.

nature of the catalyst (ligands), using different catalysts or mixtures of it (co-catalysts)
■ varying the ozone flow.

Selected experiments were performed twice in double to evaluate the reproducibility of the experiments. The reaction mixtures were sampled at defined intervals analysed by HPLC. Using optimised reaction conditions and stoichiometry we were able to increase the conversion of the azepine derivatives up to 99%.