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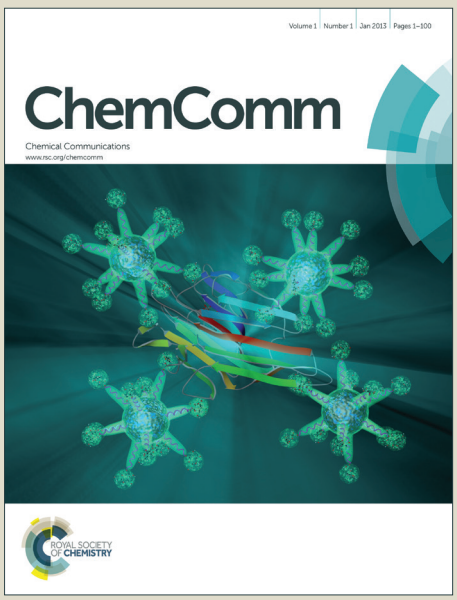

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COMMUNICATION

Oxidation of Allylic and Benzylic Alcohols to Aldehydes and Carboxylic Acids†

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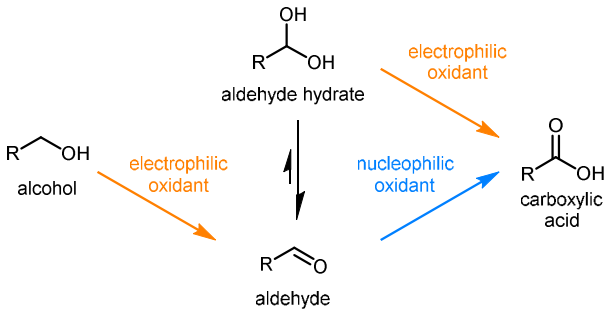
An oxidation of allylic and benzylic alcohols to the corresponding carboxylic acids is effected by merging a Cu-catalyzed oxidation using O_2 as terminal oxidant with a subsequent chlorite oxidation (Lindgren oxidation). The protocol was optimized to obtain pure products without chromatography or crystallization. Interception at the aldehyde stage allowed for a *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. The latter strategy requires significant population of the hydrate,[2] which is not very favorable in 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, $NaClO_2$)



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

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 a Lindgren oxidation[12] ($NaClO_2$ as oxidant) to give the desired carboxylic acid.

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] Our studies resulted in a protocol using 1 mol% $Cu^{I}OTf$/TEMPO/diMeObpy and DMAP (2 mol%) in

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† Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic data for all compounds. See DOI: 10.1039/b000000x/

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3 J. C. Qiu, P. P. Pradhan, N. B. Blanck, J. M. Bobbitt, W. F. Bailey, *Org. Lett.* 2012, **14**, 350.
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10 M. Shibuya, T. Sato, M. Tomizawa, Y. Iwabuchi, *Chem. Commun.* 2009, 1739.
11 D. B. Dess, J. C. Martin, *J. Org. Chem.* 1983, **48**, 4155.
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15 R. A. Sheldon, I. W. C. E. Arends, G.-J. ten Brink, A. Dijksman, *Acc. Chem. Res.* 2002, **35**, 774.
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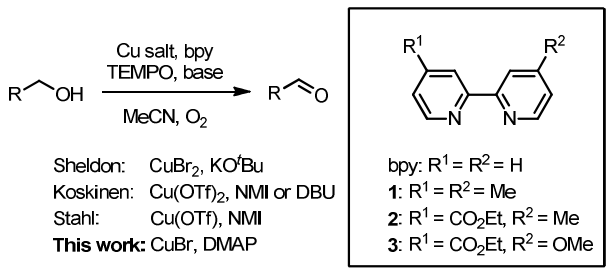
18 J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* 2011, **133**, 16901.

acetonitrile as the solvent with oxygen as stoichiometric oxidant.



Scheme 2 Development of Cu-catalyzed aerobic oxidations.

DMAP was shown to play an active role in both, the oxidation reaction as well as the isomerization step.[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-catalyzed oxidation protocol with Lindgren's oxidation.

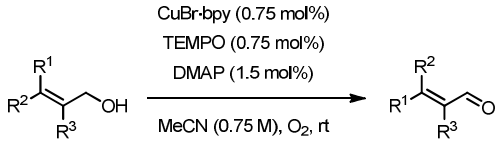
Results and Discussion

The overall goal in the first oxidation step (alcohol to aldehyde) was to lower the catalyst loading as far as possible in order to minimize interference with subsequent steps. Our starting point 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 one 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.

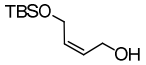
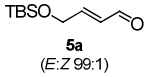
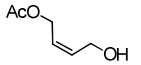
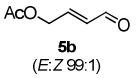
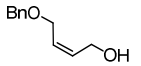
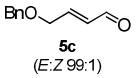
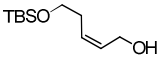
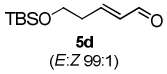
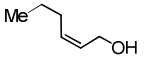
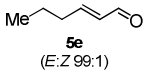
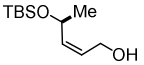
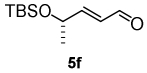
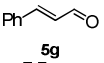
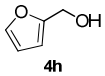
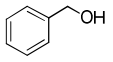
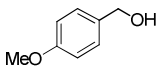
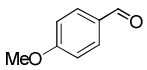
With our substrates limited to allylic and benzylic alcohols, we considered it necessary to re-evaluate Cu^{I} salts together with symmetrically(**1**) and newly synthesized[23] unsymmetrically substituted bpy ligands (**2**-**3**). Using **4a** as test substrate, we found that 0.5 mol% CuI or slightly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

In order to compare the efficacy 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** gave 90% conversion whereas the unsymmetrically substituted bipyridines **2** and **3** led to 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) for practical reasons as our standard protocol since we regard these reagents as inexpensive and in stock at most organic laboratories.

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 1, the oxidation of the alcohols relevant to our total synthesis proceeded smoothly with TBS (**4a**), Ac (**4b**) and Bn (**4c**) protecting groups. The difference in the rate of oxidation is negligible, while rate of the *Z*/*E*-isomerization is strongly dependent on the substitution of the Michael acceptor aldehyde. For the 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] as a more nucleophilic analogue of 4-DMAP was used. The lower yield of the volatile aldehyde **5d** reflects the difficulties associated with its distillative isolation. The oxidation of furfuryl alcohol **4h** and the benzyl alcohols **4i**-**j** afforded the corresponding aldehydes in moderate to excellent yields. With

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20 J. M. Hoover, B. L. Ryland, S. S. Stahl, *J. Am. Chem. Soc.* 2013, **135**, 2357.
21 J. E. Steves, S. S. Stahl, *J. Am. Chem. Soc.* 2013, **135**, 15742.
22 M. B. Lauber, S. S. Stahl, *ACS Catal.* 2013, 2612.
23 S. Duric, C. C. Tzschucke, *Org. Lett.* 2011, **13**, 2310.
24 I. Held, S. Xu, H. Zipse, *Synthesis* 2007, 1185.

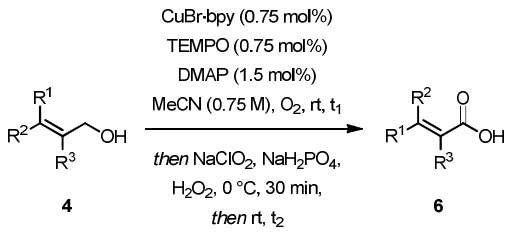
this protocol in hand, we next turned our attention to the development of a one-pot oxidation of the alcohols **4a-j** to the corresponding carboxylic acids. The Lindgren oxidation of aldehydes to the corresponding carboxylic acids with sodium chlorite is a straightforward reaction. However, the formation of the stronger oxidant hypochlorite as 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 scavenger previously used by Dalcanale and Montanari.[28] Since an 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 to join both subsequent oxidations steps as a one-pot procedure.

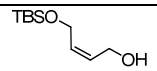
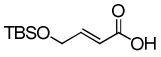
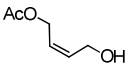
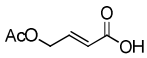
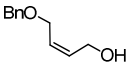
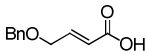
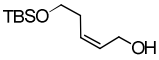
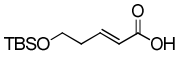
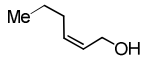
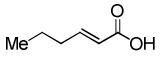
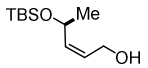
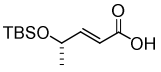
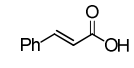
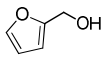
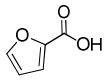
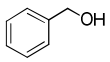
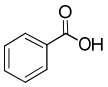
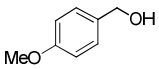
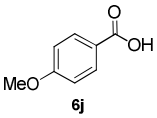
As shown in Table 2, after completion of the formation of the *E*-α,β-unsaturated aldehydes, a Lindgren oxidation was conducted without prior isolation of the aldehydes. The corresponding carboxylic acids were obtained in high purity and good to excellent yields without further need of chromatography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

Conclusions

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 to 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 in sufficient purity without the need of further chromatographic purification thus rendering this protocol both cost- and time-efficient.

Table 2 Oxidation of alcohols to carboxylic acids.



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.

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30 The NMR spectra of the carboxylic acids shown in the Supporting Information were recorded on the crude material obtained after extractive workup.