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Oxidation of allylic and benzylic alcohols to aldehydes and carboxylic acids†

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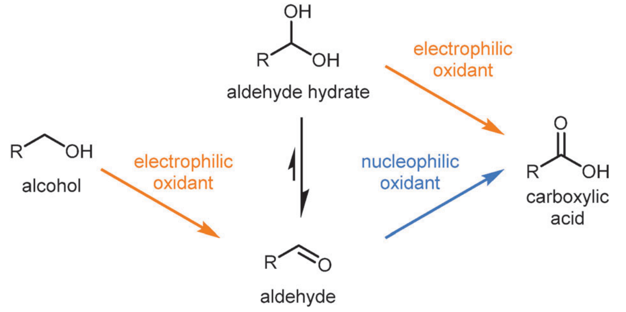
An oxidation of allylic and benzylic alcohols to the corresponding carboxylic acids is effected by merging a Cu-catalyzed oxidation using O_2 as a terminal oxidant with a subsequent chlorite oxidation (Lindgren oxidation). The protocol was optimized to obtain pure products without chromatography or crystallization. Interception at the aldehyde stage allowed for *Z*/*E*-isomerization, thus rendering the oxidation stereoconvergent with respect to the configuration of the starting material.

The direct oxidation of primary alcohols to their corresponding carboxylic acids is an important synthetic transformation that consists of two successive steps.[1] While the first step (alcohol to aldehyde) is usually performed with an electrophilic oxidant, the second oxidation (aldehyde to carboxylic acid) often involves a nucleophilic attack of the oxidant. Alternatively, it is possible to intercept the aldehyde–hydrate equilibrium with an electrophilic oxidant (Scheme 1). The latter strategy requires a significant population of the hydrate,[2] which is not very favorable in the case of aromatic aldehydes.[3]

Alcohol-to-carboxylic-acid oxidations can be conducted either in a one-pot fashion or as a two-step procedure with isolation of the intermediate aldehyde. Classical one-pot methods involve chromium-,[4] tungsten-[5] or ruthenium-based[6] oxidants as well as hypervalent iodine derivatives such as IBX.[7] The Zhao-modification[8] of Anelli's oxidation[9] (TEMPO, $NaClO_2$) constitutes another alternative but also has some drawbacks and, like the other above mentioned oxidants, may give rise to unwanted side reactions.

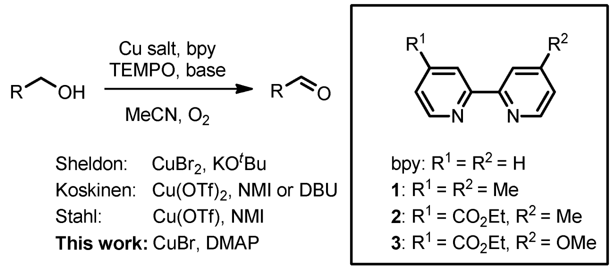
An elegant solution to these problems has been provided by using oxoammonium salts in combination with $NaClO_2$.[10] For sensitive substrates however, a two-step protocol is often preferred over the one-pot process using a mild oxidant (*e.g.* Dess–Martin periodinane[11]) for the initial oxidation to the aldehyde followed by Lindgren oxidation[12] ($NaClO_2$ as the oxidant) to give the desired carboxylic acid.



Scheme 1 Oxidation pathways of alcohols and aldehydes to carboxylic acids.

We recently investigated[13] the stereoconvergent conversion of *E*- and *Z*-allylic alcohols into *E*-α,β-unsaturated aldehydes following in the footsteps of Semmelhack,[14] Sheldon,[15] Markó,[16] Koskinen,[17] and Stahl[18] (Scheme 2). Our studies resulted in a protocol using 1 mol% Cu^IOTf/TEMPO/diMeObpy and DMAP (2 mol%) in acetonitrile as the solvent with oxygen as stoichiometric oxidant.

DMAP was shown to play an active role in both the oxidation reaction and the isomerization steps.[19] Herein, we report a two-step one-pot conversion of *E*- and *Z*-allylic alcohols into *E*-α,β-unsaturated carboxylic acids by joining a further refined Cu/TEMPO-catalyzed aerobic oxidation protocol[31,32] with Lindgren's oxidation.



Scheme 2 Development of Cu-catalyzed aerobic oxidation.

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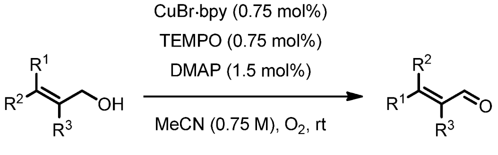
The goal in the first oxidation step (alcohol to aldehyde) was to lower the catalyst loading as much as possible in order to minimize interference with the subsequent steps. Our starting point was built upon important findings from Sheldon, Koskinen and Stahl. Sheldon found the accelerating effect of 2,2′-bipyridine (bpy) ligands while Koskinen's careful kinetic studies[17] established optimal ratios within the catalyst system. Recently, Stahl *et al.* demonstrated the importance of Cu^I salts[18] supported by mechanistic investigations. As a key result in their subsequent mechanistic studies,[20] aliphatic primary[21] and secondary alcohols[22] showed a clearly different behavior from allylic and benzylic primary alcohols.[33]

With our substrates limited to allylic and benzylic alcohols, we considered it necessary to re-evaluate Cu^I salts together with symmetrically (**1**) and newly synthesized[23] unsymmetrically substituted bpy ligands (**2–3**). Using **4a** as test substrate, we found that 0.5 mol% CuI or slightly more reactive CuBr and 1 mol% DMAP resulted in a quantitative conversion of the substrate within 3 h, whereas reactions using Cu(OTf) and CuCl were not complete within 5 h.

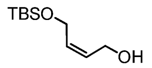
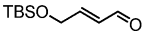
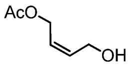
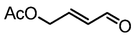
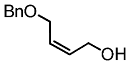
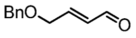
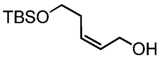
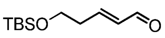
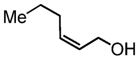
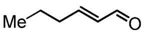
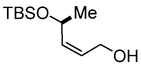
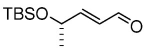
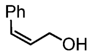
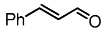
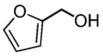
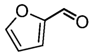
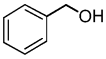
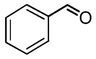
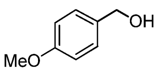
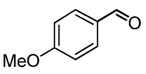
In order to compare the efficacies of different bpy derivatives, we further lowered the catalyst loading to 0.4 mol% CuBr·ligand·TEMPO and 0.8 mol% DMAP. The reaction using the parent 2,2′-bipyridine stopped at 70% conversion after 6 h. Ligand **1** afforded 90% conversion whereas the unsymmetrically substituted bipyridines **2** and **3** led to a quantitative conversion, with **3** being significantly faster than **2**. Despite these encouraging results, we selected 0.75 mol% CuBr·bpy·TEMPO and 1.5 mol% DMAP in MeCN (0.75 M) as our standard protocol for practical reasons, since we consider these reagents to be inexpensive and in stock in most organic laboratories.

As shown in Table 1, the oxidation of alcohols relevant to our synthetic endeavoura proceeded smoothly with TBS (**4a**), Ac (**4b**) and Bn (**4c**) protecting groups. The difference in the rate of oxidation is negligible, while the rate of the *Z*/*E*-isomerization is strongly dependent on the substitution of the Michael acceptor aldehyde. For substrates **4d–4f**, the catalyst loading was increased to 1 mol% in order to ensure complete oxidation. In order to accelerate the *Z*/*E*-isomerization (entries 4, 5 and 7) 9-azajulolidine,[24] a more nucleophilic analogue of 4-DMAP was used. The low yield of volatile aldehyde **5e** reflects the difficulties associated with its distillative purification. The oxidation of furfuryl alcohol **4h** and the benzyl alcohols **4i–j** afforded the corresponding aldehydes in moderate to excellent yields. With this protocol in hand, we next turned our attention to the development of a one-pot oxidation of the alcohols **4a–j** to the corresponding carboxylic acids. The Lindgren oxidation of aldehydes to the corresponding carboxylic acids with sodium chlorite is a straightforward reaction. However, the formation of the stronger oxidant hypochlorite as the by-product is often a source of side-reactions. As a result, a variety of hypochlorite scavengers[25] such as 2-methyl-2-butene[26,27] have been in use. In order to avoid by-products that are soluble in organic solvents and allow for the isolation of the clean carboxylic acids by extraction, we selected H_2O_2 as a scavenger that was previously used by Dalcanale and Montanari.[28] Since oxidation of **4a** with $NaClO_2/H_2O_2$ has been carried out in acetonitrile as the solvent by Sorensen *et al.* in their hirsutellone studies,[29] we were confident of combining both subsequent oxidation steps in a one-pot procedure.

Table 1 Oxidation of alcohols to aldehydes



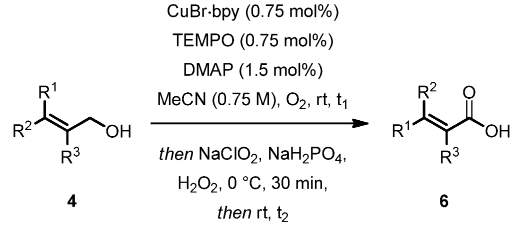
4 **5**

Entry	Alcohol	Aldehyde	*t* [h]	[%][a]
1	 **4a** (*E*:*Z* 1:99)	 **5a** (*E*:*Z* 99:1)	2.5	99
2	 **4b** (*E*:*Z* 1:99)	 **5b** (*E*:*Z* 99:1)	1.75	92
3	 **4c** (*E*:*Z* 1:99)	 **5c** (*E*:*Z* 99:1)	4	98
4[b,c]	 **4d** (*E*:*Z* 10:90)	 **5d** (*E*:*Z* 99:1)	25	89
5[b,c]	 **4e** (*E*:*Z* 3:97)	 **5e** (*E*:*Z* 99:1)	18	63
6[b]	 **4f** (*E*:*Z* 1:99)	 **5f** (*E*:*Z* 99:1)	17	97
7[c]	 **4g** (*E*:*Z* 2:98)	 **5g** (*E*:*Z* 99:1)	16.5	98
8	 **4h**	 **5h**	6	55
9	 **4i**	 **5i**	1	84
10	 **4j**	 **5j**	1	96

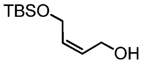
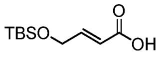
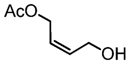
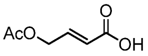
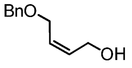
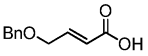
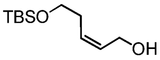
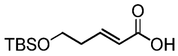
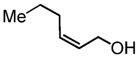
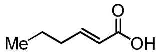
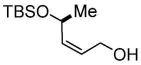
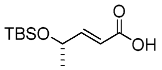
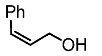
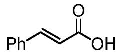
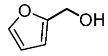
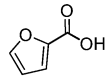
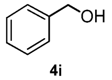
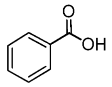
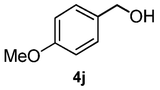
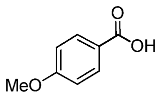
[a] Isolated yield. [b] 1 mol% catalyst loading. [c] 9-Azajulolidine was used instead of DMAP.

As shown in Table 2, after formation of the *E*-α,β-unsaturated aldehydes, a Lindgren oxidation was conducted without prior isolation of the aldehydes. The corresponding carboxylic acids were obtained in high purity and good to excellent yields without further chromatographic purification.[30] Furfuryl alcohol was the only problematic substrate in both oxidations. Skipping the isolation of the intermediate volatile aldehyde **5e** resulted in a clean conversion of **4e** into carboxylic acid **6e** and a higher yield (compared to **5e**).

Table 2 Oxidation of alcohols to carboxylic acids



4 6

Entry	Alcohol	Carboxylic acid	t_1 [h]	t_2 [h]	[%][a]
1	 **4a** (*E*:*Z* 1:99)	 **6a** (*E*:*Z* 99:1)	3	6.25	93
2	 **4b** (*E*:*Z* 1:99)	 **6b** (*E*:*Z* 99:1)	3	6.75	86
3	 **4c** (*E*:*Z* 1:99)	 **6c** (*E*:*Z* 99:1)	5	6	97
4[b,c]	 **4d** (*E*:*Z* 10:90)	 **6d** (*E*:*Z* 99:1)	15	19	94
5[b,c]	 **4e** (*E*:*Z* 3:97)	 **6e** (*E*:*Z* 99:1)	16	12	82
6[b]	 **4f** (*E*:*Z* 1:99)	 **6f** (*E*:*Z* 99:1)	15	12	95
7[c]	 **4g** (*E*:*Z* 2:98)	 **6g** (*E*:*Z* 99:1)	13	9	95
8	 **4h**	 **6h**	5	8.5	53
9	 **4i**	 **6i**	1	1.25	95
10	 **4j**	 **6j**	1	9	96

[a] Isolated yield. [b] 1 mol% catalyst loading. [c] 9-Azajulolidine was used instead of DMAP.

In conclusion, we have developed an inexpensive system for the aerobic oxidation of allylic and benzylic alcohols to the corresponding aldehydes and carboxylic acids. For the first time, submol% quantities of a Cu^I catalyst were sufficient for converting alcohols into the corresponding aldehydes. The subsequent oxidation to the corresponding carboxylic acids was performed in the same reaction vessel, thereby avoiding isolation of the labile aldehydes. The carboxylic acids were isolated by extraction with sufficient purity without the need for further chromatographic purification thus rendering this protocol both cost and time efficient.

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