A Bifunctional Copper Catalyst Enables Ester Reduction with H_2: Expanding the Reactivity Space of Nucleophilic Copper Hydrides

Birte M. Zimmermann, Trung Tran Ngoc, Dimitrios-Ioannis Tzaras, Trinadh Kaicharla, and Johannes F. Teichert*

Institut für Chemie, Technische Universität Berlin, Straße des 17. Juni 115, 10623 Berlin, Germany

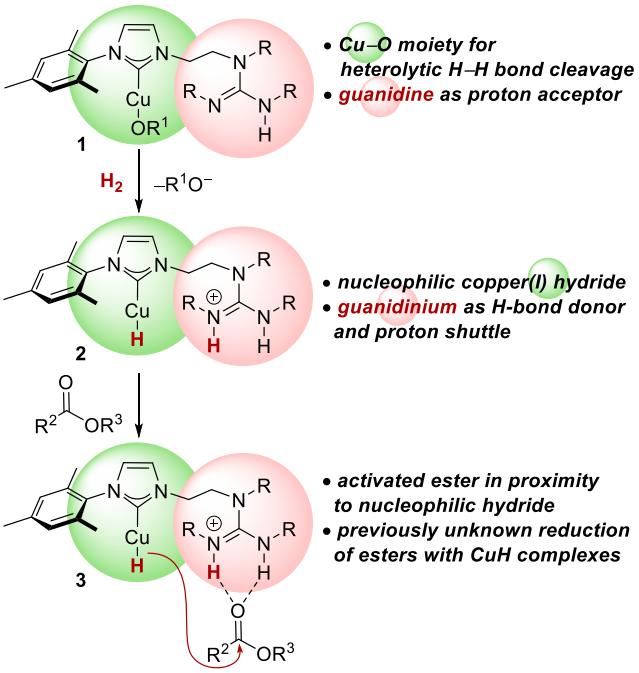
ABSTRACT: Employing a bifunctional catalyst based on a copper(I)/NHC complex and a guanidine organocatalyst, catalytic ester reductions to alcohols with H_2 as terminal reducing agent are facilitated. The approach taken here enables the simultaneous activation of esters through hydrogen bonding and formation of nucleophilic copper(I) hydrides from H_2, resulting in a catalytic hydride transfer to esters. The reduction step is further facilitated by a proton shuttle mediated by the guanidinium subunit. This bifunctional approach to ester reductions for the first time shifts the reactivity of generally considered "soft" copper(I) hydrides to previously unreactive "hard" ester electrophiles and paves the way for a replacement of stoichiometric reducing agents by a catalyst and H_2.

The combination of transition metal catalysts and organocatalysts is a powerful approach furnishing synthetic methods with high efficiency, selectivity and rapid build-up of structural complexity.[1] Along these lines, single catalysts bearing both the transition metal as well as the organocatalyst in one molecular framework have been disclosed (so-called bifunctional catalysts).[2,3] Underscoring the strength of bifunctional catalysis, highly efficient catalysts for the control of regio- or stereoselectivity have been reported.[4] However, the controlled shift of traditional reactivity towards new, previously unreactive functional groups, in other words, the overcoming of established chemoselectivity, is limited so far.[5]

In earlier studies from our laboratories we have studied the generation of nucleophilic copper(I) hydrides from dihydrogen (H_2).[6] In this vein, we have established that copper(I)/*N*-heterocyclic carbene (NHC) complexes bearing a Cu–O-bond are preactivated for the heterolytic cleavage of H_2 into a formal proton and hydride equivalent.[7,8] The thus generated copper(I) hydrides can be employed in a catalytic setting for reductions or hydride transfer reactions.[9]

We envisioned that while keeping the copper(I)/NHC complex for H_2 activation intact, a second catalytic moiety could serve as additional steering unit to extend the reactivity of copper(I) hydrides towards previously unreactive functional groups. A bifunctional catalyst bearing a guanidine,[10,11] such as **1** (Scheme 1) would fulfil such design principles. We foresaw a possible multiple role of the guanidine subunit: In **1**, it would serve as a base to accept the proton after heterolytic H–H bond cleavage.[12] In this manner, a guanidinium (as in **2**) would be formed which could then act as a hydrogen bond donor[13] for the activation of substrates such as carboxylic esters or carbonyl compounds (Scheme 1).[14] Additionally, the protonated guanidinium could serve as assisting proton shuttle.[15] Following this design principle, the copper(I)/NHC complex would remain with its known reactivity, which however, would be enhanced through the double role of the guanidine organocatalyst. In this genuine bifunctional catalysis approach, the nucleophilic copper(I) hydrides, which are generally characterized as "soft"[16] would remain unchanged in principle. However, through the action of the second catalytic unit and the concomitant activation of the ester substrates, the classic reactivity of copper(I) hydride complexes could be shifted towards "hard" electrophiles such as esters.

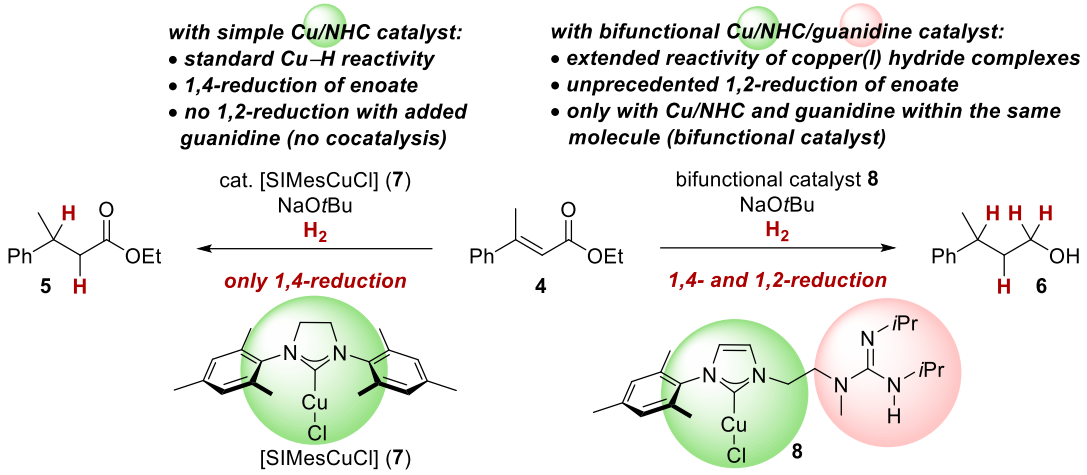
Scheme 1. Double role of guanidine: Bifunctional catalyst design enables the reduction carboxylic esters by nucleophilic copper(I) hydrides from H_2.



In fact, such a reduction of esters with copper(I) hydride compounds has not been reported.[17] Generally, this transformation requires the use of "hard" stoichiometric metal hydrides which are associated with generation of metal waste and tedious workup procedures, especially on larger scale.[18] Therefore, the approach taken here not only significantly broadens the reactivity space of copper(I) hydride complexes but also offers a desirable catalytic hydrogenation of esters,[19] circumventing the commonly employed stoichiometric reducing agents.

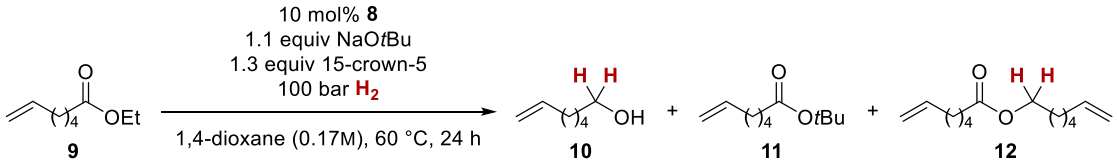
To probe the viability of our approach, we compared the reduction of ethyl cinnamate derivative **4** with bifunctional catalyst **8** vs. a previously reported copper(I)/NHC catalyst **7**[9b] in the presence of H_2. Whereas the use of **7** led to selective 1,4-reduction of **4** and formation of reduced ester **5**,[9b,20] application of bifunctional catalyst **8** gave rise to alcohol **6** as main product under unoptimized conditions. Next to the expected 1,4-reduction of the enoate **4**, the reduction of the ethyl ester to alcohol **6**, previously unknown in the realm of copper(I) hydride catalysis was thus observed.[21,22] Importantly, the external addition of catalytic or stoichiometric amounts of guanidines (1,1,3,3-tetramethylguanidine or 2,3-diisopropyl-1,1-dimethylguanidine, 10 mol% to 10 equiv) as additive in combination with standard catalyst **7** (Scheme 2, left) did not lead to any detectable amount of alcohol **6**.[22] This series of experiments supports the notion that a true bifunctional molecule with the two catalytically active subunits in vicinity and not a cocatalytic system is responsible for the observed hydride transfer to esters.

Scheme 2. Effect of bifunctional catalyst in catalytic hydrogenation of enoate 4. Additional guanidine moiety leads to unprecedented ester hydrogenation.[a]



[a]Reaction conditions: 5 mol% **7** or **8**, 1.1 equiv NaO*t*Bu, 100 bar H2, 1,4-dioxane, 60 °C, 16 h; full conversion of **4** reached in both reactions.[22]

Table 1. Optimization of copper (I)-catalyzed 1,2-reduction of esters.[a]



Entry	Catalyst loading [mol%]	Solvent	Base	Concentration [M]	Pressure [bar]	Additives	Conversion [%][b]	**10/11/12**[b]
1	5	1,4-dioxane	NaO*t*Bu	0.07	100	-	88	78:0:22
2	5	THF	NaO*t*Bu	0.07	100	-	63	49:0:51
3	5	toluene	NaO*t*Bu	0.07	100	-	39	3:26:64
4	5	1,4-dioxane	KO*t*Bu	0.07	100	-	44	52:0:48
5	5	1,4-dioxane	LiO*t*Bu	0.07	100	-	45	0:100:0
6	5	1,4-dioxane	NaOMe	0.07	100	-	62	15:0:19[c]
7	5	1,4-dioxane	NaO*t*Bu	0.17	100	-	93	77:0:23
8	10	1,4-dioxane	NaO*t*Bu	0.17	100	-	92	88:0:12
9	10	1,4-dioxane	NaO*t*Bu	0.17	100	15-crown-5	100	100:0:0
10	10	1,4-dioxane	NaO*t*Bu	0.17	20	15-crown-5	81	95:0:5

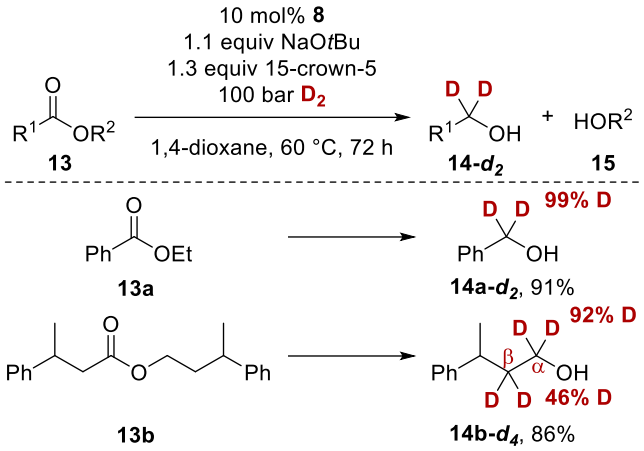
[a]All reactions were done on a 0.085 mmol scale. [b]Determined by GC analysis. [c]66% of the corresponding methyl ester detected.

After these initial findings we optimized the reaction conditions employing ethyl heptenoate (**9**) as model system for chemoselective ester reduction (Table 1).[22] As a common trend we observed that the reduction worked best in polar, non-protic solvents, with 1,4-dioxane, which also sustains solubility of the base under the reaction conditions, giving best results, (Table 1, entry 1–3). When investigating alkoxide additives required for heterolytic H–H-bond cleavage,[7] we found that sterically hindered *tert*-butoxide is required for efficient ester reduction.[22–24] The choice of counterion is crucial for chemoselectivity, with Li^+ leading only to transesterification product **11** (Table 1, entries 4–6). Higher concentration led to better conversions of **9** supporting our working hypothesis of a non-covalent interaction between catalyst and substrate. Addition of 15-crown-5 led to better solubility and availability of the alkoxide base, also visually observable (Table 1, entry 9). Gratifyingly, the catalytic ester reduction is still functional at significantly lower H_2 pressure, albeit with slightly lower conversion and selectivity (Table 1, entry 10).

To support our working hypothesis of hydride transfer to esters with bifunctional catalyst **8**, we carried out reduction of esters **13** employing D_2 (Scheme 3). As expected, the reduction of ethyl benzoate (**13a**) gave dideuterated benzyl alcohol

(**14a-*d*$_2$**) in high yield and with very high deuterium incorporation (99% D), supporting the notion of a nucleophilic hydride/deuteride originating from H_2/D_2. When ester **13b** was subjected to identical conditions, a similarly high isotope labelling was found in the α-position of the alcohol **14b-*d*$_4$**, in addition to significant deuteration (46% D) in the *β*-position. The latter can be explained by a prior formation of an ester enolate of **13b** under the basic reaction conditions followed by quenching with DO*t*Bu, stemming from the heterolytic activation of D_2.[6–9]

Scheme 3. Catalytic ester reduction, standard conditions and isotope labeling experiments.[25]



Next, we investigated the scope of the catalytic ester reduction with bifunctional catalyst **8** (Table 2). While the catalytic conversion of simple, unfunctionalized, non-enolizable ethyl esters could successfully be realized with H_2 pressure as low as 20 bar, higher pressure was necessary to ensure acceptable conversion with more sophisticated substrates. We therefore opted to apply 100 bar H_2 pressure as standard conditions.

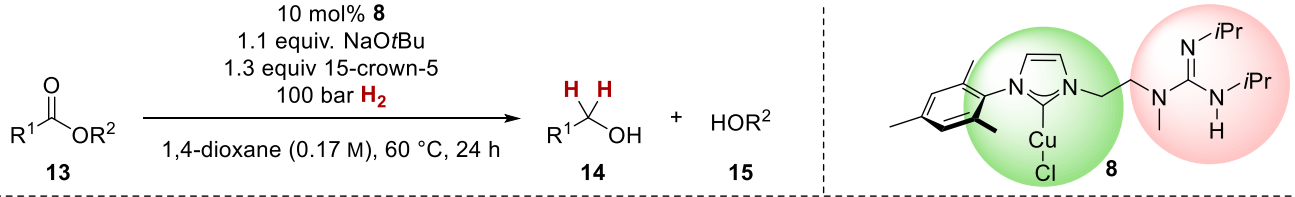
When investigating the influence of the alcohol moiety of various benzoate esters **13a** and **13c–13k**, we found that even though sterically hindered esters such as **13f–13i** reacted slower, all esters could successfully be converted with acceptable yields. It is interesting to note that under the present protocol even the sterically demanding *tert*-butyl ester **13j** could be fully converted to the corresponding alcohol **14j**.[26] This example underscores that the bifunctional catalyst **8** acts independently of steric demand of the alcohol subunit. In a similar vein, esters with sterically demanding carboxylic acid moieties such as adamantyl-derivative **13q** or dimethyl-substituted **9r** were all reduced successfully. While activated esters such as phenolate derivative **13k** led to rapid transesterification to the *tert*-butyl ester such as **13j**,[27] an additional equivalent of base ensured complete conversion to the desired alcohols **14k** and **15k**. As shown from the isotope labeling experiments (Scheme 3), esters bearing acidic C–H-bonds in the α-position can form enolates prior to reduction. Whereas esters **13l–13o** (devoid of this possibility) could be reduced successfully, enolizable esters **13b** and **13t–13w** could nevertheless be converted, albeit with slightly lower yields.

Remarkably, our method could not be employed to (partially) reduce lactones, of which one example is shown **13x**. This striking absence of reactivity indicates that stereo-electronic parameters of the employed substrates play an important role for the activation through the guanidinium moiety in the catalytic process.

Functional group tolerance of the present catalytic transformation is generally high. Halogenated benzoic esters displayed good functional group tolerance, only in the case of 2-chlorobenzoic ester **13aa** 7% of dechlorination could be observed, most probably due to proximity of the two functional groups.[28] Both electron-rich and electron-poor benzoic esters **13ab–13ae** could successfully be converted, while it became clear that electron donating groups significantly lowered the reaction rate.[29] This could be explained by the lower electrophilicity of the corresponding esters. For benzyl ethers **13ad** and **13ae** only chemoselective reduction of the ester took place whereas no cleavage of the benzyl group under hydrogenative conditions, as reported for many other transition metal catalysts,[30] was observed. Further tolerated functional groups include an acetal (**13af**, for the reduction of carbonyl compounds, see Scheme 5) and Boc-protected amine (**13ag**), which could be converted with good yield (74%). Commonly occurring heterocycles such as furan, thiophene, *N*-phenylpiperazine, thiomorpholine and morpholine (**13ah–13al**) could all sustain the catalytic ester reduction in acceptable yields (62–76%).

Catalytic alkyne semihydrogenation, one of the hallmarks of copper(I) hydride catalysis[6,8a] takes place concurrently and without diminished chemoselectivity, it does not hamper the ester reduction (**9am**). However, one key chemoselectivity of the present protocol is that the bifunctional catalyst fully tolerates simple alkenes such as in **9**, **13an** and **13ao**. This chemoselectivity is remarkable as it sets the present catalyst apart from many other transition metal complexes, for which catalytic alkene hydrogenation is one of the prime reaction pathways.[31] Therefore, the present catalyst can rather be regarded as a means to generate nucleophilic hydrides from H_2 rather than a classical transition metal-based hydrogenation catalyst. Along these lines, the tolerance of alkenes in the present protocol underlines the applicability of the bifunctional catalyst **8** as a true replacement of stoichiometric reducing agents (such as aluminum and borohydrides) with a catalyst and H_2.

Table 2. Catalytic ester hydrogenation, substrate scope.[a]



influence of alcohol

13a: R = Et, 80%
13c: R = Me, 75%
13d: R = C_6H_{13}, 70%[b]
13e: R = Bn, 77%
13f: R = *i*Bu, 62%
13g: R = *i*Pr, 51%, (89% conv.)
13h: R = Cy, 76%
13i: R = (–)-menthol, **15i** 51%, (68% conv.)
13j: R = *t*Bu, 75%
13k: R = Ph, **14k** 54%, **15k** 62%[c]

13l: 1-Np, 74%
13m: 2-Np, 72%

13n: 71%

13o: 72%

13p: 69%[d]

13q: 73%[e]

steric demand

13r: 62%
(93% conv.)

13s: 68%[e]

enolizable esters

13t: 66%

13u: R = Et, 75%
13v: R = *t*Bu, 42%,
(94% conv.)[f]

13w: 54%

13b: *d.r. = 1:1*
78%

lactone

13x
(no conv.)

functional group tolerance

13y: 4-Cl, 74%
13z: 3-Cl, 81%
13aa: 2-Cl, 70%[g]

13ab: 57%[h]

13ac: 70%
(81% conv.)

13ad: 65%
(80% conv.)

13ae: 75%
(full conv.)

13af: 74%

13ag: 74%

13ah: X = O, 70%
13ai: X = S, 74%

heterocycles

13aj: X = NPh, 67%
13ak: X = S, 76%
13al: X = O, 62%

chemoselective reduction in presence of alkenes

chemoselective alkyne semihydrogenation not affected

13am: 56%[i]

9: 58%
(volatile)

13an: (*E*), 77%[j]
13ao: (*Z*), 82%[k]

biologically relevant substrates

13ap: 77%

13aq: R = Et, 74%[e]
13ar: R = Bn, 87%[e,l]

13as: 44%[m]

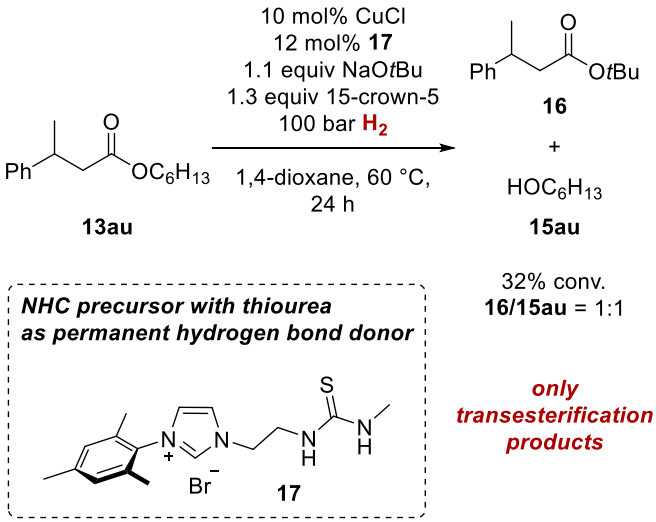
13at: 46%[n]

[a]Substrate (0.6 mmol); isolated yields denote the R¹CH2OH fragment **14**. [b]Isolated as a mixture **14d/15d** = 61:39. [c]With 3.0 equiv NaO*t*Bu and 3.3 equiv 15-crown-5. [d]With 10 mol% **8**, 75% conversion and 69% yield, with 20 mol% **8**, 77% conversion. [e]With 20 mol% **8**. [f]94% conv. to **10v**/transesterification dimer = 81:19. [g]7% Dechlorination observed. [h]13% Defluorination observed. [i]Reduction of alkyne to (*E*)-alkene. [j]Isolated as a mixture **14an/15an** = 42:58. [k]Isolated as a mixture **14ao/15ao** = 44:56. [l]Isolated as a mixture **14ar/15ar** = 56:44. [m]0.40 mmol **13as**. [n]0.37 mmol **13at**.

Finally, biologically more relevant molecules such as glycine and phenylalanine derived esters **13ap–13ar** could successfully be reduced to the corresponding amino alcohols.[32] Furthermore, steroid derivatives such as estrone and cholic acid derived esters **13as** and **13at** displayed to be viable substrates for our protocol.

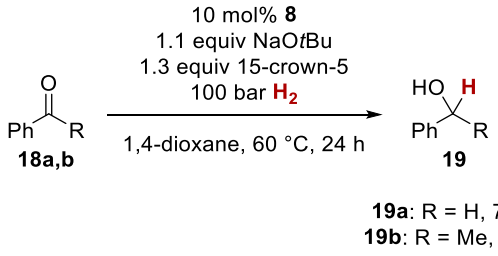
In order to probe the key role of the guanidine as a means for hydrogen-bond activation of the ester substrates,[33] we prepared bifunctional catalyst precursor **17** bearing a thiourea as permanent and efficient hydrogen bond donor.[34,35] Such a thiourea-based catalyst would serve as hydrogen bond-donor without having to be activated by protonation (as would be the case of the guanidinium moiety, which is only rendered a hydrogen bond donor after accepting the proton from H_2 activation). The resulting thiourea-based catalyst still activated ester **13au** for transesterification, as observed by the formation of *tert*-butyl ester **16**, but in contrast to **8** no further 1,2-reduction was observed with the thiourea-based catalyst (see Scheme 4).[36] This result implies that not only activation of the ester by hydrogen bonding takes place in guanidine-based catalyst **8**, but that the guanidine/guanidinium subunit plays and additional role as a proton shuttle[14] in the overall reduction.

Scheme 4. Application of a hydrogen bond donor appended bifunctional catalyst.



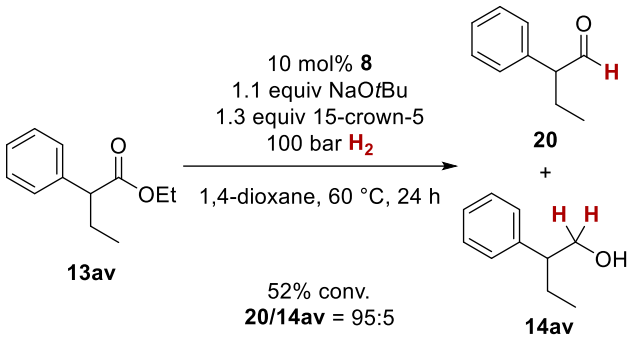
With regards to a possible mechanism of the reduction, we put forward a hydride transfer pathway of the nucleophilic copper(I) hydride to the ester, in a manner of an addition/elimination mechanism. Such a pathway would give rise to an aldehyde as intermediate. In order to probe whether an aldehyde would be a viable substrate for the bifunctional catalyst, we investigated the reduction of benzaldehyde (**18a**) (and the related acetophenone (**18b**)) by catalyst **8** (Scheme 5).[6a,16,37] We observed clean conversion of both, the possible intermediate in the catalytic reduction **18a** as well as **18b** to the corresponding alcohols **19**. These results show that the bifunctional catalyst is indeed capable of reducing the more reactive carbonyl compounds as well. Therefore, an aldehyde might serve as an intermediate on the catalytic cycle of the ester reduction.[38]

Scheme 5. Catalytic reduction of aldehydes and ketones with bifunctional catalyst 8.



Further evidence for the presence of an aldehyde as a reactive intermediate of the catalytic ester reduction was obtained in the attempted reduction of ethyl 2-phenylbutyrate (**13av**, Scheme 6). Even though under optimized conditions the conversion of **13av** reached only 52%, aldehyde **20** was observed as the major product. The formation of **20** in this experiment could be rationalized by the fact that **20** could swiftly form a well stabilized enolate which is stable until workup evading further reduction. The selective reduction of esters to aldehydes is a long-sought transformation in itself. The results presented in Scheme 6 implies a possible further application of the bifunctional catalysts **8** disclosed here.

Scheme 6. Formation of an aldehyde during ester reduction – indication for a possible reactive intermediate.



In conclusion, we have demonstrated that a bifunctional catalyst based on a copper(I)/NHC and a guanidine organocatalyst enables the catalytic reduction of esters to alcohols. This approach significantly enhances the typical reactivity of copper(I) hydrides, generally regarded as "soft" nucleophiles to "hard" electrophiles such as esters, previously unreactive. Our approach comprises the generation of nucleophilic hydrides from H_2 and concomitant activation of the ester through hydrogen bonding. The guanidine thus serves as base, hydrogen bond donor after protonation and finally as proton shuttle to facilitate the overall reduction process. Importantly, the present approach delivers a catalytically formed hydride to the ester rather than being a hydrogenation catalyst. This is underscored by the tolerance of alkenes, among other functional groups. Therefore, a tightly controlled chemoselectivity arises from the use of a bifunctional catalyst, while at the same time a possible replacement of stoichiometric reducing agents with a catalytic protocol based on H_2 is demonstrated. We think that the approach taken here employing a combination of a transition metal complex and an organocatalytic moiety to significantly alter the original chemoselectivity exerted by the transition metal could be further exploited in the realm of method development for synthetic chemistry.

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AUTHOR INFORMATION

Corresponding Author

* johannes.teichert@chem.tu-berlin.de
New address:

Institut für Chemie, Organische Chemie, Technische Universität Chemnitz, Straße der Nationen 62, 1/B115, 09111 Chemnitz, Germany. johannes.teichert@chemie.tu-chemnitz.de

ORCID

Birte M. Zimmermann: 0000-0002-4456-5877
Trung Tran Ngoc: 0000-0002-6121-7129
Dimitrios-Ioannis Tzaras: 0000-0002-7382-2860
Trinadh Kaicharla: 0000-0001-9697-6072
Johannes F. Teichert: 0000-0003-1043-8092

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Notes

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(21) See Scheme caption for conditions. 100% conversion of ⍰, 55% of **6**, 12% of **5**, 32% transesterification product of **5** with **6** as alcohol moiety, 1% of the corresponding *tert*-butyl ester of **5**.
(22) See Supporting Information for details.
(23) Otherwise, the formation of mixed esters was observed.
(24) In this regard, it should be mentioned that the *tert*-butoxide itself could act as a nucleophile with the esters yielding small quantities (<5%). *tert*-Butyl esters can indeed be observed, however, in additionally activated by the H-bonding guanidinium, these transesterification products get reduced as well.
(25) For **14b-*d4***, deuteration level in the α-position is given with respect to reduceable ester moiety of **13b**. Due to the similar structure of alcohol and acid moiety of **13b**, the experiment gives a total of 46% D.
(26) This reactivity is also of importance as in principle, during the reactions, the *tert*-butyl esters could be formed by transesterification of the substrate with the additive NaO*t*Bu.
(27) See reference (25).
(28) Small amounts of dehalogenation have been reported in previous homogeneous copper(I) hydride catalysis with H_2, see references: (6) and (9).
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(33) To probe the hypothesized mode of activation of the esters by the bifunctional catalyst (see Scheme 1), we attempted to identify the hydrogen bonding of the proposed guanidinium moiety to the ester. This interaction had previously been reported in other studies. (see reference (14)) However, the proposed interaction could not be identified via NMR and IR spectroscopy or mass spectrometry as of yet.
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(36) A prototypical copper(I)hydride semihydrogenation of an internal alkyne (tolane) was feasible with the thiourea based catalyst **17**, underlining the successful formation of the copper(I)/NHC complex (see supporting information).
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