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Copper-catalyzed *Z*-selective semihydrogenation of alkynes with hydrosilane: a convenient approach to *cis*-alkenes

Guang-Hui Wang [a], Huai-Yu Bin [a], Miao Sun [a], Shu-Wei Chen [a], Ji-Hong Liu [b], Chong-Min Zhong [a,b,*]

[a] Department of Applied Chemistry, College of Science, Northwest A&F University, Yangling 712100, PR China
[b] College of Chemistry and Chemical Engineering, Harbin Normal University, Harbin 150025, PR China

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ABSTRACT

A copper catalyst generated in situ from widely available copper salt and imidazolium salt in the presence of *t*-BuOK showed high efficiency for the semihydrogenation of a wide range of internal and terminal alkynes to their corresponding alkenes without obvious over-reduction. Functional groups, such as hydroxyl, nitro, halides, and amino, etc. were tolerated. The *Z*/*E* ratios of the obtained alkenes were generally >99%. Finally, semireduction of bulky alkynes also went smoothly.

1. Introduction

cis-Olefinic structures exist in many biologically important molecules.[1] The stereoselective semihydrogenation of internal alkynes is the simplest and most straightforward approach to achieve *cis*-alkenes,[2] and both heterogeneous and homogeneous catalytic methods have been developed to obtain the desired products. The Lindlar catalyst,[3] modified Lindlar catalysts,[4] palladium nanoparticals,[5] nickel boride on resin,[6] dispersed nickel on graphite,[7] nickel nanoparticals,[8] and nickel phosphide nanoparticles[9] are perhaps the most efficient and well known among the heterogeneous catalyst systems currently available. However, partial isomerization of the *cis*-alkene to the *trans*-alkene, double-bond shifts and over-reduction to the alkane are notable issues, especially with the Lindlar catalyst. Many attempts have been also made to develop efficient homogeneous catalyst systems based on rhodium,[10] tricarbonylchromium(0),[11] hafnium,[12] ruthenium,[13] nickel,[14] iron,[15] vanadium,[16] and palladium complexes.[17] Thus far, however, few palladium catalysts,[17c,e,g] have shown good selectivity for the formation of *cis*-alkenes as well as tolerance for a variety of functional groups. Similar to heterogeneous catalyst systems, some *trans*-alkenes and over-reduction to alkanes have also been observed in palladium catalytic systems.

The reactivity of copper hydride with unsaturated carbon—carbon bonds has been observed in its reaction with terminal alkynes,[18] internal alkynes, [19] and olefins conjugated with aromatic groups.[20] Ryo et al.[21] also reported the Cu(II) hydride-mediated stereoselective reduction of alkynes activated by electron-attracting sulfonyl groups. All of the copper species that mediate the semihydrogenation of internal alkynes show nearly perfect *cis*-selectivity.[19,21] X-ray structures of vinyl copper complexes illustrate that addition of copper hydride to triple bonds occurs via a *cis*-selective manner.[22]

Recently, significant progress has been made in the copper catalyzed semihydrogenation of alkynes.[23] Tsuji[24] and Lalic[25] reported a bisphosphine and NHC coordinated copper catalyst, respectively. However, Tsuji's method utilized different ligands and reaction conditions for different type substrates, which bring difficult choice in application. The IPrCuO—*t*-Bu catalyst, reported by Lalic, is air-unstable, which limits its wide application. Therefore a more general method is still desired. The present study shows that a copper catalyst generated in situ from air-stable and widely available $Cu(OAc)_2 \cdot H_2O$ and IPr·HCl in the presence of *t*-BuOK is highly efficient for the semihydrogenation of both internal and

* Corresponding author. E-mail addresses: zhongcm@nwsuaf.edu.cn, zhong_cm@yahoo.com (C.-M. Zhong).

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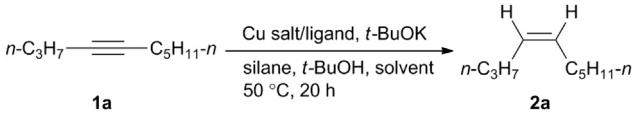
terminal alkynes and significantly suppress over-reduction to alkanes.

2. Results and discussion

We first used 4-decyne as a model substrate and polymethylhydrosiloxane (PMHS) as a reducing agent to optimize the reaction condition (Table 1). Quantitative yields of the product were obtained by using a catalytic system generated in situ from 5 mol % $Cu(OAc)_2 \cdot H_2O$, 5 mol % 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (IPr·HCl), and 10 mol % *t*-BuOK in toluene (Table 1, entry 1). The use of CuCl or CuI instead of $Cu(OAc)_2 \cdot H_2O$ resulted in very low (entry 2, 3%) or moderate (entry 3, 69%) yields. The NHC ligand generated from commercially available IPr·HCl was more active than phosphines (entries 4 and 5) and other NHC ligands (entries 6 and 7). Aside from toluene, hexane was also a good solvent for the catalytic reaction (entry 8, 68%), though the reaction in hexane went slower than in toluene. The reaction using $(EtO)_3SiH$ as the reducing agent gave a yield comparable with that of the reaction using PMHS. In the absence of ligand, the reaction resulted in only 9% yield of the desired product (Table 1, entry 11).

Table 1
Copper-catalyzed semihydrogenation of 4-decyne: condition optimization[a]



1a **2a**

Entry	Ligand	Cu salt	Silane	Solvent	Yield[b] (%)
1	IPr·HCl	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	100
2	IPr·HCl	CuCl	PMHS	Toluene	3
3	IPr·HCl	CuI	PMHS	Toluene	69
4	Xantphos	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	14
5	dppb	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	52
6	Mes·HCl	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	25
7	s-IPr·HCl	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	13
8	IPr·HCl	$Cu(OAc)_2 \cdot H_2O$	PMHS	Hexane	68
9	IPr·HCl	$Cu(OAc)_2 \cdot H_2O$	$PhSiH_3$	Toluene	62
10	IPr·HCl	$Cu(OAc)_2 \cdot H_2O$	$(EtO)_3SiH$	Toluene	96
11	None	$Cu(OAc)_2 \cdot H_2O$	PMHS	Toluene	9

[a] Reaction conditions: alkyne **1a** (0.5 mmol), copper salts (0.05 equiv), ligand (0.05 equiv), *t*-BuOK (0.01 equiv), silane (4.0 equiv, as number of Si–H unit), *t*-BuOH (2.0 equiv), solvent (1.0 ml).
[b] GC yields. No *E*-alkene and overreduction products were observed by ^1H NMR in any of the cases.

The scope of the catalytic system was examined using various alkynes (Table 2). Semihydrogenation occurred much faster in alkynes conjugated with one phenyl group (Table 2, entries 1 and 2) than in substrates conjugated with two phenyl groups (entry 3). Several functional groups on the conjugated phenyl ring were tolerated (entries 4–13). Product **2q** was contaminated by 8% over-reduced by-product due to the higher temperature and longer reaction time. For substrates bearing NH_2 and OH groups, higher temperatures were necessary for the reaction to proceed (entries 8 and 9). The low reactivity of these substrates presumably was due to the deactivation by the strong electron-donating groups or to the coordination of the groups to metals.

However, the substrates bearing electron-withdrawing groups (EWG) that have direct resonance effect with triple bonds were over-reduced completely (Table 2, entry 12) or to a large extent (entry 13). The over-reduction was considered to be resulted from the activation of the double bonds in the desired products and further hydrogenation (Eq. 1). In contrast to the strong activation effect of the conjugated electron-withdrawing groups (NO_2 and CN) on the desired

Table 2
Copper-catalyzed semihydrogenation of alkynes[a]

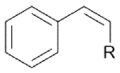
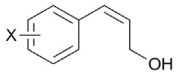
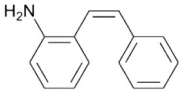
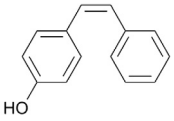
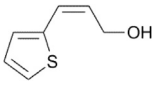
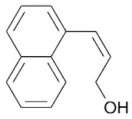
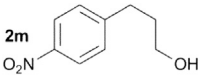
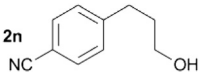
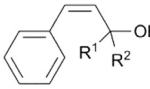
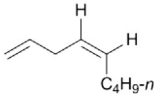
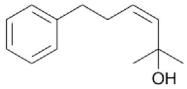
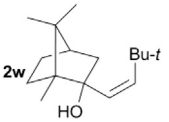
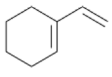
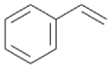
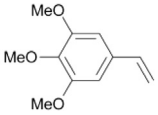
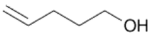
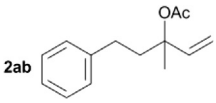
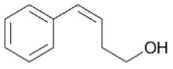
Entry	Products	PMHS equiv.	*T* (°C)	Time (h)	Yields[b] [%] (*Z*/*E*)[c]
1[d]		3.2	25	4	89 (>99/<1)
2[e]	**2c** : R=*n*-Pr	3.2	25	10	98 (100/0)
3	**2d** : R=Ph	3.2	50	18	95 (>99/<1)
4		4.0	25	25	92 (>99/<1)
5	**2f** : X=*p*-CF_3	4.0	25	25	88 (>99/<1)
6	**2g** : X=*p*-Br	4.0	25	6	92 (>99/<1)
7	**2h** : X=*p*-Cl	4.0	25	32	92 (98/2)
8	**2i** 	4.0	50	20	94 (>99/<1)
9	**2j** 	4.0	80	75	97 (>99/<1)
10	**2k** 	4.0	25	20	89 (>99/<1)
11	**2l** 	4.0	25	30	93 (>99/<1)
12[f]	**2m** 	4.0	25	25	90
13	**2n** 	4.0	25	25	80[g]
14[h]		4.0	25	16	92 (>99/<1)
15	**2p** : R^1=H, R^2=Me	4.0	50	10	92 (>99/<1)
16[i]	**2q** : R^1=H, R^2=Ph	4.0	80	48	95 (100/0)
17	**2r** : R^1=H, R^2=*t*-Bu	4.0	100	24	90 (>99/<1)
18	**2s** : R^1=Me, R^2=*i*-Pr	4.0	80	124	40 (>99/<1)
19	**2t** : R^1=Me, R^2=$PhCH_2CH_2$	4.0	80	124	65 (>99/<1)
20[d]	**2u** 	3.2	50	10	55 (>99/<1)
21	**2v** 	4.0	50	20	90 (>99/<1)
22	**2w** 	4.0	100	100	46 (>99/<1)
23[d]	**2x** 	3.2	25	3	70

Table 2 (*continued*)

Entry	Products	PMHS equiv.	*T* (°C)	Time (h)	Yields[b] [%] (*Z*/*E*)[c]
24[d]	**2y** 	3.0	24	3	99[j]
25	**2z** 	3.0	24	3	98
26	**2aa** 	4.0	25	10	60
27	**2ab** 	4.0	50	10	98
28[k]	**2ac** 	4.0	50	20	91 (>99/<1)

[a] Reaction conditions: alkynes (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 equiv), IPr·HCl (0.05 equiv), *t*-BuOK (0.1 equiv), *t*-BuOH (2.0 equiv), PMHS (3.2–4.0 equiv), toluene (0.5 M).

[b] Isolated yields after flash chromatography. For substrates with a hydroxyl group, the products were isolated after hydrolysis by addition of 1.0 M TBAF in THF.[26]

[c] Determined by ^{1}H NMR.

[d] Hexane was used as solvent for the purpose of easy separation.

[e] 6.0 mmol alkyne was used.

[f] The alkyne was completely over-reduced.

[g] The product is composed of 80% over-reduced product and 20% *cis*-alkene.

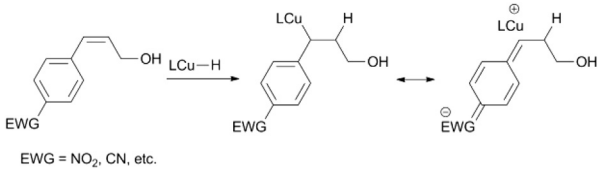
[h] 4.0 mmol alkyne was used.

[i] The product contains 8% over-reduction by-product.

[j] GC yield.

[k] 10.0 mmol alkyne was used.

products, EWG group CF_3 only has inductive effect and did not activate the product (**2f**) obviously. This is a reasoned result considering that π electrons involved in the reaction were polarized more strongly by *conjugated* EWG groups than by *inductive* EWG ones.

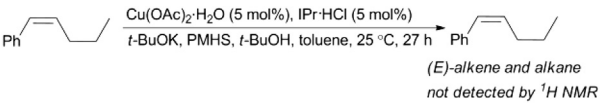


(1)

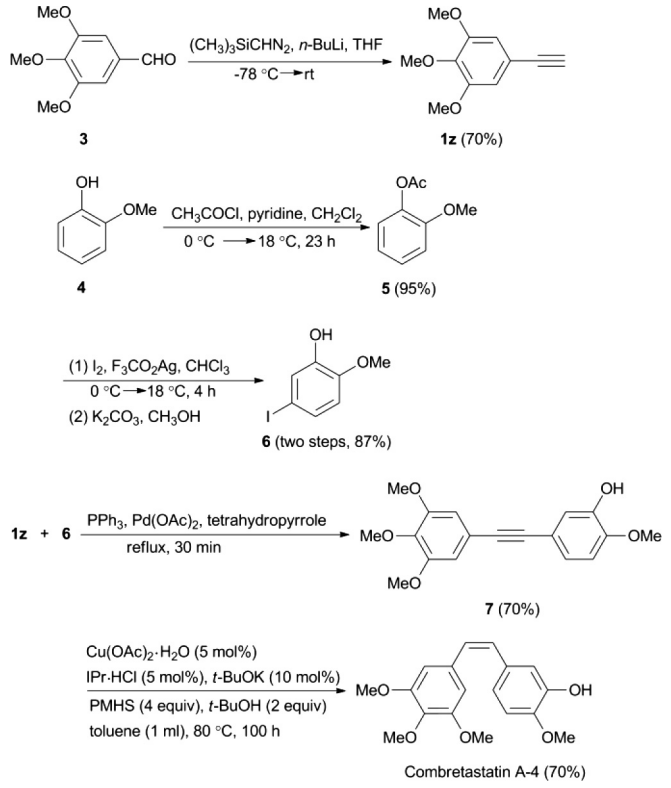
Allylic alcohols with aryl groups at the γ position are an important type of synthetic intermediates.[26] We studied the reduction of this type of substrate with different substitution groups at the α position (Table 2, entries 14–19). Substrates with larger substituents at the α position required higher reaction temperatures (entries 16 and 17) than those with smaller substituents. 8% over-reduction product was observed in the reduction of alkyne **1p** (entry 16). For tertiary allylic alcohols (entries 18 and 19), low to moderate yields were obtained. Internal alkynes with no conjugation (Table 2, entries 20–22) necessitated higher temperatures than those conjugated with one phenyl group (entries 1 and 2). Semihydrogenation was retarded by bulky substituents (entry 22) and terminal alkynes were reduced much faster than internal alkynes (Table 2, entries 23–26). For terminal aryl alkynes (entries 24 and 25), longer reaction times resulted in significant over-reaction (entry 24, 7 h, alkane yield 17%; entry 25, 9 h, alkane yield 15%). Propargyl acetate was reduced to its corresponding allyl acetate with no formation of the allene.[19,27] The reaction scale could be increased to 10 mmol without any lowering of the yield and *Z*/*E* selectivity (Table 2, entry 28).

Having established the wide scope of our methodology, we tried its application in the synthesis of *cis*-combretastatin A-4 (CA-4). CA-4 is a natural product first isolated from the bark of the South African tree *Combretum caffrum* in 1989.[28] CA-4 is a powerful inhibitor of tubulin polymerization by binding to the colchicine site. It also can induce vascular damage within tumors at doses less than one-tenth of the maximum tolerated dose.[29] Two prodrugs of CA-4 are now in clinical trials: fosbretabulin disodium in phase II and Ombrabulin in phase III. Several methods have been reported for the synthesis of CA-4.[30]

Our rout to CA-4 is shown in Scheme 1, starting from commercially available 3,4,5-trimethoxybenzaldehyde (**3**) and *o*-methoxyphenol (**4**). Compounds **1z** and **6** were prepared according to reported procedure from **3**[31] in a yield of 70% and from **4**[32] in a total yield of 83%, respectively. Palladium-catalyzed coupling of **1z** and **6** afforded CA-4 precursor **7** in a good yield (70%). Under standard reaction conditions, semihydrogenation of **7** elicited combretastatin A-4 with a yield of 70%.

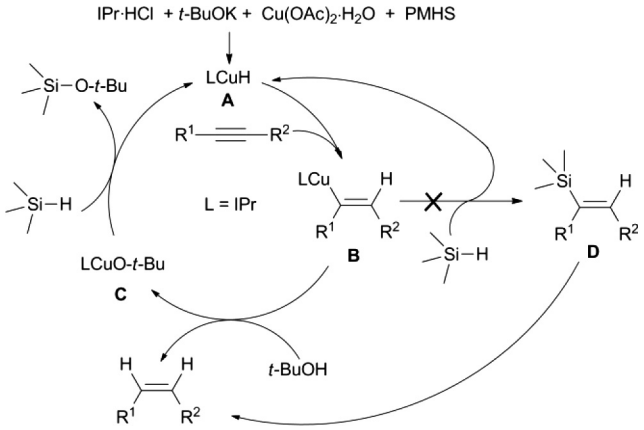


(2)



Scheme 1. Synthesis of combretasatin A-4.

A possible reaction mechanism is shown in Scheme 2. Active catalytic species **A** was generated in situ from IPr·HCl, *t*-BuOK, $Cu(OAc)_2·H_2O$, and PMHS. Alkenyl copper **B** is the key intermediate, which was formed from the *cis*-addition of copper hydride **A** to alkyne substrates. **B** was protonated by the alcohol to form species **C** and the desired product. The protonation step was supported by the fact that in the absence of *t*-BuOH, product **2b** was obtained only in a yield of 5% (GC). Hydrosilylation step (from **B** to **D**) could be excluded based on two experimental facts in the transformation from **1b** to **2b**: (1) under the standard reaction conditions, **2b** was obtained quantitatively without addition of the alkaline aqueous to hydrolyze the reaction mixture;[33] (2) In the absence of the alcohol, 92% (GC) of alkyne **1b** was recovered.[34]



Scheme 2. Proposed mechanism.

3. Conclusions

A convenient catalyst generated in situ from commercially available $Cu(OAc)_2·H_2O$, IPr·HCl, and *t*-BuOK, efficiently catalyzed the semihydrogenation of various internal and terminal alkynes to their corresponding alkenes with excellent *Z*-alkene selectivity for internal alkynes. Over-reduction was significantly suppressed in most cases, except for terminal aromatic alkynes and alkynes activated by strong electron-withdrawing groups. The catalytic reactions were carried out under mild conditions, and several functional groups were tolerated. The semireduction went smoothly even for bulky alkynes. Our catalyst can serve as a practical alternative to Lindlar catalyst in the semireduction of both internal and terminal alkynes.

4. Experimental section

4.1. Materials and analysis

Materials were obtained from commercial suppliers and purified by the standard procedure unless otherwise noted. $Cu(OAc)_2·H_2O$ (98+%, extra pure) and Polymethylhydrosiloxane (PMHS) were purchased from Acros and degassed before used. 1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) was prepared according to reported procedures.[35] *t*-BuOK was purchased from Acros and purified by sublimation. Toluene was purchased from Sinopharm Chemical Reagent Co, Ltd. (SCRC), distilled from sodium metal and degassed via three freeze–pump–thaw cycles before use.

NMR spectra were recorded on Advance Bruker 400M (^{1}H: 399 MHz; ^{13}C: 100 MHz) or Bruker Avance III 500M (^{1}H: 500 MHz; ^{13}C: 126 MHz) spectrometer. Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as internal and external standards, respectively. *J* values are given in Hertz. Gas chromatographic analyses were conducted on a Shimadzu GC-2014C equipped with a flame ionization detector. 1,3,5-Trimethylbenzene was used as internal standard. High-resolution mass spectra (HRMS) were recorded on a Micromass GCT GC–MS (Waters Corporation) or a maXis UHR-TOF HPLC-MS (Bruker Corporation) spectrometers.

4.2. General procedure for the copper-catalyzed semi-hydrogenation of alkynes: for liquid substrates (1a, b, c, e, k, o, p, q, t, u, v, x, y, aa, ab, ac)

In air, $Cu(OAc)_2·H_2O$ (5.0 mg, 5 mol %) and IPr·HCl (10.6 mg, 5 mol %) were placed in a screw-capped reaction vial. The vial was moved in to a glove box and *t*-BuOK (5.6 mg, 10 mol %) and solvent (1.0 ml) were added. The vial was moved out of the glove box and connected to an argon line through a needle. The mixture was raised to 50 °C and stirred for 1 h. PMHS (131 mg, 4.0 equiv) was then added dropwise with a microsyringe and the solution was stirred for an additional 30 min. After the mixture was changed to the specified reaction temperature, liquid alkyne (0.5 mmol) and *t*-BuOH (74 mg, 2.0 equiv) was added dropwise. The mixture was stirred for a specified period of time. The reaction mixture was subsequently hydrolyzed by adding 1 M NaOH aqueous (2 ml) (for substrates with no hydroxyl group) or 1 M TBAF in THF (2 ml) at 0 °C (for substrates with a hydroxyl group) for several hours. The mixture was extracted with ether (2 ml×3). Crude products were obtained after evaporation and purified by silica gel chromatography.

4.3. General procedure for the copper-catalyzed semi-hydrogenation of alkynes: for solid substrates (1d, f, g, h, i, j, l, m, q, r, w, z, and CA-4)

In air, $Cu(OAc)_2·H_2O$ (5.0 mg, 5 mol %), IPr·HCl (10.6 mg, 5 mol %), and solid substrates (0.5 mmol) were placed in a screw-capped reaction vial. The vial was moved into a glove box and *t*-BuOK (5.6 mg, 10 mol %) and solvent (1.0 ml) were added. The vial was moved out of the glove box and connected to an argon line through a needle. The mixture was raised to 50 °C and stirred for 1 h. The mixture was then treated in two different manners: (1) if reaction temperature ≥50 °C (**1d**, **i**, **j**, **q**, **r**, **w** and **CA-4**), PMHS (131 mg, 4.0 equiv) was then added dropwise with a microsyringe at 50 °C and the solution was stirred for an additional 30 min. After *t*-BuOH (74 mg, 2.0 equiv) was added, the mixture was raised to required reaction temperature and stirred for a specified period of time; (2) if reaction temperature <50 °C (**1f**, **g**, **h**, **l**, **m**, **z**), the mixture was first cooled to the required temperature and PMHS (131 mg, 4.0 equiv) was then added and the solution was stirred for an additional 30 min. After *t*-BuOH (74 mg, 2.0 equiv) was added, the mixture was stirred for a specified period of time. The reaction mixture was subsequently hydrolyzed by adding 1 M NaOH aqueous (2 ml) (for substrates with no hydroxyl group) or 1 M TBAF in THF (2 ml) at 0 °C (for substrates with a hydroxyl group) for several hours. The mixture was extracted with ether (2 ml×3). Crude products were obtained after evaporation and purified by silica gel chromatography.

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Supplementary data

Supplementary data associated with this article can be found. These data include additional reaction condition screening, spectra data for the main products described in this article. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.01.053. These data include MOL files and InChiKeys of the most important compounds described in this article.

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