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On the Role of CO₂ in NHC-Catalyzed Oxidation of Aldehydes

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Abstract

NHC-catalyzed oxidations using carbon dioxide as the stoichiometric oxidant have been carefully investigated. These studies support a secondary role of CO₂ in suppressing side reactions and exogenous oxygen as the actual oxidant.

Recent communications reported the intriguing oxidation of aldehydes using N-heterocyclic carbenes as catalysts and carbon dioxide as the stoichiometric oxidant (eq 1).¹ These reports postulated that CO₂ is reduced to CO under catalytic conditions, a process that would be an attractive approach to CO₂ fixation provided that an inexpensive aldehyde reaction partner could be identified. At least two different mechanisms have been proposed, one involving addition of the catalyst to the aldehyde to form the nucleophilic Breslow intermediate² and one which proposed direct activation of CO₂ by the NHC. Similar reports of NHC-mediated reduction of CO₂ with silanes have also generated considerable interest.³

(1)

We were particularly intrigued with these findings as they were contrary to the usual chemistry of NHC-catalyzed reactions of α -ketoacids, which generate aldehydes and CO₂.⁴ One postulated mechanism involved oxygen atom transfer from CO₂ to the aldehyde, a process that is counterintuitive and thermodynamically questionable.⁵ Given our interest in the chemistry of NHC catalysis and the current importance of new catalytic methods for CO₂ fixation,^{3,6} we have investigated these reactions further. Through these extensive studies, we conclude that the actual oxidant in these reactions is exogenous oxygen.^{7,8}

Our studies began with a careful investigation of the CO₂ fixation reaction with the goal of using labelled CO₂ as a mechanistic probe. Despite dozens of attempts, we were unable to reproduce the reported yields and observations of either Zhang (entries 1–3) on the oxidation of freshly purified cinnamaldehyde to cinnamic acid or those Nair on the oxidation of either cinnamaldehyde or *para*-fluorobenzaldehyde (entry 4 and Supporting Information).^{9,10} After extensive optimization, we found that reproducible formation of cinnamic acid could be achieved under slightly modified Zhang conditions: with 5 mol % IMesCl (**3**) and 2 equiv K₂CO₃ in DMF (entries 5–8). Rigorously dried reaction conditions gave lower yields or irreproducible production of cinnamic acid, which was overcome by the addition of a small

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

amount of water (1 equiv).^{8,11} To be consistent with Zhang's experiments, we also attempted the reactions for 3 days, which gave slightly higher conversions under all conditions (entry 6). Higher concentration did not provide improved results due to competing dimerization and other side reactions (entry 7). A more extensive list of reaction conditions attempted can be found in the Supporting Information. Unpurified NMR spectra from the reaction mixtures under various atmospheres show clean formation of the acid under air, trace conversion under CO₂, and the formation of byproducts under N₂ or vacuum.¹²

Our studies confirmed that IMesCl (**3**) was essential for formation of the carboxylic acid product; only trace amounts of cinnamic acid were observed in its absence (entry 8). Triazolium precatalysts favored the formation of hydrocinnamic acid *via* the known internal redox reaction (entry 9).¹³ The increased formation of hydrocinnamic acid under CO₂ is likely due to the formation of carbonic acid that serves as the proton source for β -protonation. Thiamine, a thiazolium salt, did not give significant amounts of any product (entry 10). Control experiments and careful analysis of the reaction mixtures and products excluded a Cannizzaro-type reaction¹⁴ as the origin of the cinnamic acid.

The use of air as an oxidant in NHC-catalyzed oxidations of electron-deficient aldehydes to acids and esters has been previously reported by Yoshida using a slightly different imidazolium catalyst.⁸ Their mechanistic proposal invokes the formation of an acyl azolium, which undergoes esterification or hydrolysis. This mechanism is consistent with numerous reports of NHC-catalyzed oxidative esterification of aldehydes with oxidants including azobenzene,¹⁵ diphenoquinone,¹⁶ and MnO₂.¹⁷ To test if our observations followed this proposal, we conducted the reaction under air in the presence of MeOH; to our surprise only the acid, rather than the expected ester was detected (entry 11). In contrast, the use of *trans*-azobenzene as the oxidant afforded cinnamic acid in the presence of water (entry 12) and methyl cinnamate in the presence of MeOH (entry 13). These observations indicate that under these conditions the oxidation occurs by addition of the NHC-aldehyde complex to molecular oxygen rather than oxidation of the Breslow intermediate to the acyl azolium.¹⁸

The only experimental observation of both Zhang and Nair that is not consistent with exogenous air acting as the oxidant is their detection of CO at the completion of the reaction. According to the experimental procedures, this was achieved by injecting the residual gas in the balloon of CO₂ into a solution of PdCl₂ in acidic water. After 2 hr of stirring, the formation of Pd black was taken as an indication that CO was present in the reaction atmosphere. The long reaction times needed for formation of Pd black suggested to us that factors other than CO may be responsible for its formation.¹⁹

Although all of these results strongly suggested that CO₂ was not playing a direct role in the reaction, we consistently noted that reactions performed under a CO₂ atmosphere were cleaner, albeit with lower conversion, than those conducted under N₂ or in completely degassed solvents. We postulated that CO₂ played a role in reducing the formation of side products, possibly by attenuating the activity of the N-heterocyclic carbenes.²⁰ This could deter, for example, the formation of benzoin,²¹ Stetter,²² or especially γ -lactone products²³ that could be the origin of the messy reaction mixtures observed when conducted under a N₂ atmosphere. To test this hypothesis, we examined the effect of CO₂ on a different NHC-catalyzed reaction, the formation of cyclopentenones from the same substrate (cinnamaldehyde, **1**) and chalcone (**8**) in the presence of either imidazolium or triazolium precatalysts (Table 2).²⁴ These experiments revealed a pronounced rate deceleration in the presence of CO₂, diminishing product formation but without causing the formation of side products. This effect was also observed on the oxidation of cinnamaldehyde using azobenzene under CO₂ (Table 1, entry 12).

We have previously found that cinnamaldehydes are particularly prone to air oxidation in the presence of NHC-catalysts.^{13a} To confirm this, we briefly explored the application of the open-air oxidation conditions to other substrate classes (Scheme 1).

In general, we observed results similar to the reported CO₂ conditions: cinnamaldehyde gave quantitative yield of the corresponding acid and reasonable isolated yields of carboxylic acids were obtained from simple aromatic aldehydes. Aliphatic and sterically hindered aldehydes gave lower conversions. These observations are consistent with a number of reports of NHC-catalyzed oxidations of aldehydes with air or added stoichiometric oxidants.^{7,8,15–17}

In light of these investigations, we conclude that the apparent NHC-catalyzed oxidation of aldehydes with CO₂ actually involves exogenous O₂ as the stoichiometric oxidant. The observed effect of CO₂ lies in a reduction of the side products formed by aldehyde dimerization or oligomerization under the reaction conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
¹H NMR comparison in different atmospheres.

Scheme 1. Substrate scope of aerobic oxidation of aldehydes.^a^a All of the reactions were carried out in 0.5 mmol scale; isolated yields of pure products after acid-base extraction ^b 10 mol % IMesCl was used.

Table 1

Oxidation of cinnamaldehyde with NHCs.

entry	conditions	CO ₂ ^a	N ₂ ^a	air ^a
1	dry, K ₂ CO ₃ (2 equiv), DMSO	8%	4%	–
2	dry, K ₂ CO ₃ (2 equiv), DMF	4%	3%	–
3	dry, <i>t</i> -BuOK ((2 equiv), DMF	8%	45%	–
4	dry, DBU (20 mol %), THF ^b	10%	20%	13%
5	as shown in reaction scheme	14%	23%	57%
6	0.1 M/ 3 days	17%	27%	64%
7	0.5 M/ 3 days	14%	40%	32%
8	without NHC precatalyst	2%	1%	0%
9	triazolium cat. 4 ^c (5 mol %)	12% ^e	15% ^f	–
10	thiazolium cat. 5 ^d (5 mol %)	5%	2%	2%
11	dry, MeOH (2 equiv)	–	–	64%
12	<i>trans</i> -azobenzene (1.0 equiv)	21%	52%	–
13	MeOH (2 equiv), azobenzene	0% ^g	0% ^h	–

^a See Supporting Information for detailed conditions. Conversion to cinnamic acid **2** was calculated from ¹H NMR of crude mixtures.^b Purged with a slow stream of gas for 30 min. Hydrocinnamic acid was the major product regardless of reaction atmospheres.^c 1,4-Dimethyl-4*H*-1,2,4-triazol-1-ium iodide (**4**, CAS No. 120317-69-3) was used.^d Thiamine•HCl (**5**, CAS No. 67-03-8) and 3 equiv K₂CO₃ were employed.^e 92% yield of hydrocinnamic acid.^f 30% yield of hydrocinnamic acid.^g 4% yield of methyl cinnamate.^h 44% yield of methyl cinnamate.

Table 2CO₂ effect in NHC-catalyzed annulation.

entry	conditions	yield of cyclopentene
1	CO ₂ , IMesCl	8%
2	N ₂ , IMesCl	59%
3	CO ₂ , RMeScI	36%
4	N ₂ , RMeScI	62%