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Copper-catalyzed hydroformylation and hydroxymethylation of styrenes†‡

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Hydroformylation catalyzed by transition metals is one of the most important homogeneously catalyzed reactions in industrial organic chemistry. Millions of tons of aldehydes and related chemicals are produced by this transformation annually. However, most of the applied procedures use rhodium catalysts. In the procedure described here, a copper-catalyzed hydroformylation of alkenes has been realized. Remarkably, by using a different copper precursor, the aldehydes obtained can be further hydrogenated to give the corresponding alcohols under the same conditions, formally named as hydroxymethylation of alkenes. Under pressure of syngas, various aldehydes and alcohols can be produced from alkenes with copper as the only catalyst, in excellent regioselectivity. Additionally, an all-carbon quaternary center containing ethers and formates can be synthesized as well with the addition of unactivated alkyl halides. A possible reaction pathway is proposed based on our results.

Introduction

Hydroformylation was discovered by Otto Roelen in 1938 for the synthesis of aldehydes by the addition of syngas (a mixture of CO and H$_2$) to olefins (Scheme 1, eqn (a)).[1,2] As one of the most important homogeneously catalyzed industrial processes, millions of tons of aldehydes and related chemicals including bulky compounds and fine chemicals are produced annually by transition metal-catalyzed hydroformylation of alkenes.[3,4] Although several transition metal catalysts have been explored in this transformation,[5] most of the applied procedures use rhodium or cobalt catalysts.[6] Rhodium catalysts are applied due to their exceptionally high catalytic reactivity, but the high cost of rhodium is considered a significant disadvantage. Hydroformylation was originally discovered by the use of a non-expensive cobalt catalyst;[7] however, the connected regioselectivity issues of cobalt, which give a mixture of linear and branched products, and its inert state with ligand tuning diminished its applicability and diversity.[8]

On the other hand, copper is known as an environmentally benign metal catalyst that is non-expensive and abundant and has been extensively explored and applied in various organic transformations.[9] Its outstanding catalytic activity in cross-coupling chemistry (with bond formation including C–N, C–O, *etc.*) is even better than that of noble metal catalysts such as palladium. Its powerful catalytic ability can also be proven by the known named reactions based on copper catalysts, for example the Chan–Lam reaction, Ullmann coupling, Glaser reaction, and so on.[10–13] In particular, copper(I) hydride reagents have played a great role in organic synthesis as a long-established complex, especially in reduction reactions.[14,15] In recent years, copper(I) hydride complex catalyzed carbonylative coupling reactions have been explored by

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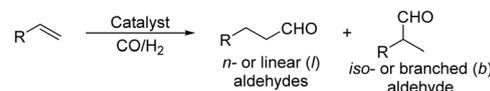
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Scheme 1 (a) Hydroformylation reaction of alkenes. (b) Hydroxymethylation of alkenes. (c) This work.

Mankad's group,[16–20] our group,[21,22] and others.[23–25] Notably, the groups of Yu[24a] and Tsuji[24b] have explored copper catalyzed hydroxymethylation of the C–C double bond with CO_2 for the synthesis of alcohols by using silanes as the reducing agent and hydride source. Wang and co-workers developed a Ni/Cu-catalyzed carbonylation of acetylene to acrylic acid in 2009.[25] Under their best reaction conditions, the selectivity and conversion can reach up to 90%. However, a copper catalyst has not yet been reported in hydroformylation reactions of alkenes with syngas.

Herein, a copper-catalyzed hydroformylation has been realized (Scheme 1, eqn (c)). Remarkably, by using a different copper precursor, the aldehydes obtained can be further hydrogenated to give the corresponding alcohols under the same conditions, formally named as hydroxymethylation of alkenes, which was usually catalyzed by ruthenium (Scheme 1, eqn (b)).[26–29] Under pressure of syngas, various aldehydes and alcohols can be produced effectively from alkenes with copper as the only catalyst in excellent regioselectivity. Additionally, an all-carbon quaternary center containing ethers and formates can also be formed in a one-step

manner by adding alkyl halides as the fourth reaction partner.

In order to establish this new catalyst system, styrene was chosen as the model substrate and systematic optimization studies were performed (for optimization details, see the ESI‡). Under our optimized reaction conditions, by using DPPP as the ligand and NaO^{t}Bu as the base in toluene at 100 °C, 2-phenylpropan-1-ol and 2-phenylpropanal can be produced selectively under pressure of syngas with different copper precursors (CuCl produces **3a** and CuCN produces **2a**). In the catalytic system with CuCN as the catalyst for 2-phenylpropanal production, the selectivity between **2a** and **3a** decreased at lower temperature while reaction efficiency dropped at higher temperature (Table 1, entries 2–3). Different phosphine ligands were also used; however, their use decreased both reaction efficiency and selectivity (Table 1, entries 4–6). In the testing of solvents, toluene proved to be the best reaction medium for this transformation (Table 1, entries 7–11). Interestingly, by using CuCl as the catalyst, 2-phenylpropan-1-ol **3a** can be produced as the main product, which is obviously formed by the hydrogenation of the

Table 1 Variations from the optimized reaction conditions^a

Entry	Variation from the standard conditions for 2a	Conv of 1a	2a:3a	Yield
1	—	91%	92/8	68%
2	90 °C instead of 100 °C	92%	73/27	66%
3	110 °C instead of 100 °C	88%	94/6	57%
4	DPPE instead of DPPP	59%	88/12	33%
5	DPPB instead of DPPP	60%	87/17	32%
6	DPPF instead of DPPP	73%	86/14	57%
7	o-Xylene instead of toluene	88%	76/24	73%
8	Cyclohexane instead of toluene	87%	76/24	42%
9	Benzene instead of toluene	84%	74/26	68%
10	Ethylbenzene instead of toluene	69%	74/26	65%
11	Methoxybenzene instead of toluene	75%	80/20	69%
Variation from the standard conditions for 3a				
12	—	86%	<1/99	68%
13	CuBr instead of CuCl^b	95%	<1/99	54%
14	CuBr·DMS instead of CuCl^b	91%	<1/99	48%
15	Cyclohexane (1.8 mL), toluene (0.2 mL) as solvent	92%	<1/99	58%
16	Xantphos instead of DPPP^b	100%	25/75	16%
17	DPPE instead of DPPP^b	61%	75/25	28%
18	DPPB instead of DPPP^b	85%	58/42	51%
19	DPPF instead of DPPP^b	100%	80/20	51%

^{a} Conditions A: CuCN (3.1 mg, 8 mol%), DPPP (21.3 mg, 12 mol%), NaO^{t}Bu (93 mg, 2.25 equiv), toluene (2.0 mL), styrene **1a** (50 μL, 0.43 mmol), CO (20 bar), H$_2$ (10 bar), 100 °C, 20 h; conditions B: CuCl (3.4 mg, 8 mol%), DPPP (21.3 mg, 12 mol%), NaOtBu (93 mg, 2.25 equiv), toluene (2.5 mL), styrene **1a** (50 μL, 0.43 mmol), CO (10 bar), H$_2$ (20 bar), 100 °C, 24 h. Conversion of styrene, the ratio of **2a** and **3a**, and the yields were measured by GC using hexadecane as the internal standard. ^{b} Cyclohexane (1.8 mL), toluene (0.2 mL) as solvent, 20 h. DPPE: 1,2-bis(diphenylphosphino)ethane. DPPP: 1,3-bis(diphenylphosphino)propane. DPPB: 1,4-bis(diphenylphosphino)butane. DPPF: 1,1′-bis(diphenylphosphino)ferrocene. CuBr·DMS: copper(I) bromide dimethyl sulfide complex. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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hydroformylation product. In order to facilitate the hydrogenation step, the ratio of CO and H_2 was modified and 68% yield of **3a** was finally achieved. Copper salts, organic solvents and phosphine ligands were screened; without exception no better results can be obtained concerning reaction selectivity and efficiency (Table 1, entries 13–19). It is important to mention that ethylbenzene can be detected as the main by-product during the optimization process. By the addition of a catalytic amount of KCN or NaCN into the CuCl catalytic system, the aldehyde can immediately become the main product. Hence, the coordinating behavior of –CN plays an important role in the reaction selectivity. The possible effects of rhodium and cobalt impurities have been considered as well, and control experiments and ICP measurements were carried out to exclude their presence and ensure that they don't act as the real catalysts here (for details, see the ESI‡).

Under our best reaction conditions, the testing of different substrates was subsequently carried out. Under the reaction conditions for aldehydes production, various styrenes were tested (Table 2). Substrates with various substituents were tested and converted into the desired aldehydes with moderate to good yields. Notably, substrates containing a terminal aliphatic alkene group can also be well tolerated (**2v** and **2w**). This reaction can be easily enlarged to the 5 mmol scale without losing reaction efficiency and selectivity. Complexed alkenes can be applied under our standard conditions without any problem. A one-pot two-step synthesis of Naproxen (**2u′**) via Pinnick oxidation was proven to be possible as well.
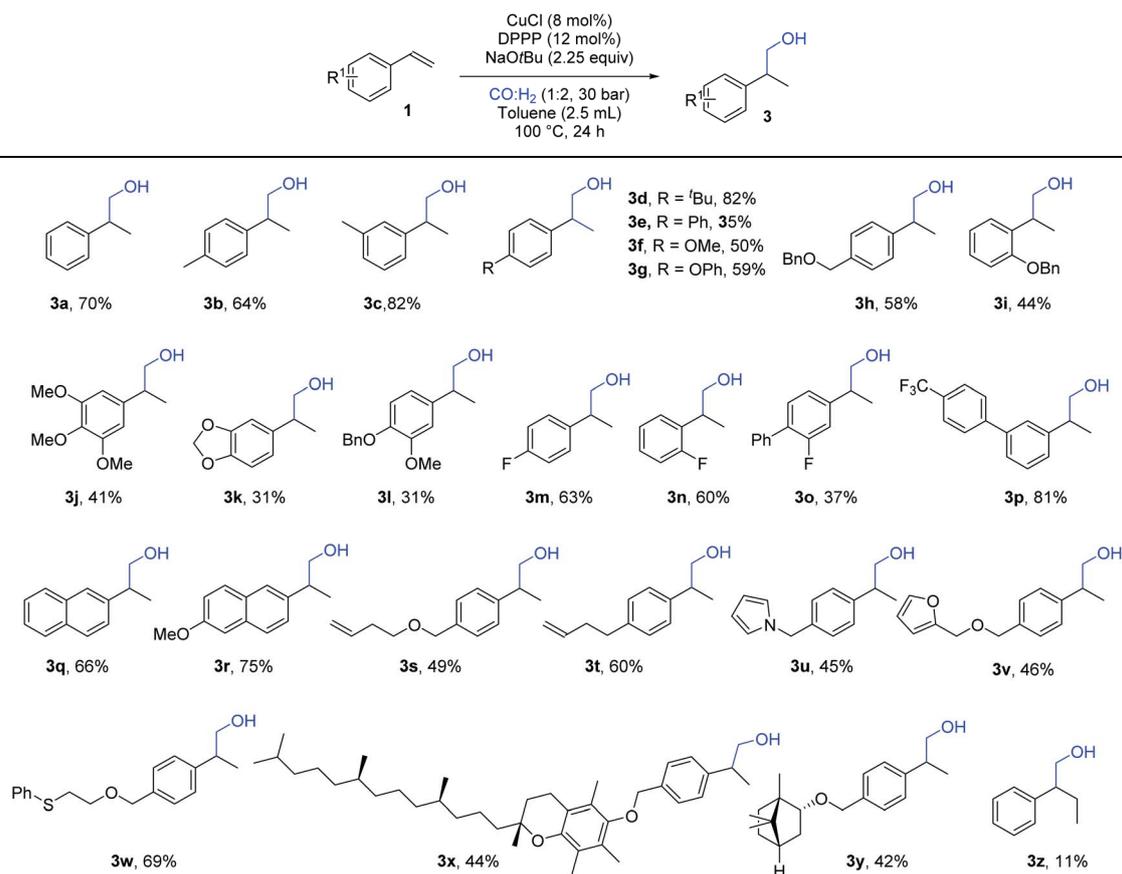
With the use of CuCl as the catalyst, the synthesis of alcohols was subsequently performed (Table 3). Moderate to good yields of the desired alcohols can be obtained successfully without further optimization. Functional groups including methoxy,

Table 2 Cu-catalyzed hydroformylation of alkenes[a]
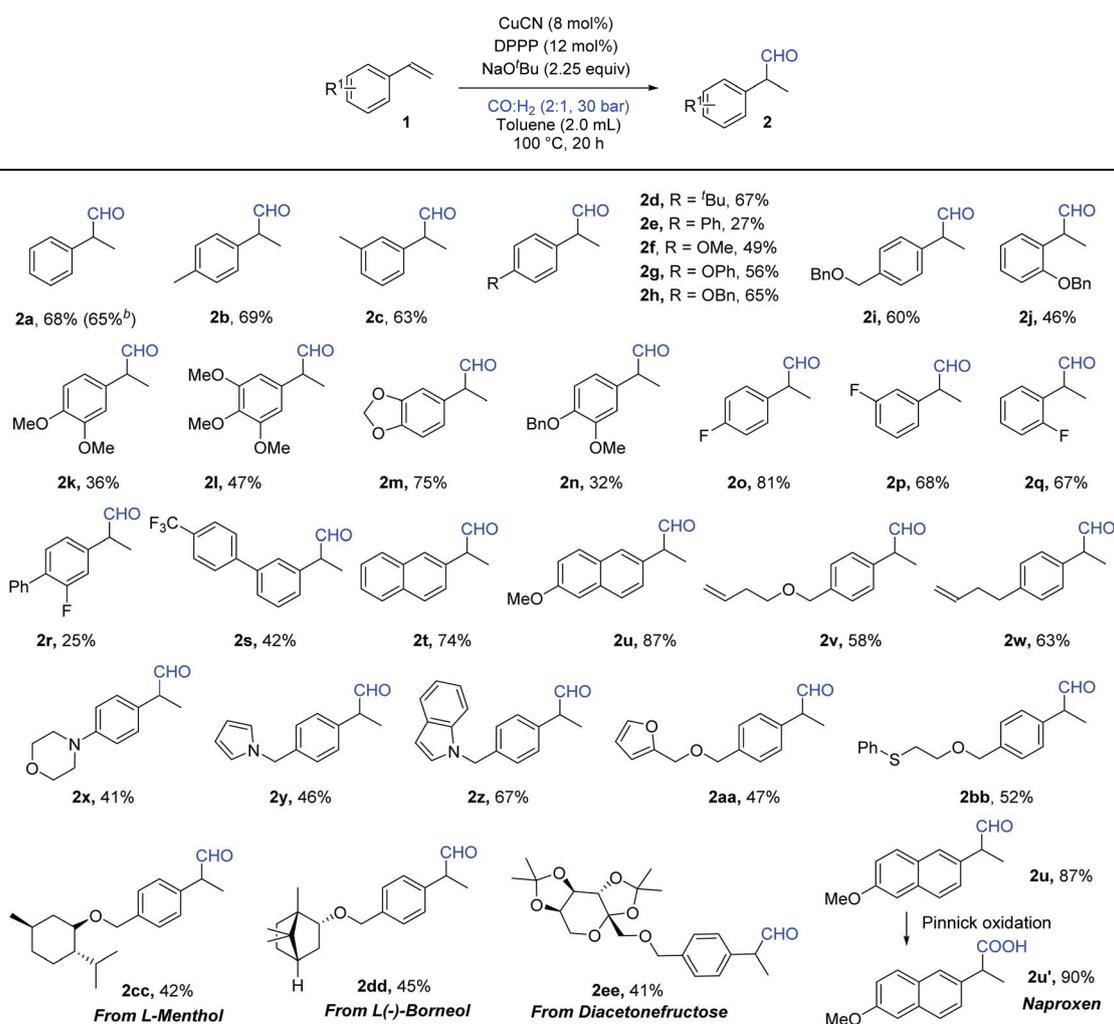
[a] Standard conditions: **1** (0.43 mmol, 1 equiv), CuCN (8 mol%), DPPP (12 mol%), NaO^{t}Bu (2.25 equiv), toluene (2.0 mL), CO : H$_2$ (2 : 1, 30 bar), 100 °C, 20 h, isolated yield. [b] 5 mmol scale.

Table 3 Cu-catalyzed hydroxymethylation of alkenes[a]

Reaction scheme: CuCl (8 mol%), DPPP (12 mol%), NaOtBu (2.25 equiv); CO:H₂ (1:2, 30 bar), Toluene (2.5 mL), 100 °C, 24 h. R^1–styrene (1) → product (3).

3a, 70% · **3b**, 64% · **3c**, 82% · **3d**, R = ^{t}Bu, 82%; **3e**, R = Ph, 35%; **3f**, R = OMe, 50%; **3g**, R = OPh, 59% · **3h**, 58% · **3i**, 44%

3j, 41% · **3k**, 31% · **3l**, 31% · **3m**, 63% · **3n**, 60% · **3o**, 37% · **3p**, 81%

3q, 66% · **3r**, 75% · **3s**, 49% · **3t**, 60% · **3u**, 45% · **3v**, 46%

3w, 69% · **3x**, 44% · **3y**, 42% · **3z**, 11%

[a] Standard conditions: **1** (0.43 mmol, 1 equiv), CuCl (8 mol%), DPPP (12 mol%), NaO^{t}Bu (2.25 equiv), toluene (2.5 mL), CO (10 bar), H₂ (20 bar), 100 °C, 24 h, isolated yield. Yield of **3z** was determined by NMR.

phenoxy, fluoro, trifluoromethyl, pyrrole, thioether, *etc.* can be well tolerated. Besides the naphthyl group, even a terminal alkene group can survive under our standard conditions (**3s** and **3t**). More complexed styrenes were also tested, and it was found that the targeted products can be isolated without any problem (**3x** and **3y**). Without exception, the internal alkene was checked; however, only an 11% yield of the target product could be detected (**3z**). Additionally, several chiral phosphine ligands were checked with the target to obtain a chiral alcohol product. However, low or no enantioselectivity was obtained (For details see the ESI‡).

By adding unactivated halides as the fourth reaction partner together with styrene under a CO and H₂ atmosphere, we can obtain different types of product depending on whether alkyl iodides or alkyl bromides was added. After optimizing the reaction conditions (for details see the ESI‡), an all-carbon quaternary center containing ethers can be synthesized by Cu-catalyzed reaction of olefins with alkyl bromides under a syngas atmosphere. We evaluated the reactivity of various alkenes (Table 4). Functionalized aryl alkenes with alkyl, phenyl, alkyl olefine, fluoro, and indole groups can be

tolerated and gave the corresponding products in moderate yields (**4a**–**4i**). The use of alkyl bromide with a longer chain length has less effect on the reaction result (**4j**). An all-carbon quaternary center containing formates can be obtained by using alkyl iodides as the reaction partner and all the corresponding products were obtained in moderate yields (**5a**–**5d**). Several other alkyl iodides were tested as well; however, besides the low yields (15–26%), it was also difficult to obtain the products.

In order to understand the reaction pathway, control experiments were performed (Scheme 2). In our standard procedure, the addition of water was involved in the work-up part. Instead of water, heavy water (D₂O, 1 mL) was used for the work-up and 86% of benzylic deuterated aldehyde was obtained (Scheme 2, eqn (a)). However, no deuterated aldehyde could be detected under the same conditions starting from an aldehyde (Scheme 2, eqn (b)). These results imply that a vinyloxyl intermediate was most likely involved and that it had been hydrolyzed by water during the work-up process to give the final products. Under the standard conditions of the Cu-catalyzed reaction of styrene with alkyl bromide, the

Table 4 Cu-catalyzed tandem reaction of aryl olefines with unactivated halides[a]
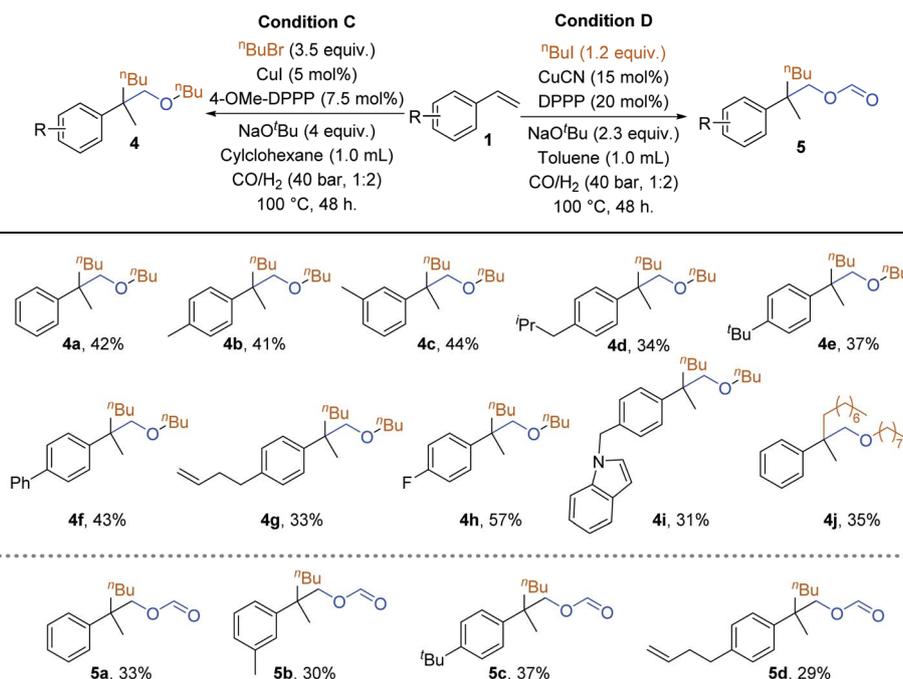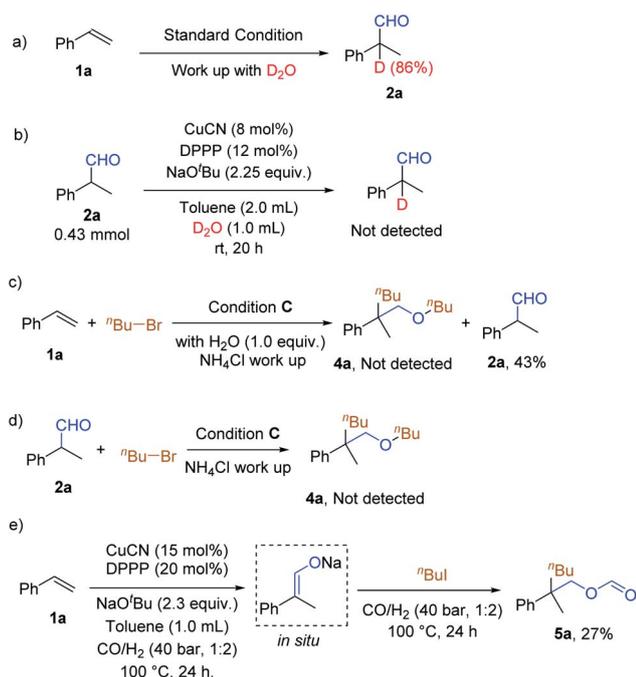
Scheme 2 Control experiments.

addition of 1 equivalent of H$_2$O will inhibit the reaction (Scheme 2, eqn (c)). No ether could be detected, while the aldehyde can be obtained in 43% yield. Using aldehyde **2a** as

the starting material under conditions C, the corresponding ester **4a** cannot be detected (Scheme 2, eqn (d)). These results suggest that aldehydes are not the intermediates for producing ethers. The reaction using styrene as the starting material proceeded for 24 h under conditions D without *n*-butyl iodide. Then *n*-butyl iodide was added, and the reaction was continued for another 24 h under a CO and H$_2$ atmosphere (Scheme 2, eqn (e)). **5a** was obtained in 27% yield, showing that the sodium vinyloxyl may be the key intermediate of these transformations.

Based on our results, a possible reaction pathway is proposed (Scheme 3). The reaction starts with the formation of a LCuO^{t}Bu complex, which will produce LCuH after reaction with H$_2$. Subsequently, the LCuH inserts into the double bond of the alkene to give an alkylcopper intermediate which will react with CO to produce an acylcopper complex. A vinyloxyl copper complex will be formed after rearrangement of the acylcopper intermediate. Finally, sodium vinyloxyl will be eliminated which will give the final product after the hydrolysis work-up. This step is different from the traditional hydro-formylation pathway (*via* δ bond metathesis or oxidative addition between acylmetal and H$_2$) and explains the excess amount of base needed. The key intermediate of these Cu-catalyzed tandem reactions is the sodium vinyloxyl species. After the (L) CuH inserts into the double bond of sodium vinyloxyl, alkyl halides react with the alkyl-copper complex to produce the final products.[30]
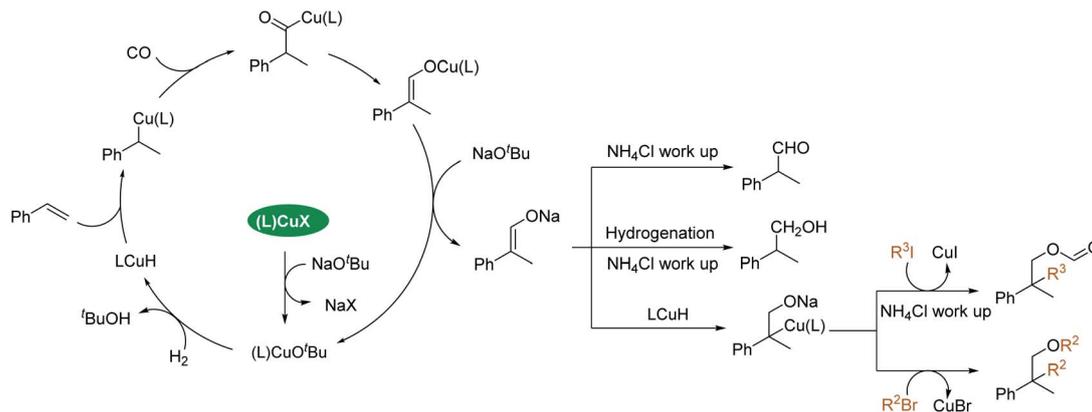
Scheme 3 Proposed reaction mechanism.

Conclusions

In summary, a copper-catalyzed hydroformylation of alkenes has been developed. With CuCN as the catalyst under pressure of syngas, various aldehydes can be produced with good functional group tolerance. Notably, by using CuCl as the catalyst precursor, alcohols can be formed, named as hydroxymethylation of alkenes. Derivatization reactions have also been developed; when unactivated halides were applied, an all-carbon quaternary center containing ethers and formates can be formed in a one-pot manner. A possible reaction pathway is proposed based on our results which is fundamentally different from known mechanisms.

Author contributions

XFW directed this project. HQG and TM performed all the experiments. HQG, RF and XFW prepared the draft and XFW revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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