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Highly Chemoselective Catalytic Hydrogenation of Unsaturated Ketones and Aldehydes to Unsaturated Alcohols Using Phosphine-Stabilized Copper(I) Hydride Complexes

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Abstract—A base metal hydrogenation catalyst composed of the phenyldimethylphosphine-stabilized copper(I) hydride complex provides for the highly chemoselective hydrogenation of unsaturated ketones and aldehydes to unsaturated alcohols, including the regioselective 1,2-reduction of α,β-unsaturated ketones and aldehydes to allylic alcohols. The active catalyst can be derived in situ by phosphine exchange using commercial $[(Ph_3P)CuH]_6$ or from the reaction of copper(I) chloride, sodium *tert*-butoxide, and dimethylphenylphosphine under hydrogen. The catalyst derived from 1,1,1-tris(diphenylphosphinomethyl)ethane is mechanistically interesting but less synthetically useful.
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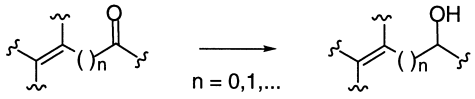
Introduction

Despite the considerable potential for applications to large-scale reduction of polyfunctional carbonyl-containing compounds, hydrogenation catalysts rigorously chemoselective for carbonyl reduction over alkene hydrogenation remain very rare.[1] With the exception of the ruthenium/diamine/base catalyst system recently disclosed by Noyori et al.,[2] the reported catalysts[3–5] reveal only modest selectivity or limited substrate range for conjugated or non-conjugated substrates, with the highest and most general selectivity obtained for the hydrogenation of α,β-unsaturated aldehydes.[4] Greater selectivity for carbonyl reduction can be obtained by using catalytic hydrosilylation methodology,[6] but this approach is accompanied by the additional costs associated with using a silane reductant and the subsequent hydrolysis of the resultant silyl ethers.

In this report, we describe phosphine-stabilized copper(I) hydride hydrogenation catalysts chemoselective for the reduction of ketones in the presence of alkenes and a broad range of other functionality typically reactive toward conventional hydrogenation catalysts (Eq. (1)). The copper(I) hydride catalyst stabilized by dimethylphenylphosphine is particularly selective, providing complete chemoselectivity for carbonyl reduction in nonconjugated unsaturated ketones and aldehydes and moderate to high levels of 1,2-reduction selectivity in the hydrogenation of α,β-unsaturated ketones and aldehydes.



(1)

We previously reported that the hydrogenation catalyst derived from the thermally stable copper(I) hydride complex $[(Ph_3P)CuH]_6$[7] (**1**) and excess triphenylphosphine mediates the chemoselective reduction of α,β-unsaturated ketones to saturated ketones or to saturated alcohols, depending on reaction conditions, yet is completely unreactive toward the hydrogenation of isolated alkenes, even under high hydrogen pressure and prolonged reaction time.[8] The hexameric complex **1**, however, is itself unreactive toward isolated ketones, leading to the conclusion that the hexamer must be transformed into more reactive copper(I) hydride species during the hydrogenolysis of the copper(I) enolate intermediate formed by initial conjugate hydride addition.[8a] Mechanistic investigations[8b,c] revealed that although the conjugate reduction is *inhibited* by the presence of excess triphenylphosphine, the ketone reduction is *accelerated*, suggesting that the catalyst responsible for ketone reduction is probably a lower aggregate (possibly monomeric) with a phosphine/copper stoichiometry of 2:1. Such complexes are expected to be both kinetically more reactive and more hydridic than the hexamer, leading to the subsequent reduction of the isolated ketone.

We therefore initiated an investigation of sterically smaller and more basic phosphine ligands, including multidentate phosphines, to develop catalysts capable of ketone

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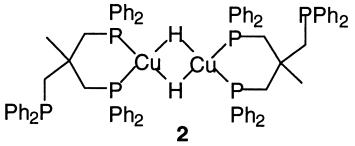
hydrogenation under mild conditions. Since the inhibition of conjugate reduction was a function of phosphine concentration, it also appeared reasonable to propose that catalysts of the composition $[(R_3P)_2CuH]_n$ might show selectivity for direct 1,2-reduction of α,β-unsaturated ketones and aldehydes.

Results and Discussion

Catalytic ketone hydrogenation using [η²-(1,1,1-tris(diphenylphosphinomethyl)ethane)CuH]₂

Copper(I) hydride complexes incorporating nominally bidentate phosphine ligands do not function as robust hydrogenation catalysts. The known complex $[(dppp)_4Cu_8H_8]$[9] (dppp=1,3-bis(diphenylphosphino)propane), for example, is a poor catalyst for ketone reduction, even in the presence of excess dppp ligand.[10] Catalysts derived in situ by phosphine exchange using 1,2-bis(dimethylphosphino)ethane or 1,2-bis(methylphenylphosphino)ethane[11] (stoichiometrically or in excess) and $[(Ph_3P)CuH]_6$ are also ineffective. Surprisingly, however, the known binuclear *bidentate* complex $[(\eta^2\text{-tripod})CuH]_2$[12] (**2**, tripod=1,1,1-tris(diphenylphosphinomethyl)ethane) indeed provides a synthetically modest but mechanistically interesting catalyst for chemoselective ketone reduction.



2

An initial investigation of ketone hydrogenation using $[(\eta^2\text{-tripod})CuH]_2$ as the catalyst revealed several highly unusual features. In contrast to $[(Ph_3P)CuH]_6$, the tripod catalyst decomposes slowly in aromatic solvents, requiring the use of tetrahydrofuran as solvent. The catalyst essentially ignores the anticipated beneficial effects of chelation: to sustain turnover and maintain catalyst homogeneity, the presence of excess tripodal phosphine (≥2 equiv./Cu) is required. This suggests that in the absence of free tripod, catalyst decomposition is triggered by total dissociation of the chelating tris(phosphine) ligand from the metal. This conclusion is supported by an independent assessment: upon addition of triphenylphosphine (1 equiv./Cu) to a solution of $[(\eta^2\text{-tripod})CuH]_2$ in benzene-d_6, a dynamic equilibrium with $[(Ph_3P)CuH]_6$ and free tripod is established in which a surprising 17% of the copper content is present as the hexamer, as established by NMR spectroscopic analysis.

Reaction conditions were optimized for the reduction of *tert*-butylcyclohexanone, a substrate that also allows for a sterically unbiased evaluation of the stereoselectivity of the reaction. The rate of catalytic hydrogenation is concentration dependent, with faster turnover observed upon *decreasing* the catalyst concentration. Thus, turnover increases from 1.2 h^{-1} at 0.2 M (in substrate) to 3.5 h^{-1} at 0.05 M (in substrate) for reactions run at 50 psi (gauge pressure) of hydrogen pressure and 2.5 mol% $[(\eta^2\text{-tripod})CuH]_2$, but then decreases upon further dilution.[13] This behavior is consistent with a mechanism involving equilibrium dissociation of the catalytically inactive dimer **2** into reactive monomeric fragments.[14]

The pressure dependence of the hydrogenation reaction is most unusual. Slow catalyst decomposition is observed at hydrogen pressures below 50 psi, but sustained turnover and optimum reaction rate are obtained at pressures from 50–70 psi. At higher pressure, however, *turnover is strongly inhibited*. To confirm this unexpected observation, the pressure dependence was evaluated at two different concentrations; the results are presented in Fig. 1. While the observation of saturation kinetics in homogeneous hydrogenation at higher pressures is not unusual, turnover *inhibition* by hydrogen is, to our knowledge, unique. The origin of this phenomenon was probed in a series of control experiments in which the catalyst alone and catalytic reduction reaction mixtures were 'aged' under hydrogen pressure (both high and low) for an extended period. No decomposition of $[(tripod)CuH]_2$ was observed under these conditions and the rates of catalytic hydrogenation were fully restored upon returning to typical operating pressures. The catalyst is thus *reversibly* inhibited by hydrogen at high pressure. Although no supporting evidence can be provided, we speculate that the reversible formation of a catalytically inactive Cu(I) dihydrogen complex, e.g. $[(\eta^2\text{-tripod})CuH(H_2)]$, may be responsible for the observed pressure dependence. A simple, but related, copper(I) dihydrogen complex $[Cu(\eta^2\text{–}H_2)Cl]$ has been prepared and characterized by infrared spectroscopy at low temperature in an argon matrix; the structure assignment is also supported by ab initio calculations.[15] The rate inhibition is thus analogous to that observed in enzyme-catalyzed two-substrate compulsory order reactions in the presence of a high concentration of the second substrate.[16] Consistent with this proposal, a normal concentration dependence for the rate of hydrogenation is restored at very high hydrogen pressure (see Fig. 1): the coordination of dihydrogen by the monomeric copper fragment displaces the dimer/monomer equilibrium toward a monomeric precatalyst complex. The reduction of *tert*-butylcyclohexanone is markedly inhibited by the presence of cyclohexene or stilbene, neither of which is consumed in the reaction. Nonpolar double bonds thus coordinate to, but are not reduced by, this catalyst.

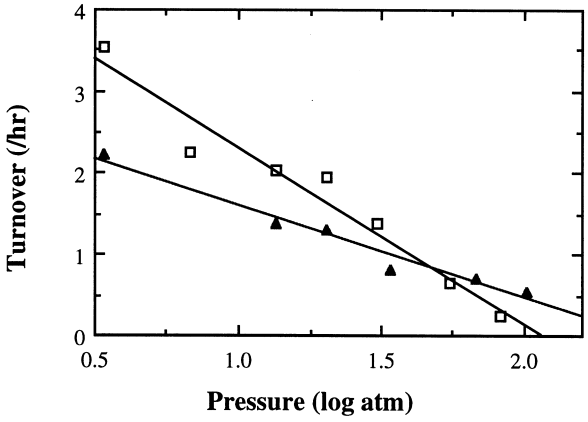
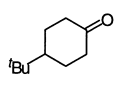
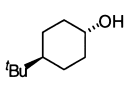
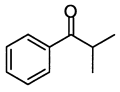
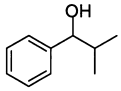
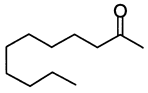
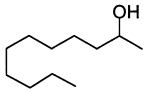
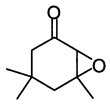
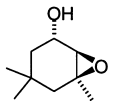
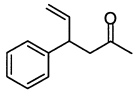
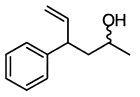
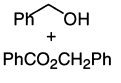


Figure 1. Pressure dependence in the reduction of *tert*-butylcyclohexanone. Conditions: 2.5 mol% **2**, 10 mol% tripod, THF, RT, H_2 as noted. Concentration, in substrate: ▲=0.2 M; □=0.1 M.

Table 1. Catalytic reduction of ketones and aldehydes using $[(\eta^2\text{-tripod})CuH]_2$ and H_2

Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b]	Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b]
							
1	A	7	92 (8 : 1)[c]	**5**	E	24	91
2	B	24	98 (4 : 1)[c]	**6**	F	48	90
							
3	C	36	90	**7**	D	30	95 (11 : 1)[c]
							
4	D	60	94 (~3 : 2)[d]	**8**	C	20	84 (1 : 1)[e]
				9	G	25	100 (19 : 1)[e]

[a]Reduction conditions: A, 2.5 mol% $[(tripod)CuH]_2$, 2 equiv. tripod/Cu, THF, 0.1 M in substrate, 50–60 psi H_2, RT; B, as A, except 0.8 mol% $[(Ph_3P)CuH]_6$, 3 equiv. tripod/Cu, 0.2 M; C, as A, except 0.2 M; D, as A, except 0.05 M; E, as C, except 5 mol% catalyst; F, as B, except 0.1 M; G, as B, except 500 psi H_2.
[b]All yields refer to isolated purified products, assignments by comparison to known compounds or authentic materials. All reactions were set up under N_2; quenched by exposure to air and addition of sat. aq NH_4Cl. Products were purified by flash chromatography.
[c]Minor isomer is epimeric at the hydroxy center.
[d]Stereoisomer unassigned.
[e]Conversions and product ratios determined by ^1H NMR spectroscopy.

Under optimized conditions, the synthetic scope of catalytic hydrogenation using $[(\eta^2\text{-tripod})CuH]_2$ is somewhat limited, principally by the slow rates observed for substrates with even modest steric hindrance. Nonetheless, reductions that do proceed are clean and nearly quantitative (Table 1). The reduction of cyclic ketones proceeds with reasonable stereoselectivity (entries **1**, **7**).[17] The catalyst can be prepared conveniently by in situ phosphine exchange starting with commercially available hexamer **1**, although catalyst turnover is attenuated and the stereoselectivity diminished (entries **2**, **6**).[18] While turnover is again inhibited, no reduction of isolated olefins is observed (entry **4**), but the catalyst maintains a preference for conjugate reduction of α,β-unsaturated ketones. The catalyst neither opens epoxides (entry **7**) nor reduces carboxylic esters. Nitrile functionality, such as is present in 5-cyano-2-pentanone, inhibits all catalytic activity. The catalyst is very sensitive to steric effects neighboring the carbonyl group, requiring higher catalyst loading to achieve complete conversion in a reasonable reaction time (entry **5**). Cyclopentanone substrates (e.g. indanone, 2-allyl-2-carboethoxycyclopentanone) are reduced very slowly by this catalyst. Catalytic reduction of aldehydes (entries **8**, **9**) requires elevated pressure to suppress the competitive Tishchenko condensation.[19]

Catalytic ketone hydrogenation using dimethylphenylphosphine-derived copper(I) hydride catalysts

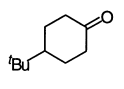
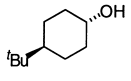
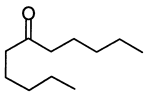
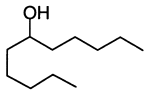
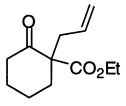
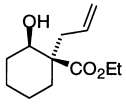
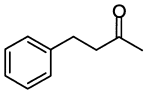
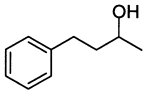
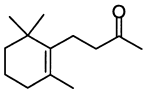
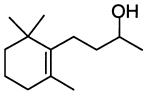
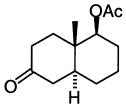
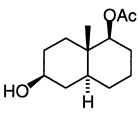
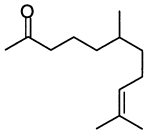
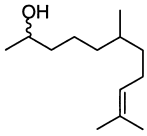
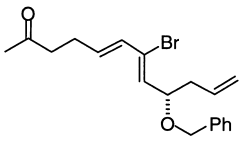
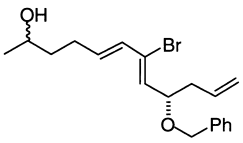
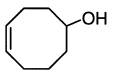
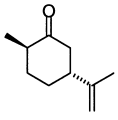
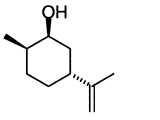
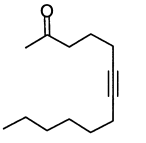
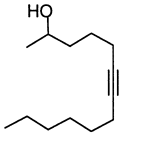
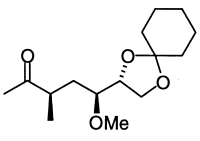
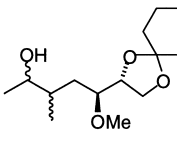
Given the apparent failure of chelation to limit phosphine lability in copper(I) hydride complexes, an empirical investigation of ligand effects on the structure and hydrogenation reactivity of copper(I) hydride complexes was initiated. Our preliminary evaluation of simple, strongly basic monophosphine ligands revealed that very subtle alterations of the phosphine structure lead to incommensurate changes in the structure and function of the resulting copper complexes.[20] Thus, although discrete, isolable hexameric copper(I) hydride complexes are formed from the hydrogenolysis of copper(I) *tert*-butoxide in the presence of either *ethyl*diphenylphosphine or di*ethyl*phenylphosphine,[21] neither complex is an effective hydrogenation catalyst. The corresponding *methyl*diphenylphosphine and di*methyl*phenylphosphine derivatives, however, manifest dramatically different structure and reactivity properties, despite the closely analogous steric and electronic character of the ligands themselves. While methyldiphenylphosphine has a slightly smaller cone angle[22] and marginally greater nucleophilicity[23] than does ethyldiphenylphosphine, no change in the stretching frequency of coordinated carbon monoxide is observed when these phosphines are interchanged at various metal centers.[24] In other catalytic hydrogenation reactions, the function of these two ligands is virtually indistinguishable.[5b]

Nonetheless, no well-defined copper(I) hydride complex can be isolated from the hydrogenolysis of $[Cu(O^tBu)]_4$ in the presence of excess methyldiphenylphosphine. Instead, a thermochromic oil is obtained, which varies in color from deep red at ambient temperature to yellow at −40°C.[20] The product is thus variable in composition, *suggesting* an equilibration between a red hexameric aggregate of 1:1 phosphine/copper stoichiometry and a yellow dimeric complex with a 2:1 phosphine/copper ratio

over this temperature range, consistent with analysis of the product by variable temperature ^1H and ^{31}P NMR spectroscopy. Under otherwise identical conditions, the hydrogenolysis of $[CuO^tBu]_4$ in the presence of excess dimethylphenylphosphine leads initially to the formation of a yellow solution, which darkens rapidly and deposits an intractable precipitate. Similarly, addition of excess dimethylphenylphosphine to a solution of $[(Ph_3P)CuH]_6$ initially gives an orange–yellow solution, which deteriorates visibly within a few hours at room temperature.

Despite—or perhaps because of—this instability, the dimethylphenylphosphine-derived copper(I) hydride complex is an excellent catalyst for the chemoselective hydrogenation of ketones under very mild conditions (Table 2). The catalyst can be conveniently generated in situ by one of two procedures: (i) ligand exchange using

Table 2. Catalytic reduction of ketones using Me_2PPh-stabilized copper(I) hydride and H_2

Substrate/ Entry	Conditions[a]	Time (h)[b]	Product(s)/ Yield (%)[c,d]	Substrate/ Entry	Conditions[a]	Time (h)[b]	Product(s)/ Yield (%)[c,d]
							
1	A (50 h) or B (18 h)		96 (3 : 1)	**8**	C	48	83 (25 : 1)
							
2	C (28 h) or D (12 h)		95	**9**	D	30	79 (10 : 1)
							
3	C	30	95	**10**	D	60	76 (1.6 : 1)[e]
							
4	C	24	98	**11**	C	27	93 (16 : 1)
							
5	C	36	87 (1 : 1)	**12**	D	30	89 (1 : 1)
							
6	C	24	98	**13**	C	36	90 (6 : 3 : 1)[f]
							
7	C	24	99	**14**	C	30	93 (1 : 1 : 1 : 1)

[a]Conditions. A, 0.33 mol% $[(Ph_3P)CuH]_6$ (2 mol% Cu), Me_2PPh (6 equiv./Cu), 1 atm H_2, C_6H_6 (0.4–0.8 M in substrate), *tert*-butanol (10–20 equiv./Cu), RT; B, as A, except 5 mol% CuCl and NaO^tBu, Me_2PPh (6 equiv./Cu); C, as A, except 0.83 mol% $[(Ph_3P)CuH]_6$ (5 mol% Cu); D, as A, except 1.67 mol% $[(Ph_3P)CuH]_6$ (10 mol% Cu).

[b]Many reaction times not optimized.

[c]Major stereoisomer; minor epimeric at alcohol center. Stereochemical ratio in parentheses; determined by isolation and separation or by ^1H NMR integration of crude product.

[d]Isolated yields after purification by chromatography. Products identified by comparison with authentic materials prepared by unambiguous synthesis.

[e]16% starting material recovered.

[f]Second isomer epimeric at methyl and alcohol centers; third isomer epimeric at alcohol position.

commercially available $[(Ph_3P)CuH]_6$ (**1**) and excess dimethylphenylphosphine, or (ii) direct synthesis from cuprous chloride, sodium *tert*-butoxide, and dimethylphenylphosphine (1:1:6) in anhydrous benzene under a hydrogen atmosphere at room temperature. The exchange procedure is operationally simpler, but for some substrates (vide infra) leads to a deterioration in stereoselectivity, arising from the presence of triphenylphosphine in the reaction medium. The latter procedure is most attractive, using only inexpensive, commercially available reagents, but proceeds via in situ formation of the oxygen-sensitive copper(I) *tert*-butoxide complex and demands greater attention to reagent purity and experimental technique.

The dimethylphenylphosphine-derived catalyst functions slowly, normally requiring between 2 and 10 mol% copper to obtain reasonable reaction time. Excess phosphine (6 equiv. per copper) is required for sustained turnover; the use of lower phosphine concentration leads to slow decomposition of the catalyst during the reduction of some substrates. The catalyst does not tolerate high temperatures, but appears to be reasonably robust at room temperature: the reduction of *tert*-butylcyclohexanone proceeds to completion at atmospheric hydrogen pressure using as little as 0.5 mol% copper. The infusion of additional substrate to a completed hydrogenation reaction results in resumption of conversion with a negligible impact on turnover, provided the catalyst mixture is not allowed to age for a prolonged period in the absence of substrate. The catalyst exhibits normal pressure dependence, but for *some* substrates, the use of higher pressure leads to slow deterioration of the catalyst, a phenomenon that is, as yet, poorly understood. Finally, the presence of *tert*-butanol (10–20 equiv./copper) in the reaction medium prolongs the lifetime of the catalyst, presumably by inducing alcoholysis of less stable copper(I) alkoxide intermediates to give the thermally more robust copper(I) *tert*-butoxide complex,[8] which then undergoes hydrogenolysis without competitive decomposition.

Synthetically, the system functions for a broad range of organic substrates and shows *unparalleled* chemoselectivity, reducing ketones in the presence of isolated alkenes (entries **4**–**6**, **9**), alkynes (entry **7**), dienes (entry **12**), vinylic halides (entry **12**) and allylic and benzylic oxygenates (entry **12**), all functionality typically reduced by standard hydrogenation catalysts. The hydridic catalyst does not open epoxides (entry **8**) nor reduce esters (**9**, **11**). Primary *p*-toluenesulfonate functionality survives this reduction reaction, but the catalyst slowly deactivates during the course of the reduction, which does not proceed to completion even at a catalyst loading of 10 mol% (entry **10**). The hydrogenation rate is inhibited by the presence of sterically accessible alkene functionality (e.g. entries **9**, **12**), suggesting that the catalyst binds competitively to alkenes. The catalyst generally provides the same sense of stereoinduction as that delivered by standard hydride reagents, but the stereoselectivity of the catalytic reduction is generally superior. Stereogenic centers adjacent to the ketone functionality are unfortunately epimerized during the reduction, presumably as a consequence of the strongly basic copper(I) alkoxide intermediates formed during the reaction (entries **13**, **14**). Cyclopentanone substrates are reduced only very slowly by this catalyst; such reactions generally do not proceed to completion at 10 mol% catalyst.[25]

Catalytic 1,2-reduction of α,β-unsaturated aldehydes and ketones

In contrast to the reactivity of catalysts derived from $[(Ph_3P)CuH]_6$[8] and $[(\eta^2\text{-tripod})CuH]_2$, the dimethylphenylphosphine-stabilized copper(I) catalyst retains its selectivity for carbonyl reduction in the hydrogenation of α,β-unsaturated ketones and aldehydes. The hydrogenation reaction tolerates the use of either benzene or tetrahydrofuran as solvent, but requires a somewhat higher concentration of *tert*-butanol as a co-solvent to ensure sustained turnover and reaction homogeneity. In contrast to the reduction of isolated ketones, hydrogen pressures above one atmosphere are generally required to obtain complete conversion of conjugated substrates, *perhaps* due to greater competitive inhibition arising from coordination of the electron-deficient olefin of the substrate or product to an unsaturated copper(I) intermediate.[26] In the reduction of conjugated aldehydes, the higher hydrogen pressure also inhibits the formation of pseudo-dimeric esters from competitive Tishchenko reaction.

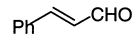
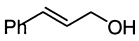
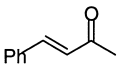
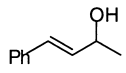
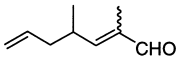
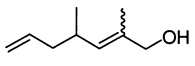
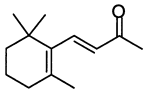
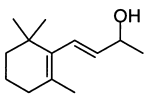
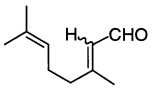
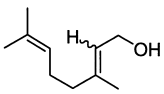
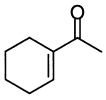
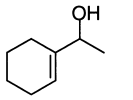
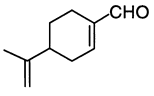
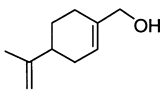
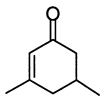
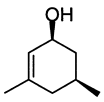
Under optimized conditions, the catalytic hydrogenation of α,β-unsaturated aldehydes is general for the formation of allylic alcohols in high yield (Table 3, entries **1**–**4**). The reaction is highly regioselective regardless of substitution pattern, but returns a minor amount of the saturated alcohol from complete reduction of both the conjugated double bond and the carbonyl group. Control experiments establish that the minor product arises from the competitive conjugate reduction followed by subsequent reduction of the carbonyl; allylic alcohols are completely unreactive toward this catalyst.[27]

The selectivity obtained in the hydrogenation of α,β-unsaturated ketones is more variable (Table 3, entries **5**–**9**). Acyclic substrates are reduced with high selectivity for the formation of the corresponding allylic alcohol, but the reduction of cyclohexenones (e.g. entry **8**) is more problematic, delivering a modest 2.7:1 selectivity using standard exchange conditions. The selectivity is improved by removing the triphenylphosphine from the reaction medium (entry **9**): by generating the catalyst from copper(I) chloride, sodium *tert*-buoxide, and dimethylphenylphoshine, the product ratio is raised to approximately 4.4:1 in favor of the allylic alcohol. Although we do not understand the origin of the lower regioselectivity observed for the reduction of cyclohexenones, it is interesting to note that these derivatives also return the poorest selectivity in hydrogenations catalyzed by Noyori's ruthenium system.[2] The reduction of cyclohexenone substrates using catalysts derived from methyldiphenylphosphine, triethylphosphine, and tri-*n*-butylphosphine all proceed with high conversion, but deliver markedly lower selectivity for allylic alcohol formation. Structurally related ligands such as trimethylphosphine and tricyclohexylphosphine do not provide productive hydrogenation catalysts.

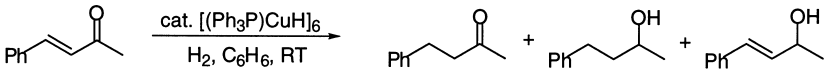
The reactivity of copper(I) hydride hydrogenation catalysts

is thus exceptionally sensitive to the structure of the phosphine ligand. In the hydrogenation of 4-phenyl-3-buten-2-one, for example, it is possible to obtain each of the three reduction products with high selectivity, simply by varying the ancillary ligand added to the reaction mixture (Eq. (2)). exhibits an *unprecedented* level of chemoselectivity in the hydrogenation of highly functionalized ketone substrates, with a reactivity profile more consistent with classical hydride reagents than with typical hydrogenation catalysts. The dramatic differences observed in the

Table 3. Catalytic reduction of α,β-unsaturated ketones and aldehydes using Me_2PPh-stabilized copper(I) hydride and H_2

Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b,c]	Substrate/ Entry	Conditions.[a]	Time (h)	Product(s)/ Yield (%)[b,c]
							
1	A	4	94 (32 : 1)[d]	**5**	C	18	84 (12 : 1)[g]
							
2[e]	B	30	91 (16 :1)[e]	**6**	C	26	89 (49 : 1)
							
3[f]	C	15	90 (11 : 1)[f]	**7**	C	20	94 (17 : 1)
							
4	C	18	95 (32 : 1)	**8** **9**	C D	30 25	90 (2.7 : 1)[h] 92 (4.4 : 1)[h]

[a]Reaction conditions. A, 0.83 mol% $[(Ph_3P)CuH]_6$ (5 mol% Cu), $PhPMe_2$ (6 equiv./Cu), 70 psi H_2, C_6H_6 (0.4–0.8 M in substrate), *tert*-butanol (40 equiv/Cu), RT; B, as A, 400 psi H_2; C, as A, except 500 psi H_2; D, as A, except copper introduced as CuCl (5 mol%) with NaO^tBu (5 mol%), 1000 psi H_2.
[b]Major product indicated; minor product is saturated alcohol (1,4+1,2 reduction). Product ratio is given in parentheses.
[c]Isolated yields after purification by chromatography. Products identified by comparison with authentic materials prepared by unambiguous synthesis (see Experimental).
[d]Remaining material identified (NMR spectroscopy) as the Tishchenko reaction product $PhCH{=}CHCH_2OC(O)CH{=}CHPh$.
[e]*E/Z*=10:1 (substrate), 10:1 (product).
[f]*E/Z*=2:1 (substrate and product).
[g]Isolated yield after acetylation (Ac_2O/pyr) and purification.
[h]Major allylic alcohol stereoisomer indicated (12:1); minor epimeric at hydroxyl center.



(1)	No added phosphine, 10h 2.7 mol% **1**, 1000 psi H_2	91	:	9	:	0	89%[8]
(2)	Ph_3P (12 equiv/Cu), 24h 2.7 mol% **1**, 1700 psi H_2	0	:	92	:	8	95%[8]
(3)	Me_2PPh (6 equiv/Cu), 18h 0.83 mol% **1**, 500 psi H_2	0	:	8	:	92	91%

(2)

Compared to Noyori's ruthenium catalyst,[2] the copper(I)-based catalyst functions more slowly and, for the hydrogenation of conjugated ketones and aldehydes, is less regioselective for 1,2-reduction. Nonetheless, the selectivity is impressive and examples of inexpensive base metal hydrogenation catalysts remain very rare. The dimethylphenylphosphine-stabilized copper(I) system structure, dynamics, and function of copper(I) hydride complexes derived from closely related phosphine derivatives are difficult to rationalize, although an understanding of this subtle interplay of steric and electronic factors is critical to the development of an asymmetric version of this highly chemoselective catalytic reduction.

Experimental

General experimental

Unless otherwise noted, all manipulations were performed under an inert atmosphere using standard Schlenk techniques or in a glove box (≤1 ppm O_2). Reactions run under hydrogen pressure were performed in a Fischer & Porter (Andrews Glass) medium pressure bottle[28] (20–75 psi) or in a magnetically stirred, glass-lined, Parr stainless steel autoclave (75–1500 psi), each equipped with Swagelok Quick-connects and pressure gauges. Vacuum transfers of known amounts of air sensitive volatile compounds were performed at high vacuum (10^{-5} mmHg) using MKS Baratron digital pressure transducers for measurement of vapor pressures in known volume flasks. All solvents, reagents, and commercial substrates were used as received or purified by standard methods. Toluene, benzene, benzene-d_6, diethyl ether, hexanes, pentane, and tetrahydrofuran were dried and deoxygenated by distillation from sodium or potassium benzophenone ketyl. Acetonitrile, dichloromethane, and pyridine were distilled from calcium hydride and deaerated by repeated freeze–pump–thaw cycles or by purging with nitrogen. Chromatography solvents were used as received. Product purification was performed by preparative-layer chromatography on precoated glass-backed silica gel plates (E. Merck 60 F_{254}, 0.5–1.0 mm) or by flash chromatography[31] using E. Merck Kieselgel 60, 230–400 mesh.

Materials

tert-Butanol was distilled from sodium, deaerated and stored under nitrogen. $[(Ph_3P)CuH]_6$[29] and $[(\eta^2\text{-tripod})CuH]_2$[12] were prepared and purified according to literature procedures. All tertiary phosphines except commercial triphenylphosphine and triethylphosphine were prepared by literature methods[11,30] and deoxygenated before use. 2-Undecanone, 6-undecanone, 4-*tert*-butylcyclohexanone, 4-phenyl-2-butanone, 2-methyl-1-phenyl-1-propanone, dihydrocarvone (2 isomers), benzaldehyde, cinnamaldehyde, 2,4-dimethyl-2,6-heptadienal, citral, perillaldehyde, β-ionone, 1-acetyl-1-cyclohexene, and 3,5-dimethylcyclohexenone were purchased from commercial suppliers. 4-Phenyl-5-hexen-2-one,[32] isophorone oxide,[33] dihydro-β-ionone,[34] 6,10-dimethyl-9-undecen-2-one,[35] 2-allyl-2-carbethoxycyclohexan-1-one,[36] and 1(β)-acetoxy-8a(β)-methyl-1,2,3,4,4a(α),5,8,8a-octahydronaphthalene-6(7H)-one[37] were prepared according to literature procedures. Cyclooct-4-en-1-one was prepared by the oxidation of cyclooct-4-en-1-ol[38] (aqueous chromic acid, acetone, 0°C). Trideca-2-one-6-yne was prepared by alkylation of 1-lithio-1-octyne (1-octyne, *n*-BuLi, NH_3, −78°C) with the ethylenedioxy acetal of 5-chloro-2-pentanone (NH_3, −33°C), followed by hydrolysis (0.5N HCl, THF). 3-[4-(*p*-Toluenesulfonyloxy)butyl]-2-cyclohexanone[39a] was prepared by tosylation of 3-(4-hydroxybutyl)-2-cyclohexanone[39b] under standard conditions. 4-Benzyloxy-6-bromo-(5*E*,7*E*)-1,5,7-undecatrien-11-ol[40] was furnished by Prof. W. R. Roush (University of Michigan) and converted to 4-benzyloxy-6-bromo-(5*E*, 7*E*)-1,5,7-dodecatrien-11-one by oxidation (aqueous chromic acid, acetone, 0°C), followed by conversion of the resulting carboxylic acid to the acid chloride (oxalyl chloride, benzene, RT) and treatment with $LiMe_2Cu$ (Et_2O, −78°C). 5(*S*),6-(Cyclohexylidenyl-1,1-dioxy)-4(*S*)-methoxy-2(*R*)-methylhexanoic acid[41] was furnished by Prof. D. R. Williams (Indiana University) and converted to 6(*S*),7-(cyclohexylidenyl-1,1-dioxy)-5(*S*)-methoxy-3(*R*)-methylheptan-2-one by treatment with oxalyl chloride followed by $LiMe_2Cu$, as described above.

Product identification

Reaction products were identified spectroscopically and compared to authentic materials prepared by unambiguous synthesis. Isolated alcohols were prepared by standard ketone reduction using $NaBH_4$ in methanol or $LiAlH_4$ in diethyl ether. Allylic alcohols were prepared from α,β-unsaturated aldehydes and ketones by treatment with $NaBH_4/CeCl_3$ in methanol.[42] Fully reduced alcohols were prepared by catalytic hydrogenation of the allylic alcohols using Pd/C and H_2 (1 atm)[43] or, in the case of α,β-unsaturated aldehydes, by reduction using stoichiometric $[(Ph_3P)CuH]_6$ (0.4–0.5 equiv.).[44] High resolution spectroscopic data are included for selected literature compounds for which the data are unreported or of poor quality.

General procedure for catalytic reductions using $[(\eta^2\text{-tripod})CuH]_2$

In the glove box (or on the bench with rigorous oxygen exclusion), the Fischer & Porter bottle was loaded with a solution with $[(\eta^2\text{-tripod})CuH]_2$ (5–10 mol% in copper) and tripod (2–3 equiv. per Cu) in THF (1–3 ml). To this solution was added the ketone in anhydrous THF (1 ml, final concentration: 0.2–0.05 M in substrate) and a stirbar. The vessel was sealed and connected via hydrogen-flushed pressure tubing to a hydrogen tank, flushed with hydrogen (pressurized to >50 psig and vented, five times), and pressurized (50–70 psig). The yellow solution was stirred vigorously for the specified length of time (Table 1) or until TLC analysis indicated complete reduction. The vessel was vented to air, quenched with a few drops of saturated aqueous NH_4Cl, diluted with ether, and dried over $MgSO_4$. After filtration through Celite and concentration, the residue was purified by chromatography.

Reduction of 4-*tert*-butylcyclohexanone using a catalyst derived from $[(Ph_3P)CuH]_6$ and tripod

In the glove box, a solution of 4-*tert*-butylcyclohexanone (62.6 mg, 0.406 mmol) in anhydrous THF (1 ml) was added to a Fischer & Porter bottle charged with a solution of $[(Ph_3P)CuH]_6$ (6.6 mg, 0.0034 mmol) and tripod (38.2 mg, 0.0612 mmol) in THF (1 ml). The vessel was sealed, removed from the glovebox, flushed with hydrogen and pressurized to 50 psig. The yellow solution was stirred vigorously for 24 h. The vessel was vented to air, quenched with a few drops of saturated aqueous NH_4Cl and diluted with ether. After drying with $MgSO_4$ and filtration through Celite, concentration and chromatography (15% EtOAc/hexanes) gave *trans* and *cis* 4-*tert*-butylcyclohexanol (62.4 mg, 98%, 4:1 *trans/cis*). Partial ^1H NMR spectrum (500 MHz, $CDCl_3$): *trans*-4-*tert*-butylcyclohexanol δ 3.51 (1H, tt, *J*=4.3, 10.9 Hz, CHO*H*), 0.84 (9H, s); *cis*-4-*tert*-butylcyclohexanol δ 4.03 (1H, quintet, *J*=2.7 Hz), 0.85

(9H, s). The products were identified by comparison to a commercial sample.

Reduction of 4-*tert*-butylcyclohexanone using [(η^2-tripod)CuH]$_2$

Using the general procedure, 4-*tert*-butylcyclohexanone (31.2 mg, 0.203 mmol), [(η^2-tripod)CuH]$_2$·2THF (7.7 mg, 0.005 mmol), and tripod (12.6 mg, 0.020 mmol) were hydrogenated for 7 h, giving 4-*tert*-butylcyclohexanol (29.0 mg, 92%, 8:1 *trans/cis*). The products were identified as described above.

Reduction of 2-undecanone

Using the general procedure, 2-undecanone (68.8 mg, 0.404 mmol), [(η^2-tripod)CuH]$_2$·2THF (15.4 mg, 0.010 mmol), and tripod (38.0 mg, 0.061 mmol) were hydrogenated for 36 h, giving 2-undecanol (62.5 mg, 90%). The product was identified by comparison to a commercial sample.

Reduction of 4-phenyl-5-hexen-2-one

Using the general procedure, 4-phenyl-5-hexen-2-one (35.5 mg, 0.204 mmol), [(η^2-tripod)CuH]$_2$·2THF (15.4 mg, 0.010 mmol), and tripod (38.0 mg, 0.061 mmol) were hydrogenated for 60 h, giving 4-phenyl-5-hexen-2-ol[45] (33.0 mg, 92%) as an unassigned 3:2 mixture of diastereomers. The products were identified by comparison to an authentic sample prepared by unambiguous synthesis.

Reduction of 2-methyl-1-phenyl-1-propanone

Using the general procedure, 2-methyl-1-phenyl-1-propanone (30.0 mg, 0.203 mmol), [(η^2-tripod)CuH]$_2$·2THF (15.4 mg, 0.010 mmol), and tripod (38.0 mg, 0.061 mmol) were hydrogenated for 24 h, giving 2-methyl-1-phenyl-1-propanol (28.0 mg, 91%). The product was identified by comparison to an authentic sample prepared by unambiguous synthesis.

Reduction of isophorone oxide using [(η^2-tripod)CuH]$_2$

Using the general procedure, isophorone oxide (31.4 mg, 0.204 mmol), [(η^2-tripod)CuH]$_2$·2THF (7.0 mg, 0.005 mmol), and tripod (12.6 mg, 0.020 mmol) were hydrogenated for 30 h, giving a mixture of isomeric 2,3-epoxy-3,5,5-trimethylcyclohexan-1-ols,[46] which were separated by chromatography (4:1 hexanes/ethylacetate) to give pure *trans*-epoxy alcohol (27.7 mg, 87%) and *cis*-epoxy alcohol (2.5 mg, 8%). Major isomer: TLC R_f=0.31, 2:1 hexanes/ethyl acetate; IR (neat, cm^{-1}) 3420, 2980–2880, 1450, 1410, 1375, 1360, 1270, 1250, 1180, 1080, 1040, 990, 940, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (1H, m), 2.95 (1H, s), 1.9 (1H, d, J=4.8 Hz), 1.70 (1H, d, J=15.2 Hz), 1.63 (1H, dd, J=5.6, 13.6 Hz), 1.51 (1H, *d*, J=15.2 Hz), 1.33 (3H, s), 1.16 (1H, dd, J=7.6, 13.6 Hz), 0.96 (3H, s), 0.90 (3H, s); Minor isomer: TLC R_f=0.22, 2:1 hexanes/ethyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (1H, m), 3.14 (1H, d, J=2.0 Hz), 1.64 (1H, d, J=14.8 Hz), 1.52–1.40 (2H, m), 1.35 (3H, s), 1.66 (1H, dd, J=11.2, 12.4 Hz), 0.89 (3H, s), 0.86 (3H, s); HRMS calcd for $C_9H_{16}O_2$=156.1146 (M^+), found=156.1150. The data are consistent with the literature values.[46]

Reduction of benzaldehyde using a catalyst derived from [(Ph_3P)CuH]$_6$ and tripod

Using the procedure described above for 4-*tert*-butylcyclohexanone, benzaldehyde (21.5 mg, 0.203 mmol), [(Ph_3P)CuH]$_6$ (6.6 mg, 0.0034 mmol), and tripod (50.4 mg, 0.081 mmol) were hydrogenated at 500 psig hydrogen in the steel autoclave for 25 h, giving a mixture of benzyl alcohol and benzyl benzoate (19:1) in quantitative yield. The products were identified by comparison to authentic samples.

General procedure for reduction of saturated ketones using [(Ph_3P)CuH]$_6$ and Me_2PPh

In the glove box, [(Ph_3P)CuH]$_6$ (1–10 mol% Cu), Me_2PPh (6 equiv./Cu) and *tert*-butanol (10–20 equiv./Cu) were combined in a Schlenk flask and dissolved in benzene. To this solution was added a solution of the substrate (10–100 equiv./Cu) in benzene (0.4–0.8 M in substrate). The flask was sealed, transported out of the drybox and placed under a slight positive pressure of hydrogen after one freeze–pump–thaw degassing cycle. The resulting yellow–orange homogeneous solution was allowed to stir until complete by TLC analysis. The reaction mixture was exposed to air, diluted with ether, and treated with a small amount of silica gel. This mixture was stirred in the air for $\geq$0.5 h prior to filtration, concentration in vacuo, and purification by flash chromatography. When the polarity of the product was similar to that of the residual phosphine, the crude mixture was treated with sodium hypochlorite (5% aqueous solution) and filtered through silica gel/$MgSO_4$ prior to chromatography.

General procedure for reduction of saturated ketones using CuCl, NaO^{t}Bu, and Me_2PPh

Under an inert atmosphere, a solution of the substrate in benzene was added to a slurry of freshly purified CuCl (5 mol%), NaO^{t}Bu (5 mol%), Me_2PPh (6 equiv./Cu) and *tert*-butanol (10 equiv./Cu) in benzene (final concentration: 0.4–0.8 M in substrate). After degassing with one freeze–pump–thaw cycle, the suspension was placed under a slight positive pressure of hydrogen and allowed to stir until complete by TLC analysis. The product was isolated and purified as described above.

Reduction of 4-*tert*-butylcyclohexanone using [(Ph_3P)CuH]$_6$ and Me_2PPh

Using the general procedure, 4-*tert*-butylcyclohexanone (0.10 g, 0.65 mmol), [(Ph_3P)CuH]$_6$ (0.0041 g, 0.0021 mmol, 1.85 mol% Cu), *tert*-butanol (0.019 g, 0.26 mmol), and dimethylphenylphosphine (0.011 g, 0.078 mmol) were combined and hydrogenated for 50 h, giving 4-*tert*-butylcyclohexanone (0.098 g, 97%, 3:1 *trans/cis*). The products were identified by comparison to commercial samples.

Reduction of 6-undecanone

Using the general procedure, 6-undecanone (0.050 g, 0.29 mmol), $[(Ph_3P)CuH]_6$ (0.0096 g, 0.0049 mmol, 10 mol% Cu), *tert*-butanol (0.022 g, 0.29 mmol), and dimethylphenylphosphine (0.024 g, 0.176 mmol) were combined and hydrogenated for 12 h, giving 6-undecanol (0.048 g, 95%). The products were identified by comparison to an authentic sample.

Reduction of 4-phenyl-2-butanone

Using the general procedure, 4-phenyl-2-butanone (0.025 g, 0.169 mmol), $[(Ph_3P)CuH]_6$ (2.8 mg, 0.0014 mmol, ~5 mol% Cu), *tert*-butanol (0.0125 g, 0.169 mmol), and dimethylphenylphosphine (7.0 mg, 0.050 mmol) were combined and hydrogenated for 30 h, giving 4-phenylbutan-2-ol (0.024 g, 95%). The products were identified by comparison to an authentic sample.

Reduction of dihydro-β-ionone

Using the general procedure, dihydro-β-ionone (0.050 g, 0.257 mmol), $[(Ph_3P)CuH]_6$ (4.2 mg, 0.0021 mmol, 5 mol% Cu), *tert*-butanol (0.0095 g, 0.13 mmol), and dimethylphenylphosphine (0.011 g, 0.077 mmol) were combined and hydrogenated for 30 h, giving 4-phenylbutan-2-ol (0.024 g, 95%). The products were identified by comparison to an authentic sample.[47]

Reduction of 6,10-dimethyl-9-undecen-2-one

Using the general procedure, 6,10-dimethyl-9-undecen-2-one (0.045 g, 0.229 mmol), $[(Ph_3P)CuH]_6$ (3.8 mg, 0.0019 mmol, 5 mol% Cu), *tert*-butanol (8.5 mg, 0.12 mmol), and dimethylphenylphosphine (9.4 mg, 0.068 mmol) were combined and hydrogenated for 36 h, giving 6,10-dimethyl-9-undecen-2-ol (0.039 g, 87%). TLC R_f=0.07, 10:1 hexanes/ethyl acetate; IR (neat, cm^{-1}) 3350, 3040, 3020, 2960–2850, 1450, 1375, 1115, 1065, 820; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (1H, tm, J=7.2 Hz), 3.79 (1H, sextet, J=5.8 Hz), 1.95 (2H, m), 1.67 (3H, d, J=0.8 Hz), 1.59 (3H, s), 1.49–1.22 (8H, m), 1.18 (3H, d, J=6.2 Hz), 1.17–1.07 (2H, m), 0.86 (3H, d, J=6.6 Hz); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$) δ 131.0, 124.9, 68.2, 39.7, 37.1, 36.9, 32.3, 25.7, 25.5, 23.5, 23.2, 19.5, 17.6; HRMS calcd for $C_{13}H_{26}O$=198.1985 (M^+), found=198.1999. The product was identical to the material prepared by unambiguous synthesis.

Reduction of 4-cyclooctenone

Using the general procedure, 4-cyclooctenone (0.050 g, 0.403 mmol), $[(Ph_3P)CuH]_6$ (6.6 mg, 0.0034 mmol, 5 mol% Cu), *tert*-butanol (0.015 g, 0.201 mmol), and dimethylphenylphosphine (0.017 g, 0.121 mmol) were combined and hydrogenated for 30 h, giving 4-cyclooctenol[38] (0.024 g, 95%). The products were identified by comparison to literature data and an authentic sample.

Reduction of trideca-2-one-6-yne

Using the general procedure, trideca-2-one-6-yne (0.050 g, 0.26 mmol), $[(Ph_3P)CuH]_6$ (4.2 mg, 0.0021 mmol, 5 mol% Cu), *tert*-butanol (0.0095 g, 0.130 mmol), and dimethylphenylphosphine (0.011 g, 0.077 mmol) were combined and hydrogenated for 24 h, giving trideca-2-ol-6-yne (0.050 g, 99%). TLC R_f =0.25, 5:1 hexanes/ethyl acetate; IR (neat, cm^{-1}) 3350, 2960–2840, 1430, 1370, 1325, 1120, 1080, 985, 935; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (1H, sextet, J=6.4 Hz), 2.17 (2H, tt, J=2.4, 6.8 Hz), 2.13 (2H, tt, J=2.4, 6.8 Hz), 1.65–1.41 (7H, m), 1.40–1.22 (6H, m), 1.19 (3H, d, J=6.4 Hz), 0.88 (3H, t, J=6.8 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 80.7, 79.8, 67.7, 38.4, 31.4, 29.1, 28.5, 25.3, 23.5, 22.6, 18.7, 14.0. The product was identical to the material prepared by unambiguous synthesis.

Reduction of isophorone oxide using $[(Ph_3P)CuH]_6$ and Me_2PPh

Using the general procedure, isophorone oxide (0.050 g, 0.324 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.012 g, 0.162 mmol), and dimethylphenylphosphine (0.0134 g, 0.097 mmol) were combined and hydrogenated for 48 h (unoptimized), giving a mixture of isomeric of 2,3-epoxy-3,5,5-trimethylcyclohexan-1-ols[46] (25:1, 0.042 g, 83%), which were separated by flash chromatography. Major, *trans* epoxy-alcohol: 0.0403 g, 80%; minor, *cis* epoxy-alcohol: 0.0017 g, 3%. The products were spectroscopically identical to those described above.

Reduction of 2-allyl-2-carbethoxycyclohexan-1-one

Using the general procedure, 2-allyl-2-carbethoxycyclohexan-1-one (0.080 g, 0.38 mmol), $[(Ph_3P)CuH]_6$ (12.7 mg, 0.0065 mmol, 10 mol% Cu), *tert*-butanol (0.029 g, 0.39 mmol), and dimethylphenylphosphine (0.032 g, 0.23 mmol) were combined and hydrogenated for 30 h. Purification by flash chromatography gave the two diastereomers of the 2-allyl-2-carbethoxycyclohexan-1-ol, identified by spectroscopic comparison to literature data[36] (10:1, 0.063 g, 79%). Major isomer (alcohol *cis* to ester): 0.057 g. TLC R_f=0.34, 5:1 hexanes/ethyl acetate; IR (neat, cm^{-1}) 3500, 3080, 2980–2860, 1720, 1635, 1450, 1220, 1200, 1130, 980, 915; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, m), 5.09–5.04 (2H, m), 4.18 (2H, m, ABX_3), 3.54 (1H, d, J=10.0 Hz), 3.43 (1H, apparent dt, J=3.6, 10 Hz), 2.54 (1H, dd, J=7.6, 13.6 Hz), 2.37 (1H, dd, J=7.6, 13.6 Hz), 2.14–2.08 (1H, m), 1.92–1.84 (1H, m), 1.72–1.64 (1H, m), 1.56–1.4 (2H, m), 1.34–1.14 (3H, m), 1.27 (3H, t, J=7.2 Hz); Minor isomer (alcohol *trans* to ester): 0.006 g. TLC R_f=0.29, 5:1 hexanes/ethyl acetate; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, m), 5.10–5.03 (2H, m), 4.18 (2H, m, ABX_3), 3.96 (1H, apparent dt, J=3.6, 8.8 Hz), 2.8 (1H, bs), 2.59 (1H, dd, J=7.6, 13.6 Hz), 2.40 (1H, dd, J=7.6, 13.6 Hz), 1.84–1.18 (8H, m), 1.28 (3H, t, J=7.2 Hz).

Reduction of 3-[4-(*p*-toluenesulfonyloxy)butyl]-2-cyclohexanone

Using the general procedure, 3-[4-(*p*-toluenesulfonyloxy)-butyl]-2-cyclohexenone (0.050 g, 0.15 mmol), $[(Ph_3P)CuH]_6$ (5.0 mg, 0.0025 mmol, 10 mol% Cu), *tert*-butanol (0.0011 g, 0.15 mmol), and dimethylphenylphosphine (0.013 g, 0.093 mmol) were combined and hydrogenated

for 60 h. Purification by flash chromatography (8:1 hexanes/ethyl acetate) gave the starting ketone (0.008 g, 16%) and a separable mixture of 3-[4-(*p*-toluenesulfonyloxy)butyl]cyclohexan-1-ol diastereomers (1.6:1, 0.38 g, 76%). Minor *trans*-isomer (0.015 g, 30%): TLC R_f=0.1, 2:1 hexanes/ethyl acetate; IR ($CDCl_3$, cm^{-1}) 3600, 2925, 2850, 1595, 1350, 1180, 1170, 1060, 1020, 960; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J=8.3 Hz), 7.34 (2H, d, J=8.3 Hz), 4.02 (3H, m, containing a 2H, t, J=6.4 Hz), 2.44 (3H, s), 1.62 (7H, m), 1.51–1.35 (3H, m), 1.30(2H, m), 1.25–1.08 (3H, m), 0.90 (1H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 133.3, 129.8, 127.9, 70.6, 66.7, 39.5, 35.7, 33.3, 32.0, 31.3, 29.0, 22.7, 21.6, 19.9. Major *cis*-isomer (0.0235 g, 47%): TLC R_f=0.07, 2:1 hexanes/ethyl acetate; IR ($CDCl_3$, cm^{-1}) 3620, 2950, 2875, 1595, 1360, 1190, 1180, 1080, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J=8.0 Hz), 7.34 (2H, d, J=8.0 Hz), 4.0 (2H, t, J=6.5 Hz), 3.52 (1H, tt, J=4.3, 10.9 Hz), 2.45 (3H, s), 1.93 (2H, bm), 1.74 (1H, dp, J=13.4, 3.4 Hz), 1.65–1.55 (3H, m), 1.47 (1H, bs), 1.35–1.05 (7H, m), 0.81 (1H, apparent q, J=11.6 Hz), 0.71 (1H, apparent qd, J=11.6, 3.7); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 133.3, 129.8, 127.9, 70.7, 70.5, 42.5, 36.2, 35.8, 31.9, 29.0, 24.0, 22.7, 21.6; HRMS cacld for $C_{17}H_{26}O_4S$=326.1553 (M^+), found=326.1544.

Reduction of 1(β)-acetoxy-8a(β)-methyl-1,2,3,4,4a(α),5,8,8a-octahydronaphthalene-6(7H)-one

Using the general procedure, 1(β)-acetoxy-8a(β)-methyl-1,2,3,4,4a(α),5,8,8a-octahydronaphthalene-6(7H)-one (0.075 g, 0.33 mmol), $[(Ph_3P)CuH]_6$ (5.5 mg, 0.0028 mmol, 5 mol% Cu), *tert*-butanol (0.015 g, 0.21 mmol), and dimethylphenylphosphine (0.018 g, 0.13 mmol) were combined and hydrogenated for 27 h. Spectroscopic analysis of the crude reaction mixture (^1H NMR, 400 MHz, $CDCl_3$) showed 1(β)-acetoxy-6(β)-hydroxy-*trans*-decalin[37] and 1(β)-acetoxy-6(α)-hydroxy-*trans*-decalin[37] in a ratio of 16:1 along with two other very minor components. Purification by flash chromatography (8:1 hexanes/ethyl acetate) gave 1(β)-acetoxy-6(β)-hydroxy-*trans*-decalin and 1(β)-acetoxy-6(α)-hydroxy-*trans*-decalin (12:1, 0.070 g, 93%), spectroscopically consistent with data from the literature.[37] Major isomer (0.065 g, 86%): TLC R_f=0.14, 2:1 hexanes/ethyl acetate; IR ($CDCl_3$, cm^{-1}) 3610, 3450, 2980, 2940, 2860, 1725, 1470, 1450, 1380, 1260, 1160, 1110, 1090, 1040, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (1H, dd, J=4.5, 11.5 Hz), 3.59 (1H, tt-apparent septet, $J_{apparent}$=6.1 Hz), 2.02 (3H, s), 1.80 (1H, m), 1.72 (2H, m), 1.63 (3H, m), 1.53 (1H, m), 1.41 (2H, m), 1.33–1.18 (4H, m), 1.09 (1H, dt, J=3.8, 13.5 Hz), 0.91 (3H, s). Minor isomer (0.0055 g, 7%): TLC R_f=0.19, 2:1 hexanes/ethyl acetate; IR ($CDCl_3$, cm^{-1}) 3610, 3450, 2930, 2860, 1725, 1470, 1450, 1380, 1260, 1070, 1095, 1030, 1010, 995, 975; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (1H, dd, J=4.2, 11.4 Hz), 4.05 (1H, m), 2.03 (3H, s), 1.77–1.64 (4H, m), 1.63–1.36 (8H, m), 1.30–1.08 (2H, m), 0.89 (3H, s).

Reduction of 4-benzyloxy-6-bromo-(5*E*,7*E*)-1,5,7-dodecatrien-11-one

$[(Ph_3P)CuH]_6$ (0.0045 g, 0.0023 mmol), *tert*-butanol (0.010 g, 0.14 mmol), and dimethylphenylphosphine (0.012 g, 0.083 mmol) were combined in benzene (1 ml) in the drybox. Of this solution, 0.20 ml (10 mol% Cu) was added to a small volume glass reaction bomb containing 4-benzyloxy-6-bromo-(5*E*,7*E*)-1,5,7-dodecatrien-11-one (0.010 g, 0.028 mmol) in benzene (0.50 ml) and a stir bar. The reaction vessel placed under a slight positive pressure of hydrogen and stirred for 30 min. Standard work-up and purification by flash chromatography (20:1 hexanes/ethyl acetate) gave recovered starting material (0.0008 g, 8.0%) and 4-benzyloxy-6-bromo-(5*E*,7*E*)-1,5,7-dodecatrien-11-ol (0.0090 g, 89%) as an inseparable 1:1 mixture of diastereomers. TLC R_f=0.22, 4:1 hexanes/ethyl acetate; IR (CCl_4, cm^{-1}) 3620, 3350, 3060, 3030, 2970, 2930, 2860, 1940, 1870, 1830, 1800, 1640, 1605, 1490, 1450, 1370, 1330, 1260, 1240, 1200, 1025, 985, 950, 915, 850, 840, 730, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (5H, m), 6.22–6.06 (2H, m), 5.92–5.78 (2H, m), 5.14–5.02 (2H, m), 4.50 (2H, AB quartet), 4.47 (1H, m), 3.84 (1H, apparent sextet, J=6.0 Hz), 2.55–2.21 (4H, m), 1.59 (2H, m), 1.31 (1H, bs), 1.22 (3H, d, J=6.8 Hz); HRMS calcd for $C_{16}H_{20}O_2Br$ 323.0641 (M^+-allyl), found=323.0635.

Reduction of *trans*-dihydrocarvone [2(*R*)-methyl-5(*R*)-(2-propenyl)cyclohexan-1-one]

Using the general procedure, dihyrocarvone (0.070 g, 0.459 mmol), $[(Ph_3P)CuH]_6$ (7.5 mg, 0.0038 mmol, 5 mol% Cu), *tert*-butanol (0.017 g, 0.23 mmol), and dimethylphenylphosphine (0.025 g, 0.184 mmol) were combined and hydrogenated for 24 h. Purification by flash chromatography (10:1 hexanes/ethyl acetate) gave 0.064 g (90%) of the following mixture dihydrocarveol[48] isomers: 2(*R*)-methyl-5(*R*)-(2-propenyl)cyclohexan-1(*S*)-ol (60%), 2(*R*)-methyl-5(*R*)-(2-propenyl)cyclohexan-1(*R*)-ol (30%), and 2(*S*)-methyl-5(*R*)-(2-propenyl)cyclohexan-1(*R*)-ol (10%), as determined by analysis of the 500 MHz ^1H NMR spectrum and comparison to literature values. The fourth isomer, 2(*S*)-methyl-5(*R*)-(2-propenyl)cyclohexan-1(*S*)-ol was not detected. A similar reaction run to low conversion gave recovered dihydrocarvone as a mixture of *cis* and *trans* isomers (ca. 1:1).

Reduction of 6(*S*),7-(cyclohexylidenyl-1,1-dioxy)-5(*S*)-methoxy-3(*R*)-methylheptan-2-one

Using the general procedure, 6(*S*),7-(cyclohexylidenyl-1,1-dioxy)-5(*S*)-methoxy-3(*R*)-methylheptan-2-one (0.050 g, 0.185 mmol), $[(Ph_3P)CuH]_6$ (3.0 mg, 0.0015 mmol, 5 mol% Cu), *tert*-butanol (7.0 mg, 0.091 mmol), and dimethylphenylphosphine (0.010 g, 0.074 mmol) were combined and hydrogenated for 30 h. Purification by flash chromatography (3:1 hexanes/ethyl acetate) gave 6(*S*),7-(cyclohexylidenyl-1,1-dioxy)-2-hydroxy-5(*S*)-methoxy-3-methylheptane (0.047 g, 93%) as an approximately 1:1:1:1 mixture of four diastereomers. IR (neat, cm^{-1}) 3440, 2980–2850, 1460–1430, 1360, 1320, 1280, 1260, 1220, 1160, 1140–1060, 1030, 920; partial ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (3H, s), 3.47 (3H, s), 3.46 (3H, s), 3.42 (3H, s); 2.85 (1H, d, J=3.6 Hz), 2.25 (1H, d, J=5.2 Hz), 2.16 (1H, d, J=4.4 Hz), 2.01 (1H, d, J=4.4 Hz); 1.17–1.13 (overlapping d's, 4×3H); 0.94–0.90 (overlapping d's, 4×3H); HRMS calcd. for $C_{15}H_{28}O_4$=272.1988 (M^+),

found=272.1989. Starting material recovered from a hydrogenation run to low conversion was completely equilibrated.

General procedure for reduction of α,β-unsaturated ketones and aldehydes using $[(Ph_3P)CuH]_6$ and Me_2PPh

In the glove box, $[(Ph_3P)CuH]_6$ (5 mol% Cu), Me_2PPh (6 equiv./Cu) and *tert*-butanol (40 equiv./Cu) were dissolved in benzene. The substrate (20 equiv./Cu) was added and the resulting solution was rapidly transferred to a Fischer & Porter bottle equipped with a magnetic stirbar or to a similarly equipped steel autoclave (total volume: 0.4–0.8 M in substrate). The apparatus was sealed, transported out of the glove box, and connected to a tank of prepurified hydrogen. After pressurizing and releasing several times to flush the apparatus, the vessel was charged to the desired pressure and stirred for the indicated reaction time. After releasing the pressure, the contents were exposed to air, stirred several minutes, and filtered through celite. The solvent was removed in vacuo and the crude mixture analyzed by ^{1}H NMR spectroscopy (integration at long pulse delay) to determine product ratios. Purification and isolation of the product(s) was accomplished by flash chromatography on silica gel.

Reduction of *trans*-cinnamaldehyde

Using the general procedure, cinnamaldehyde (0.043 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 70 psig of hydrogen for 4 h. ^{1}H NMR spectroscopic analysis of the crude mixture indicated the formation of cinnamyl alcohol and 3-phenyl-1-propanol in a ratio of 32:1, identified by comparison to authentic samples. The inseparable products (0.041 g 94%) were isolated via flash chromatography on silica gel (10:1 hexane/ethyl acetate), along with an impure by-product (ca. 0.002 g) tentatively identified as $PhCH{=}CHCH_2O$-$C(O)CH{=}CHPh$: ^{1}H NMR (200 MHz, C_6D_6) δ 4.75 (dd, J=7.5, 1.5 Hz, 2H), 6.20 (dt, J=15.5, 7.5 Hz, 1H), 6.49 (d, J=15.5 Hz, 1H), 6.68 (d, J=15.5 Hz, 1H), 6.9–7.3 (m, aromatic-H), 7.85 (d, J=15.5 Hz, 1H).

Reduction of 2,4-dimethyl-2,6-heptadienal

Using the general procedure, 2,4-dimethyl-2,6-heptadienal (0.045 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 400 psig of hydrogen for 30 h. ^{1}H NMR spectroscopic analysis of the crude mixture indicated the formation of 2,4-dimethyl-2,6-heptadien-1-ol and 2,4-dimethyl-6-hepten-1-ol[44] in a ratio of 16:1, identified by comparison to authentic samples (2,4-dimethyl-2,6-heptadien-1-ol is commercially available). The inseparable products (0.042 g, 91%) were isolated by flash chromatography (3:1 hexane/ethyl acetate).

Reduction of citral

Using the general procedure, citral (0.049 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 15 h. ^{1}H NMR spectroscopic analysis of the crude mixture indicated the formation of geraniol (mixture of *E* and *Z* isomers) and citronellol in a ratio of 11:1, identified by comparison to authentic (commercial) samples. The inseparable products (0.045 g, 90%) were isolated by flash chromatography (7:1 hexane/ethyl acetate).

Reduction of perillaldehyde

Using the general procedure, (*S*)-(−)-perillaldehyde (0.049 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 18 h. ^{1}H NMR spectroscopic analysis of the crude mixture indicated the formation of (*S*)-(−)-perillyl alcohol and 1-hydroxymethyl-4-isopropenyl-1-cyclohexane[49] (stereochemistry unassigned) in a ratio of 32:1. The major product was identified by comparison to an authentic (commercial) sample; the minor was identified by comparison to the literature data. The inseparable products (0.047 g, 95%) were isolated by flash chromatography (7:1 hexane/ethyl acetate).

Reduction of *trans*-4-phenyl-3-buten-2-one

Using the general procedure, *trans*-4-phenyl-3-buten-2-one (0.047 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 18 h. After releasing the pressure, the solution was cooled to 0°C and acetic anhydride (0.5 ml) and pyridine (1 ml) were added. The solution was stirred at 0°C for 1 h and warmed to room temperature until the reaction was complete by TLC analysis. The volatiles were evaporated in vacuo and the residue was purified by flash chromatography to give the inseparable *trans*-2-acetoxy-4-phenyl-3-butene and 2-acetoxy-4-phenylbutane as a 12:1 mixture (0.051 g, 84%). The products were identified by comparison to samples prepared by unambiguous synthesis. ^{1}H NMR (300 MHz, C_6D_6), *trans*-2-acetoxy-4-phenyl-3-butene: δ 1.21 (d, J=7.5 Hz, 3H), 1.72 (s, 3H), 5.58 (m, 1H), 6.08 (dd, J=15.5, 7.5 Hz, 1H), 6.51 (d, J=15.5 Hz, 1H), 6.95–7.25 (m); 2-acetoxy-4-phenylbutane: δ 1.11 (d, J=6.1 Hz, 3H), 1.79 (s, 3H), 1.83 (s, 2H), 2.45–2.70 (m, 2H), 4.90–5.08 (m, 1H), 7.02–7.38 (m).

Reduction of β-ionone

Using the general procedure, β-ionone (0.062 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 26 h. NMR spectroscopic analysis of the crude product indicated the formation of the allylic alcohol and saturated alcohol in a ratio of 49:1. The inseparable products (0.056 g, 89%) were purified by flash chromatography (10:1 hexane/ethyl

acetate). The allylic alcohol was identified by comparison to an authentic sample: ^{1}H NMR (300 MHz, C_6D_6) δ 1.02 (s, 6H), 1.18 (d, J=6.1 Hz, 3H), 1.41 (m, 2H), 1.52 (m, 2H), 1.67 (s, 3H), 1.90 (m, 2H), 4.13 (m, 1H), 5.47 (dd, J=15.5, 6.2 Hz, 1H), 6.03 (d, J=15.5 Hz, 1H). The minor saturated alcohol was identified by comparison to an authentic sample and literature data.[47]

Reduction of 1-acetyl-1-cyclohexene

Using the general procedure, 1-acetyl-1-cyclohexene (0.040 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 20 h. ^{1}H NMR spectroscopic analysis of the crude product indicated the formation of the 1-cyclohexenylethanol and the commercially available 1-cyclohexylethanol in a ratio of 17:1. The inseparable products (0.038 g, 94%) were purified by flash chromatography (4:1 hexane/ethyl acetate) and identified by comparison to authentic materials. 1-Cyclohexenylethanol: ^{1}H NMR (400 MHz, C_6D_6) δ 1.16 (d, J=6.5 Hz, 3H), 1.35–1.60 (m, 4H), 1.75–2.05 (m, 4H), 3.94 (q, J=6.3 Hz, 1H), 5.53 (br s, 1H).

Reduction of 3,5-dimethylcyclohexenone using $[(Ph_3P)CuH]_6$ and Me_2PPh

Using the general procedure, 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol), $[(Ph_3P)CuH]_6$ (5.3 mg, 0.0027 mmol, 5 mol% Cu), *tert*-butanol (0.048 g, 0.65 mmol), and dimethylphenylphosphine (0.013 g, 0.097 mmol) were combined and hydrogenated under 500 psig of hydrogen for 30 h. ^{1}H NMR spectroscopic analysis of the crude product indicated the formation of the 3,5-dimethyl-2-cyclohexen-1-ol (12:1 mixture of stereoisomers) and 3,5-dimethyl-1-cyclohexanol (~3:1 mixture of stereoisomers) in a ratio of 2.7:1. The inseparable products (0.036 g, 90%) were purified by flash chromatography (3:1 hexane/ethyl acetate) and identified by comparison to authentic materials. The isomeric 3,5-dimethyl-2-cyclohexen-1-ols were identified by comparison to authentic materials prepared by unambiguous synthesis; ^{1}H NMR (400 MHz, C_6D_6, resonances used in product identification only), major *cis*-isomer: δ 5.45 (br s, 1H), 4.19 (complex m, width at half-height ~21 Hz, 1H), 1.53 (s, 3H), 0.81 (d, J=6.4 Hz, 3H); minor *trans*-isomer: δ 5.5 (m, 1H), 4.10 (br s, width at half-height ~7 Hz, 1H). The 3,5-dimethyl-1-cyclohexanols were identified by comparison to the commercial material; ^{1}H NMR (400 MHz, C_6D_6, resonances used in product identification only): major isomer, 3,5-*cis*-dimethyl-1-*trans*-cyclohexanol: δ 4.05 (tt, J=2.9, 2.7 Hz, 1H), 0.86 (d, J=6.7 Hz, 3H); minor isomer, 3,5-*cis*-dimethyl-1-*cis*-cyclohexanol: δ 3.57 (tt, J=10.9, 4.2 Hz, 1H), 0.74 (d, J=6.6 Hz, 6H).

Reduction of 3,5-dimethylcyclohexenone using CuCl

Cuprous chloride (0.0016 g, 0.016 mmol), NaO^tBu (0.0015 g, 0.016 mmol), Me_2PPh (0.0134 g, 0.096 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol) were combined in C_6H_6 (0.6 ml), transferred to a steel autoclave, removed from the glove box, pressurized to 1000 psi of hydrogen, and allowed to stir for 24 h. After work up as described in the general procedure, analysis of the crude product mixture by ^{1}H NMR spectroscopy indicated the formation of the 3,5-dimethyl-2-cyclohexen-1-ol (12:1 mixture of stereoisomers) and 3,5-dimethyl-1-cyclohexanol (~3:1 mixture of stereoisomers) in a ratio of 4.4:1. The inseparable products (0.037 g, 92%) were isolated via flash chromatography (3:1 hexane/ethyl acetate) and identified as described above.

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18. The attenuation of stereoselectivity is attributed to the incomplete phosphine exchange, resulting in the presence of the triphenylphosphine-derived catalyst in low concentration. This catalyst is also stereoselective for cyclohexanone reduction, but favors the formation of the epimeric alcohol.[8a]

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