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Copper Hydride-*Catalyzed* Tandem 1,4-Reduction/Alkylation Reactions

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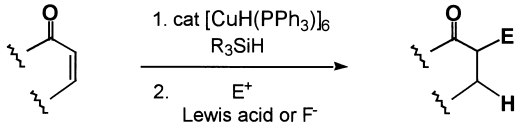
Abstract—Exposure of an enone to a catalytic quantity of $[CuH(PPh_3)]_6$ in the presence of one of several silyl hydrides ($PhMe_2SiH$, PMHS, $HMe_2SiOSiMe_2H$) leads to conjugate reduction with concomitant formation of the corresponding silyl enol ether. Without isolation, treatment of these intermediates with a Lewis acid at low temperatures in the presence of an aldehyde, or with fluoride ion together with an activated halide, affords good yields of the product of 3-component coupling (3-CC) in a single reaction flask.

Introduction

One approach to site-specific α-alkylations of ketones is to rely on a chemospecific conjugate reduction followed by trapping of the resulting enolate or equivalent with an electrophile. While several methods for effecting 1,4-reductions exist,[1] transition metal-catalyzed processes offer convenience and efficiency, as well as prospects for subsequent use of an in situ generated reactive intermediate. In an earlier report from these laboratories,[2] we described an expedient process for effecting such reductions which utilized ≤5 mol% of Stryker's reagent, $[CuH(PPh_3)]_6$,[3,4] together with stoichiometric amounts of phenylsilane ($PhSiH_3$). By switching to other silyl hydrides, such as dimethylphenylsilane ($PhMe_2SiH$), tetramethyldisiloxane ($HMe_2SiOSiMe_2H$), or polymethylhydrosiloxane (PMHS), a far more economical process results. In the case of the latter two reagents, a remarkable rate enhancement is noted thus allowing for reduction in the amount of copper to 1 mol% or less with selected substrates. The intermediate silyl enol ethers generated can be utilized in C–C bond formations, all in a one-pot process. We now describe the details surrounding this facile sequence (Eq. (1)).

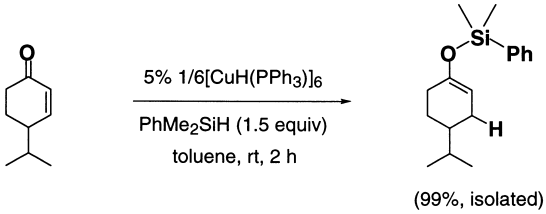


(1)

Results and Discussion

Conjugate reductions

Dimethylphenylsilane (Me_2PhSiH), popularized as a precursor to silyl higher order cyanocuprates (e.g. $(PhMe_2Si)_2Cu(CN)Li_2$),[5] is commercially available and relatively inexpensive. Importantly, it can serve the same role as $PhSiH_3$ in the presence of $[CuH(PPh_3)]_6$ to efficiently reduce α,β-unsaturated ketones in the desired 1,4-sense affording isolable silyl enol ethers (Eq. (2)). Related work by Mori has shown[6] that an excess of this silane is effective for this purpose in the presence of half an equivalent of either $CuF(PPh_3)\cdot 2EtOH$ or $CuCl/PPh_3$/TBAF in *N*,*N*-dimethylacetamide (DMA).



(2)

Reactions were initially run under argon using 5 mol% $[CuH(PPh_3)]_6$ at concentrations of ca. 0.5 M in substrate, and tended to require between one and two hours to reach the initial stage of completion (i.e. formation of the silyl enol ether). TLC analysis of these clean reactions using $[CuH(PPh_3)]_6/PhMe_2SiH$ in toluene at ambient temperatures indicates, in addition to the desired silyl enol ether, small amounts (<5% by GCMS integration) of the 1,4-reduced ketone product may be produced. Also seen is residual silane, which is employed in slight excess

Keywords: conjugate reduction; copper hydride; silyl hydrides.
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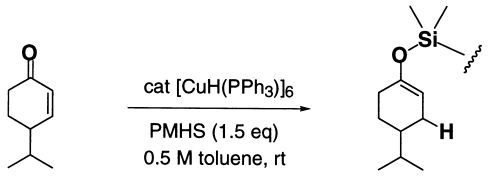
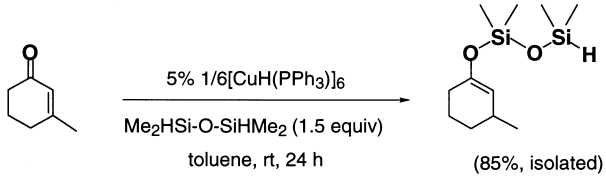


amount of 1/6[CuH(PPh$_3$)]$_6$	time needed for reduction
1.0 mol %	< 5 min
0.7 mol %	10 min
0.2 mol %	12 h

Scheme 1.

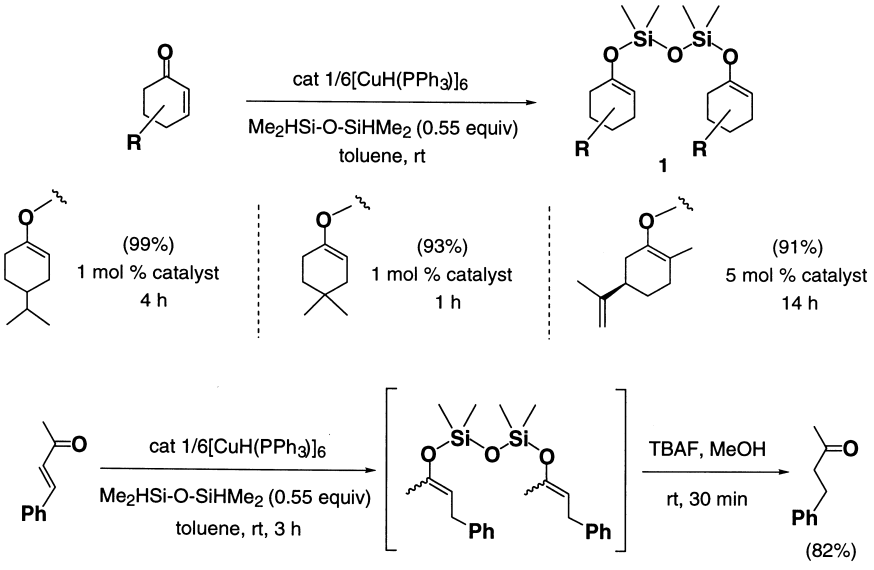
(1.2–1.5 equiv.). The variation in time was found to be dependent upon the quality of the silane, and especially that of the catalyst (vide infra).

Although use of Me_2PhSiH is an advance with respect to reagent cost and stability (vs. $PhSiH_3$) of the resulting enol ether, it was recognized that there are other commercially available silanes that are less expensive. More reactive silanes could enhance the rate of copper hydride regeneration, thus creating opportunities for decreasing the amount of catalyst and/or silane required. Upon switching to tetramethyldisiloxane ($HMe_2SiOSiMe_2H$), reactions that usually took hours occurred in minutes. With this more reactive silyl hydride, the β,β-disubstituted 3-methylcyclohexenone could be converted to its silyl enol ether in 85% isolated yield (Eq. (3)).



(3)

Most noteworthy is the observation that both hydrides within this silane are available for use, thereby reducing the net amount of this hydride source to *half the stoichiometric level*. A few examples of products derived from this especially efficient, mild, and economical method for conjugate reduction are shown above, involving educts cryptone, 4,4-dimethyl-2-cyclohexenone, and carvone, respectively (Eq. (4)). Moreover, usually 1 mol% [CuH(PPh$_3$)]$_6$ is all that is needed for consumption of enone within a few hours time. The intermediate bis-enol ethers **1** could readily be isolated and characterized. Conversion to the derived ketones, typified by the one case studied (Eq. (5)), occurs readily upon treatment with fluoride ion.



(4)

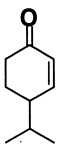
(5)

With unhindered enones, PMHS appears to be even more effective than $HMe_2SiOSiMe_2H$ as a hydride donor to copper(I). Cryptone was reduced to its enol ether within 10 min using only 0.7 mol% of [CuH(PPh$_3$)]$_6$ (Scheme 1), while catalyst levels as low as 0.2 mol% can be used but take several hours to consume enone. Under a standard set of conditions, side-by-side comparisons of four sources of hydride clearly indicated that PMHS offers the fastest rate of 1,4-reduction (Table 1).

Conjugate reduction/alkylation reactions

Once a conjugate reduction of an α,β-unsaturated ketone is complete, cooling the reaction mixture to −78°C is followed by introduction of the electrophile, e.g., an aldehyde (1.25 equiv.). Subsequent slow addition of $BF_3{\cdot}OEt_2$ or $TiCl_4$ (1.0 M in CH_2Cl_2; 1.25 equiv.)[7] leads to the desired aldol process. The overall isolated yields employing this protocol tend to be good, although considerable care is needed to ensure that secondary processes do not overshadow the desired aldol pathway (e.g. partial dehydration, polymerization, retro-aldol, etc.). Listed in Table 2 are several examples of representative enone–aldehyde combinations which participate in this process.[8] The unusual enol silanes generated using tetramethyldisiloxane (cf. Eq. (3)) react readily in Lewis acid-induced aldol reactions leading to products of 3-CC (entries 2 and 7). Also, as previously

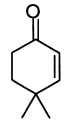
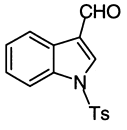
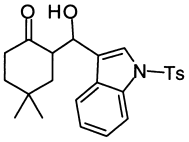
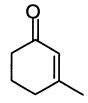
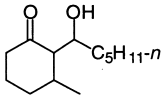
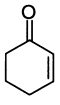
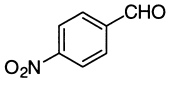
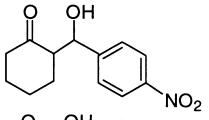
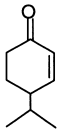
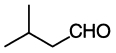
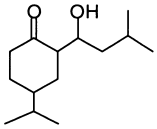
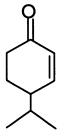
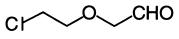
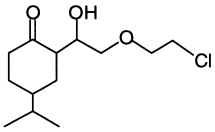
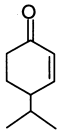
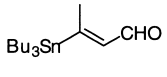
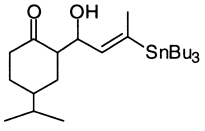
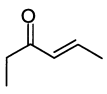
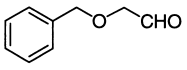
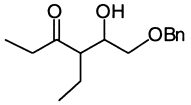
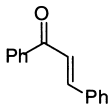
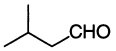
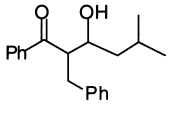
Table 1. Comparison of silyl hydrides under standard reduction conditions (reaction conditions: 2 mol% 1/6[$Cu(PPh_3)]_6$, 1.25 equiv. silane, 0.5 M in $PhCH_3$, room temperature)



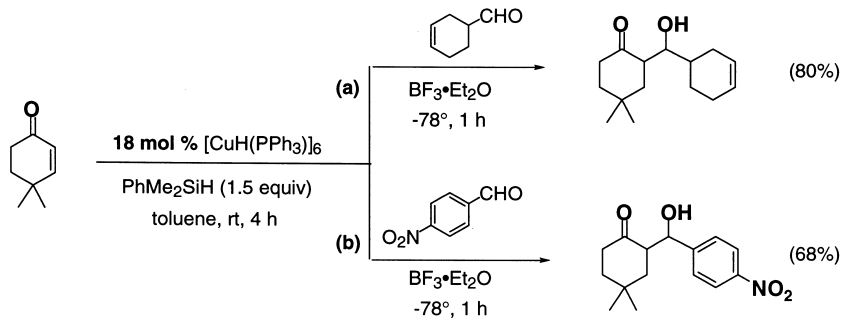
time for consumption of enone			
$PhMe_2SiH$	Et_3SiH	$(HMe_2Si)_2O$	**PMHS**
2.75 h	no rxn	0.50-0.75 h	**≤ 2 min**

observed,[2] both cyclic and acyclic educts can be viewed as Michael acceptors. Additional points concerning this conjugate reduction/alkylation sequence include: (1) diastereomeric products were formed in all cases,[9] with chromatographic separation and complete characterization carried out for each isomer where possible. In some cases, however, there was no choice but to conduct analyses on mixtures of isomers, although the confluence of GCMS, ^1H and ^{13}C NMR, and high resolution mass spectral data led to unequivocal identification of the products formed; (2) placement of an aldehyde in the reaction flask along with the enone prior to introduction of the $[CuH(PPh_3)]_6$/silane ultimately afforded reduced aldehyde at the expense of the conjugate addition/aldol product(s). Since the silane itself is

Table 2. 3-Component couplings: 1,4-reduction/aldol reactions

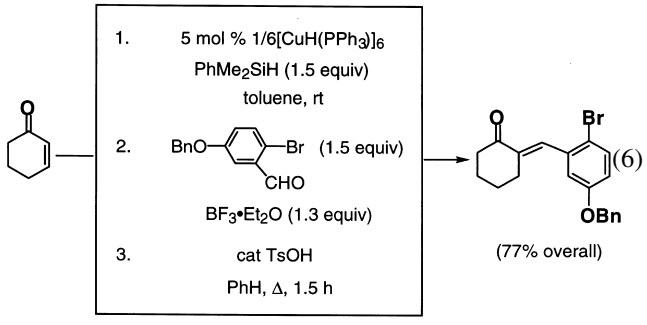
Entry	Enone	Cu (%)[a]	Silane[b]	Time (h)	Aldehyde	Lewis acid[c]	Aldol product	Yield (%)[d]
1		5	**A** (1.5 equiv)	4		$TiCl_4$		82
2		5	**B** (1.5 equiv)	39		$TiCl_4$		72
3		3	**A** (1.5 equiv)	1		BF_3		73
4		3	**A** (2.5 equiv)	3		BF_3		89
5		5	**A** (1.5 equiv)	2		BF_3		87
6		5	**A** (1.5 equiv)	2		BF_3		76
7		1	**B** (1.3 equiv)	1		$TiCl_4$		79
8		5	**C** (1.5 equiv)	0.5		BF_3		73

[a] Refers to 1/6[$CuH(PPh_3)]_6$.
[b] **A**=PhM_eSiH; **B**=Me_2HSi-O-$SiHMe_2$; **C**=$PhSiH_3$.
[c] BF_3=$BF_3{\cdot}Et_2O$.
[d] Isolated, chromatographically pure materials.



Scheme 2.

not capable of effecting 1,2-addition to aldehydes, the presence of a Cu(I) species, even a copper(I) hydride, provides enough Lewis acidity to induce competitive hydride delivery; (3) chalcone (entry 8) was very sluggish toward reduction using Me_2PhSiH. The 1,4-reduction/aldol sequence was therefore successfully tested using $PhSiH_3$, which had not been examined in our previous study;[2] (4) treatment of a crude product resulting from a 3-CC under acidic conditions is sufficient to force dehydration, typified by the example illustrated in Eq. (6).

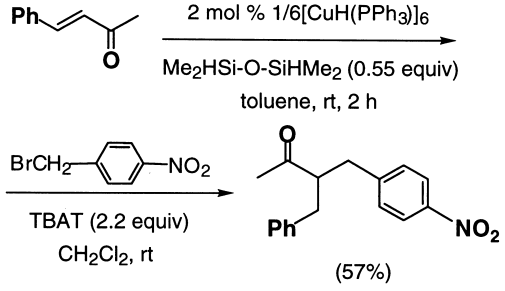


(6)

With this aldehyde, essentially a single isomer of *E* stereochemistry was obtained; and (5) for certain synthetic situations, it may be necessary to increase the amount of catalyst significantly in order to drive a conjugate reduction to completion. In questioning the presence of greater amounts of copper(I) in the medium on the subsequent aldol event, an enone was carried through the sequence employing 18 mol% $[CuH(PPh_3)]_6$. Notwithstanding the known tendency of copper enolates to function poorly as nucleophiles toward aldehydes,[10] and to the extent that such enolates may be involved in this chemistry, the reactions proceeded to give the anticipated products via routes **(a)** and **(b)** in good isolated yields (Scheme 2).

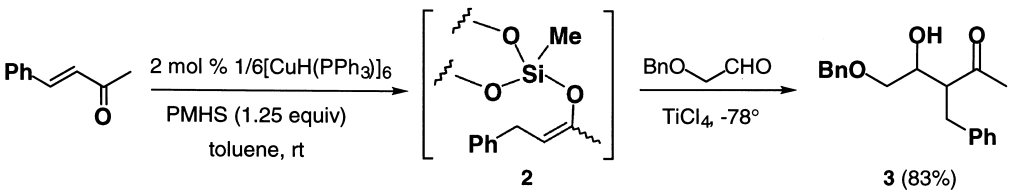
Intermediates formed from 1,4-reductions employing PMHS are not discrete species, as expected given the polymeric nature of this silane. Nonetheless, while these enol derivatives cannot be readily isolated, they can be utilized directly in a 3-CC. As illustrated below (Scheme 3), treatment of an in situ derived species **2**, following the same protocol as used for enol ethers derived from Me_2PhSiH or $HMe_2SiOSiMe_2H$, affords the product of 3-CC (**3**) in good yield.

Another option for these in situ-derived silyl enol ethers is their fluoride ion-induced alkylation, which can be initiated using DeShong's tetrabutylammonium (triphenylsilyl)-difluorosilicate (TBAT)[11] in the presence of a reactive halide (Eq. (7)).[6]



(7)

Lastly, a comment with regard to the key ingredient in this sequence, the $[CuH(PPh_3)]_6$ complex. This reagent is a well-known source of hydride used mainly for stoichiometric conjugate reductions,[3] and continues to be sold commercially. During the course of our study we had the opportunity to utilize different samples of this complex, and noticed that the quality of the commercially supplied material varies considerably as evidenced by their ^1H NMR spectra taken in distilled (Na/benzophenone) and degassed benzene-d_6 (Fig. 1). The first sample of commercial $[CuH(PPh_3)]_6$ (spectrum **A**) had a dark brown, heterogeneous appearance in benzene and did not function in our conjugate reduction catalytic cycle to any significant extent. The second sample, which led to spectrum **B**, was also noticeably dark brown–red and heterogeneous in



Scheme 3.

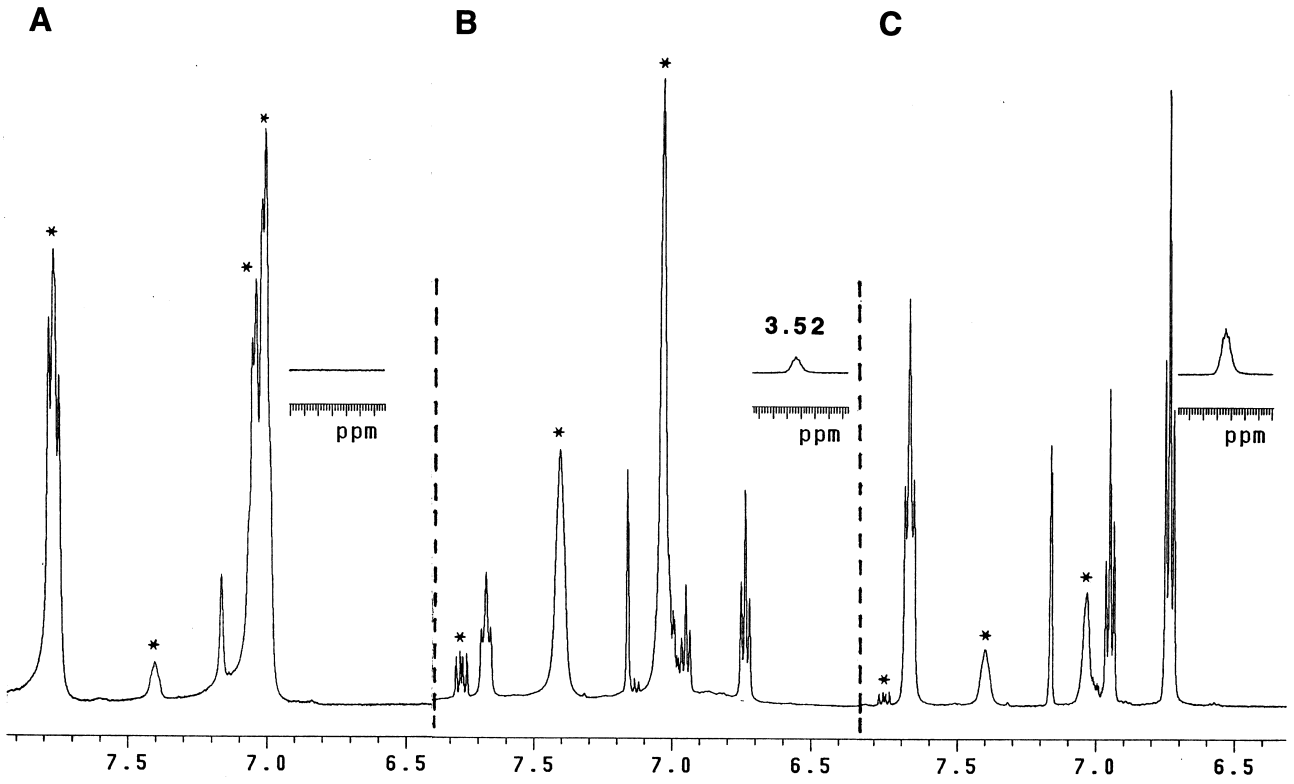


Figure 1. ^{1}H NMR spectra of $[CuH(PPh_3)]_6$ from: A, Aldrich, 1st sample; B, Aldrich, 2nd sample; C, freshly made according to the Stryker literature method; * denotes impurities in the $[CuH(PPh_3)]_6$.

benzene. It was to some degree catalytically active, but only when used in amounts in considerable excess to that eventually needed to consume starting materials in reasonable timeframes (ca. 6 times the 'usual' amount). On the other hand, a sample of red, powdery material which fully dissolved in benzene (spectrum **C**) allowed for continuation of the work reported herein. Comparison of these spectra reveals that the sample giving rise to spectrum **A** contains virtually none of the active hydride, a signal for which would appear at 3.52 ppm (see inserts). It is comprised of essentially all impurities (cf. peaks labeled by an asterisk). The second commercial sample (spectrum **B**) shows evidence of the Stryker reagent but consists mainly of the same impurities. This accounts for the limited reactivity observed and the required excess reagent. The third sample of $[CuH(PPh_3)]_6$ was prepared on a multi-gram scale in a straightforward manner following the Stryker protocol.[3] This route provided nearly pure material (spectrum **C**)[12] which was used for optimum results in our conjugate reductions and 3-CC sequences.

Summary and Conclusions

In summary, a mild and efficient method for the single-flask conjugate reduction–alkylation of an α,β-unsaturated ketone has been developed. It relies on the catalytic use of Stryker's reagent $[CuH(PPh_3)]_6$, presumed to be the species delivering the hydride, together with stoichiometric amounts of either of three inexpensive silanes (Me_2PhSiH, $HMe_2SiOSiMe_2H$, or PMHS). The latter reagent, PMHS, which is used without further handling out of the bottle and costs only pennies per gram, is noteworthy in its effectiveness. Indeed, the combination of 1–2% $[CuH(PPh_3)]_6$ together with a slight excess of PMHS represents a method which may be one of the most user-friendly, economical and efficient processes known for carrying out conjugate reductions of enones.[1,3,13] Subsequent C–C bond formations from intermediate silyl enol ethers (which may be isolated when using Me_2PhSiH or $HMe_2SiOSiMe_2H$, if desired) can be effected via Mukaiyama aldols, or fluoride-induced alkylations with activated halides.

Experimental

General. Reactions were performed using standard Schlenk techniques in oven-dried glassware under an argon atmosphere with Teflon coated stir bars and double septa tops. All solvents were freshly distilled from sodium benzophenone ketyl or CaH_2 under argon before use. The copper hydride hexamer $[CuH(PPh_3)]_6$ was stored and weighed out as a red powder in an inert atmosphere (e.g. glovebox) using a Teflon-coated spatula. All commercially obtained reagents were distilled either from CaH_2 or molecular sieves under an inert atmosphere before use. Melting points were measured on a Mel-Temp II and are uncorrected. Products were purified by chromatography on 200–425 g mesh Fisher brand silica gel pretreated with either 2% triethylamine or pyridine, or which had been deactivated with 2% aqueous acetone. TLC analyses were performed on commercial Kieselgel 60 F_{254} silica gel plates. NMR spectra were obtained on Varian Inova systems using $CDCl_3$ or C_6D_6 solvents with proton and carbon resonance at 400 or

500 MHz and 100 or 125 MHz, respectively; the δ scale was referenced to $CDCl_3$ or C_6D_6 based on residual lines at δ 7.27 and 7.15 ppm, respectively, or to 2% TMS as an additive. FTIR spectra were obtained on an ATI Mattson Infinity Series spectrometer neat on NaCl plates or as KBr pellets, and are reported in cm^{-1}. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

General procedure I for the 1,4-reduction of α,β-unsaturated ketones: (4-isopropyl-1-cyclohexenyloxy)-dimethylphenylsilane (Eq. (2)). To a homogeneous red solution of copper hydride $[CuH(PPh_3)]_6$ (18.7 mg, 0.01 mmol, 5.6 mol% Cu) in toluene (1.5 mL) was added dropwise dimethylphenylsilane (0.23 mL, 1.5 mmol, 1.5 equiv.) and the solution stirred at room temperature for approximately 3–5 min. To the resulting red solution, dropwise 4-isopropyl-2-cyclohexen-1-one was added (0.15 mL, 1.0 mmol). After 5–7 min the color of the solution had darkened to a heterogeneous brown/black. After 2 h, the reaction mixture was filtered through a pad of sand/Celite/charcoal with excess washing using toluene. The solvent was removed in vacuo and the crude product purified by Kugelrohr distillation (205–210°C, 1.5 Torr) affording the corresponding silyl enol ether as a colorless oil (0.273 g, 99%). R_f=0.83 (1:10 EtOAc/hexanes); IR (thin film) 3413, 3069, 2959, 2873, 1716, 1674, 1593, 1428, 1371, 1254, 1182, 1119, 1061, 884, 832, 789, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 3H), 7.43 (m, 1H), 4.89 (dt, J=2.8, 2.0 Hz, 1H), 2.06 (m, 2H), 1.78 (m, 2H), 1.49 (m, 1H), 1.30 (m, 2H), 0.92 (dd, J=4.0, 3.0 Hz), 0.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 138.3, 133.5, 133.2, 129.8, 129.4, 128.0, 127.9, 104.4, 40.1, 32.1, 30.4, 27.5, 26.6, 20.3, 20.1, 1.06, −0.80; LREI (*m/z*, rel. int.) 341(7), 277(15), 275(10), 135(100), 111(12), 95(18), 83(36), 69(48), 55(55); HRFABMS (NBA) (M+H) calcd for $C_{17}H_{26}OSi$ 275.1831, found 275.1826.

(3-Methyl-1-cyclohexenyloxy)-tetramethyldisiloxane (Eq. (3)). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (16.0 mg, 0.008 mmol, 5 mol% Cu) in toluene (2.0 mL), tetramethyldisiloxane (0.27 mL, 1.5 mmol, 1.5 equiv.), 3-methyl-2-cyclohexenone (0.11 mL, 1.0 mmol). The solution was stirred at room temperature for 24 h. Purification by Kugelrohr distillation (68–70°C, 1.5 Torr) afforded the corresponding silyl enol ether as a colorless liquid (0.207 g, 85%). R_f=0.81 (1:10 EtOAc/hexanes); IR (thin film) 2957, 2866, 2128, 1666, 1454, 1369, 1258, 1190, 1063, 906, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (m, 1H), 4.73 (sept, J=2.8 Hz, 1H), 2.25 (m, 1H), 1.99 (m, 2H), 1.74 (m, 3H), 1.57 (m, 1H), 0.96 (d, J=6.8 Hz, 3H), 0.21 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 111.6, 31.3, 29.8, 29.7, 22.6, 22.0, 0.85, −0.29, −0.43, −0.46; LREIMS (*m/z*, rel. int.) 281(9), 244(7), 229(4), 207(9), 149(100), 133(65), 119(7), 95(28), 81(90), 55(17); HREIMS calcd for $C_{11}H_{24}O_2Si_2$ 244.1314, found 244.1323.

1,3-Bis(4-isopropyl-1-cyclohexenyloxy)tetramethyldisiloxane (Eq. (4), first entry). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (7.0 mg, 0.0035 mmol, 1 mol% Cu), toluene (4.0 mL), tetramethyldisiloxane (0.18 mL, 1.02 mmol, 0.5 equiv.), and 4-isopropyl-2-cyclohexenone (0.30 mL, 2.04 mmol). The solution was stirred at room temperature for 1 h. Purification by flash chromatography (1:20 Et_2O/PE) afforded the bis-enol ether as a colorless oil (0.415 g, 99%). R_f=0.81 (1:10 EtOAc/PE); IR (thin film) 2958, 2922, 2873, 2842, 1674, 1465, 1441, 1376, 1259, 1216, 1194, 1071, 894, 856, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (dt, J=5.6, 2.0 Hz, 2H), 2.11 (m, 2H), 2.02 (m, 4H), 1.77 (m, 4H), 1.27 (m, 4H), 0.90 (d, J=4 Hz, 6H), 0.89 (d, J=4 Hz, 6H), 0.177 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 104.5, 40.2, 32.2, 30.3, 27.5, 26.7, 20.3, 20.1, −0.24, −0.28; LREIMS (*m/z*, rel. int.) 410(15), 395(5), 287(12), 271(78), 255(20), 227(55), 200(30), 149(100), 133(79), 122(19), 81(35), 69(38), 55(20), 43(33); HREIMS calcd for $C_{22}H_{42}O_3Si_2$ 410.2673, found 410.2675.

1,3-Bis(4,4-dimethyl-1-cyclohexenyloxy)tetramethyldisiloxane (Eq. (4), second entry). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (6.8 mg, 0.0034 mmol, 1 mol% Cu), toluene (4.0 mL), tetramethyldisiloxane (0.18 mL, 0.99 mmol, 0.50 equiv.), and 4,4-dimethyl-2-cyclohexenone (0.26 mL, 1.98 mmol). The solution was stirred at room temperature for 2 h. Purification by flash chromatography (1:20 Et_2O/PE) afforded bis-enol ether as a colorless oil (0.351 g, 93%). R_f=0.80 (1:10 EtOAc/PE); IR (thin film) 2952, 2919, 2872, 2835, 1672, 1459, 1367, 1260, 1200, 1170, 1070, 898, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (tt, J=4.0, 1.6 Hz, 2H), 2.03 (tq, J=6.6, 2.4, 1.6 Hz, 4H), 1.81 (dt, J=4.0, 2.4 Hz, 4H), 1.41 (t, J=6.6 Hz, 4H), 0.93 (s, 12H), 0.18 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 103.8, 38.1, 36.1, 28.8, 28.2, 27.5, −0.31; LREIMS (*m/z*, rel. int.) 382(11), 367(5), 273(8), 257(93), 239(62), 229(15), 200(96), 185(14), 149(75), 133(100), 109(34), 91(8), 81(10), 67(32), 53(39), 43(19); HREIMS calcd for $C_{20}H_{38}O_3Si_2$ 382.2360, found 382.2362.

1,3-Bis(S-5-isopropenyl-2-methyl-1-cyclohexenyloxy)-tetramethyldisiloxane (Eq. (4), third entry). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (17 mg, 0.009 mmol, 5 mol% Cu), toluene (2.0 mL), tetramethyldisiloxane (0.10 mL, 0.55 mmol, 0.55 equiv.), and (*S*)-(+)-carvone (0.16 mL, 1.03 mmol). The solution was stirred at room temperature for 14 h. Purification by flash chromatography (1:20 Et_2O/PE) afforded the bis-enol ether as a colorless oil (0.202 g, 91%). R_f=0.87 (1:10 EtOAc/PE); IR (thin film) 2964, 2920, 2856, 2835, 1693, 1644, 1439, 1260, 1183, 1063, 938, 888, 846, 802; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (m, 4H), 2.24 (m, 2H), 2.05 (m, 8H), 1.74 (m, 2H), 1.73 (br s, 6H), 1.58 (br s, 6H), 1.40 (qd, J=12.4, 5.6 Hz, 2H), 0.18 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 141.9, 111.6, 108.9, 42.6, 35.6, 30.3, 28.1, 21.0, 16.3, 0.13, 0.11; LREIMS (*m/z*, rel. int.) 434(14), 282(99), 267(13), 239(35), 215(14), 149(100), 133(67), 119(31), 107(28), 93(49), 74(36), 59(61), 43(19); HREIMS calcd for $C_{24}H_{42}0_3Si_2$ 434.2673, found 434.2669.

4-Phenyl-2-butanone (Eq. (5)). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (7 mg, 0.0035 mmol, 2 mol% Cu) in toluene (2.0 mL), tetramethyldisiloxane (0.10 mL,

0.55 mmol, 0.55 equiv.), *trans*-4-phenyl-3-buten-2-one (0.146 g, 1.0 mmol), and the solution stirred at room temperature for 3 h. MeOH (5 mL) was added, followed by TBAF·$3H_2O$ (0.946 g, 3 mmol) dissolved in 5 mL MeOH. The solution was allowed to stir for 30 min and the solvent was removed in vacuo affording a yellow oil. Purification by flash chromatography (1:10 Et_2O/PE) afforded benzyl acetone as a colorless liquid (0.12 g, 82%), whose spectroscopic properties matched literature data.[14]

2-(5-Benzyloxy-2-bromobenzylidene)-cyclohexanone (Eq. (6)). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (22 mg, 0.012 mmol, 5 mol% Cu), dimethylphenylsilane (0.34 mL, 2.2 mmol, 1.5 equiv.), 2-cyclohexenone (0.16, 1.5 mmol), 2-bromo-5-benzyloxybenzaldehyde (0.65 g, 2.2 mmol, 1.5 equiv.), and $BF_3·Et_2O$ (0.25 mL, 2.0 mmol, 1.3 equiv.). The crude aldol products were taken up into 40 mL of dry benzene to which was added 20 mg of TsOH. The mixture was then heated under a Dean-Stark trap at reflux for 90 min. The solvent was removed in vacuo and the crude elimination product taken up in 50 mL of Et_2O and extracted with saturated NH_4Cl solution (2×25 mL), washed with brine (2×25 mL), and then dried over anhydrous Na_2SO_4. Purification by flash chromatography (1:3 EtOAc/hexane) afforded a single (*E*)-alkene as a light yellow solid (0.43 g, 77%). mp=100–102°C; R_f=0.34; IR (KBr) 3065, 3029, 2943, 2862, 1672, 1586, 1231, 1006, 741, 695; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 (d, J=8.5 Hz, 1H), 7.40 (m, 5H), 7.34 (m, 1H), 6.83 (m, 2H), 5.07 (s, 2H), 2.54 (m, 4H), 1.92 (p, J=6.6 Hz, 2H), 1.71 (p, J=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 157.5, 139.0, 136.8, 136.6, 134.2, 133.6, 128.9, 128.4, 127.5, 117.4, 116.7, 116.0, 70.5, 40.9, 29.0, 24.1, 23.9; LREIMS (*m*/*z*, rel. int.) 372(1), 370(1), 292(2), 291 (2), 291(13), 115(1), 102(2), 92(6), 91(100), 65(4), 63(1), 55(1), 51(1), 43(1); HREIMS calcd for $C_{20}H_{19}O_2Br$ 370.0568, found 370.0563.

3-(4-Nitrobenzyl)-4-phenyl-2-butanone (Eq. (7)). General method **I** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (7 mg, 0.0035 mmol, 2 mol% Cu), toluene (2.0 mL), tetramethyldisiloxane (0.10 mL, 0.55 mmol, 0.55 equiv.), and *trans*-4-phenyl-3-buten-2-one (0.15 g, 1.0 mmol). The solution was stirred at room temperature for 3 h. To the resulting dark solution was added CH_2Cl_2 (5.0 mL) followed by solid 4-nitrobenzyl bromide (1.08 g, 5.0 mmol, 5 equiv.) in one portion. TBAT (1.19 g, 2.2 mmol, 2.2 equiv.) was dissolved in 5.0 mL CH_2Cl_2 and cannulated into the reaction. The resulting bright pink solution was allowed to stir at rt for 3 h, after which the solvent was removed in vacuo affording a pink residue. Purification by flash chromatography (1:10 EtOAc/PE) afforded the alkylated product as a light yellow oil (0.161 g, 57%). R_f=0.18; IR (thin film) 3063, 3028, 2924, 2854, 1711, 1602, 1517, 1346, 1161, 1110, 851, 751, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (m, 2H); 7.28 (m, 5H); 7.18 (m, 2H); 3.18 (m, 1H); 3.05 (dd, J=10 Hz, 1H); 2.97 (dd, J=8 Hz, 14 Hz, 1H); 2.79 (dd, J=5 Hz, 14 Hz, 1H); 2.73 (dd, J=7 Hz, 14 Hz, 1H); 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 147.6, 146.8, 138.6, 129.9, 129.0, 128.9, 126.9, 123.9, 56.1, 38.6, 37.4, 31.6; LREIMS (*m*/*z*, rel. int.) 283(0.03), 277(0.4), 270(0.20), 192(3), 147(100), 91(42); HRFABMS (NBA) calcd for $C_{17}H_{18}NO_3$ (M+H) 284.1287, found 284.1295.

Representative procedure A for a conjugate reduction-aldol 3-CC: 2-(1-hydroxy-3-methylbutyl)-4-isopropyl-cyclohexanone (Table 2, entry 4). To a homogeneous red solution of copper hydride $[CuH(PPh_3)]_6$ (12.2 mg, 0.006 mmol, 3.2 mol% Cu) in toluene (2.4 mL) was added dropwise dimethylphenylsilane (0.45 mL, 2.9 mmol, 2.5 equiv.) and the solution stirred at room temperature for ca. 5 min. To the resulting homogenous red solution was added dropwise 4-isopropyl-2-cyclohexenone (0.17 mL, 1.17 mmol) and the solution was stirred at room temperature. After ca. 7 min the solution had darkened to a heterogeneous brown/black color. Monitoring of the reaction by TLC showed that the enone was consumed after 3 h, and a high R_f spot corresponding to the silyl enol–ether was observed. The solution was diluted with CH_2Cl_2 (12.0 mL) and cooled to −78°C followed by dropwise addition of neat isovaleraldehyde (0.17 mL, 1.58 mmol, 1.4 equiv.), then neat $BF_3·Et_2O$ (0.16 mL, 1.50 mmol, 1.3 equiv.). Stirring was continued for 40 min and the reaction was then quenched by pouring into 9.0 mL of ice cold saturated $NaHCO_3$ solution followed by extraction with diethyl ether (3×25 mL). The combined organic portions were washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, and filtered through a plug of Celite. The solvent was removed in vacuo to afford a light yellow oil. Flash chromatography (1:10 EtOAc/PE) afforded aldol diastereomers as a colorless oil (0.24 g, 89%). R_f=0.18–0.23; IR (thin film) 3530, 2933, 2871, 1704; ^{1}H NMR (400 MHz, $CDCl_3$) [Note: integrations are not given for combined diastereomers as signals overlap] δ 4.14 (m), 3.72 (m), 3.41 (brs), 2.64 (br s), 2.30 (m), 1.95 (m), 1.80 (m), 1.56 (m), 1.42 (m), 1.17 (m), 0.96 (m), 0.86 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 67.1, 54.5, 42.8, 42.1, 32.4, 30.3, 29.5, 24.8, 23.7, 22.2, 20.2, 19.9; LRCIMS (CH_4) (*m*/*z*, rel. int.) 227(2), 209(21), 191(25), 169(11), 153(16), 141(55), 123(68), 109(11), 95(16), 81(27), 69(88), 57(36), 43(100); HRCIMS (CH_4) calcd for $C_{14}H_{27}O_2$ (M+H) 227.2011, found 227.2011.

Representative procedure B for the conjugate reduction-aldol 3-CC: 2-{hydroxy-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-methyl}-4,4-dimethylcyclohexanone (Table 2, entry 1). To a homogeneous red solution of copper hydride $[CuH(PPh_3)]_6$ (16.0 mg, 0.008 mmol, 5 mol% Cu) in toluene (2.0 mL) was added dropwise dimethylphenylsilane (0.23 mL, 1.5 mmol, 1.5 equiv.) and the solution stirred at room temperature for ca. 5 min. To the resulting red solution was added dropwise 4,4-dimethylcylohexenone (0.13 mL, 1.0 mmol) and the solution was stirred at room temperature. After ca. 7 min the solution darkened to a heterogeneous brown/black. Monitoring of the reaction by TLC showed that the enone was consumed after 3 h to form the corresponding silyl enol ether. The solution was diluted with CH_2Cl_2 (5.0 mL) and added via cannula to a solution of *N*-tosyl-indole-3-carboxaldehyde (0.45 g, 1.5 mmol, 1.5 equiv.) and $TiCl_4$ (1.5 mL of 1.0 M solution in CH_2Cl_2, 1 equiv.), in CH_2Cl_2 (7.0 mL) at −78°C. Stirring was continued for 1 h and the reaction was quenched with saturated $NaHCO_3$ solution (6.0 mL) at −78°C, and allowed

to warm to room temperature. A blue precipitate was filtered using a Buchner funnel, and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic portions were washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. Purifcation by flash chromatography (1:9 EtOAc/PE to 1:4 EtOAc/PE) afforded diastereomers as a yellow oil (combined yield 0.35 g, 82%). R_f=0.19; IR (thin film) 3523, 2956, 2928, 2864, 1700, 1447, 1369, 1173, 1121, 733; ^{1}H NMR (400 MHz, $CDCl_3$) [Note: integrations are not given for combined diastereomers as signals overlap] δ 8.00 (dd, J=11.6, 8.4 Hz, 1H), 7.74 (d, J=8.0 Hz, 2H), 7.67 (d, J=8.0 Hz), 7.55 (s), 7.50 (s), 7.41 (d, J=8.0 Hz, 1H), 7.25 (m), 5.65 (s), 5.02 (dd, J=8.4, 2.4 Hz), 4.14 (d, J=2.8 Hz), 3.19 (d, J=3.2 Hz), 3.02 (m), 2.85 (m), 2.55 (m), 2.35 (m), 2.31 (s), 2.30 (s), 1.70 (m), 1.28 (m), 1.17 (m), 0.94 (dd, J=28.1, 10.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 214.7, 145.1, 144.9, 135.6, 135.3, 130.0, 129.9, 129.2, 128.7, 126.9, 126.8, 125.0, 124.8, 124.3, 123.9, 123.5, 123.4, 123.2, 122.3, 120.8, 119.6, 114.1, 113.8, 68.7, 65.8, 51.5, 50.7, 43.4, 39.8, 39.8, 38.9, 38.7, 38.6, 31.5, 31.3, 30.6, 30.4, 24.3, 24.2, 21.6; LRFABMS (NBA) (*m/z*, rel. int.) 425(11), 408(98), 380(10), 300(100), 284(39), 254(11), 154(46), 130(25); HRFABMS (NBA) calcd for $C_{24}H_{27}O_4NS$ (M+H) 425.1660, found 425.1663.

2-(1-Hydroxyhexyl)-3-methylcyclohexanone (Table 2, entry 2). General method **B** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (16.0 mg, 0.008 mmol, 5 mol% Cu), tetramethyldisiloxane (0.27 mL, 1.5 mmol, 1.5 equiv.), 3-methyl-2-cyclohexenone (0.11 mL, 1.0 mmol, 1.0 equiv.), 1-hexanal (0.18 mL, 1.5 mmol, 1.5 equiv.), and 1.0 M $TiCl_4$ (1.50 mL, 1.5 mmol, 1.5 equiv.). Purification by flash chromatography (1:9 EtOAc/PE) afforded aldol diastereomers as a colorless oil (combined yield 0.15 g, 72%). R_f=0.25; IR (thin film) 3426, 2953, 2928, 2862, 1700, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) [Note: integrations are not given for combined diastereomers as signals overlap] δ 3.70 (m), 2.82 (s, 3H), 2.80 (s, 3H), 2.36 (m), 2.10 (m), 1.90 (m), 1.72 (m), 1.47 (m), 1.28 (m), 1.12 (s), 1.11 (s), 0.89 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 68.2, 67.8, 54.5, 42.5, 42.1, 34.4, 34.2, 33.8, 31.5, 30.3, 29.5, 24.8, 23.7, 22.2, 20.2, 19.9; LRFABMS (NBA) (*m/z*, rel. int.) 213(33), 195(100), 191(14), 177(13), 141(14), 113(83), 97(18), 95(48), 43(8); HRFABMS (NBA) calcd for $C_{13}H_{24}O_2Na$ (M+Na) 235.1674, found 235.1670.

2-(4-Nitrobenzylhydroxy)-cyclohexanone (Table 2, entry 3). General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (21.7 mg, 0.01 mmol, 3 mol% Cu), dimethylphenylsilane (0.46 mL, 3.0 mmol, 1.5 equiv.), 2-cyclohexenone (0.20 mL, 2.0 mmol), 4-nitrobenzaldehyde (0.36 g, 2.4 mmol, 1.2 equiv.), and neat $BF_3{\cdot}Et_2O$ (0.30 mL, 2.4 mmol, 1.2 equiv.). Purification by flash chromatography (1:5 EtOAc/hexane) afforded two aldol diastereomers as a yellow solid (combined yield 0.36 g, 73%). R_f=0.10–0.17; IR (thin film) 3428, 2945, 2867, 2362, 2255, 1699, 1605, 1523, 1349, 1096, 909, 734, 650; ^{1}H NMR (400 MHz, $CDCl_3$) [Note: integrations are not given for combined diastereomers as signals overlap] δ 8.22 (dd, J=2.5, 9.5 Hz, 2H), 7.50 (dd, J=2.0, 9.0 Hz, 2H), 5.50 (s, 1H), 4.91 (d, J=8.0 Hz, 1H), 4.81 (br s, 1H), 3.18 (br s, 1H), 2.62 (m), 2.51 (m), 2.39 (m), 2.13 (m), 1.86 (m), 1.64 (m), 1.41 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 149.3, 128.0, 126.8, 123.8, 74.3, 70.3, 57.4, 42.9, 31.0, 28.1, 26.1, 25.0; LRCIMS (CH_4) (M–H_2O) (*m/z*, rel. int.) 231(6), 214(13), 184(3), 150(64), 128(2), 116(5), 98(100), 77(52), 55(67); HRFABMS (NBA) (M+H) calcd for $C_{13}H_{15}NO_4$ 250.1079, found 250.1081.

2-[2-(2-Chloroethoxy)-1-hydroxyethyl]-4-isopropylcyclohexanone (Table 2, entry 5). General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (25 mg, 0.013 mmol, 5 mol% Cu), dimethylphenylsilane (0.35 mL, 2.25 mmol, 1.5 equiv.), cryptone (0.22 mL, 1.5 mmol), (2-chloroethoxy)-acetaldehyde (0.24 g, 2.0 mmol, 1.3 equiv.), and $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol, 1.3 equiv.). Purification by flash chromatography (1:3 EtOAc/hexane) afforded aldol diastereomers as a colorless oil (combined yield 0.34 g, 87%). R_f=0.19–0.27; IR (thin film) 3497, 2959, 2872, 1706, 1129, 747, 665; R_f=0.19–0.23; ^{1}H NMR (500 MHz, $CDCl_3$) [Note: integrations are not given for combined diastereomers as signals overlap] δ 4.26 (m), 4.20 (m), 3.75 (m), 3.64 (m), 3.56 (m), 3.48 (dd, J=14.1, 6.7 Hz), 2.69 (bd, J=4.3 Hz), 2.56 (dt, J=13.1, 5.4 Hz), 2.38 (m), 2.17 (m), 2.05 (m), 1.63 (m), 1.44 (m), 1.21 (dd, J=7.1, 3.0 Hz), 0.93 (dd, J=7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 215.2, 214.1, 213.8, 72.9, 72.6, 72.5, 72.3, 71.6, 71.5, 71.4, 71.2, 71.1, 71.0, 68.9, 68.4, 68.1, 68.0, 63.7, 51.5, 51.4, 50.2, 49.4, 43.1, 43.0, 42.9, 42.8, 42.7, 42.5, 42.0, 41.9, 39.4, 39.2, 38.9, 38.5, 31.2, 32.1, 32.0, 31.4, 30.7, 30.3, 29.7, 29.4, 29.0, 28.8, 28.6, 20.5, 20.4, 20.0, 19.8; LRCIMS (CH_4) (*m/z*, rel. int.) 263(14), 245(35), 227(3), 203(11), 183(33), 165(100), 149(3), 141(56), 123(67), 107(30), 93(37), 70(4), 63(53), 55(20); HRFABMS calcd for (M+H) $C_{13}H_{24}O_3Cl$ 263.1414, found 263.1415; HREIMS (CH_4) calcd for (M–H_2O) $C_{13}H_{21}O_2Cl$ 244.1230, found 244.1240.

2-(*E*-1-Hydroxy-3-tributylstannanyl-2-butenyl)-4-isopropylcyclohexanone (Tabel 2, entry 6). General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (24 mg, 0.012 mmol, 5 mol% Cu), dimethylphenylsilane (0.34 mL, 2.2 mmol, 1.5 equiv.), cryptone (0.22 mL, 1.5 mmol), *E*-3-tributylstannanyl-2-butenal (0.70 g, 2.0 mmol, 1.3 equiv.), and $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol, 1.3 equiv.). Purification by flash chromatography (1:10 Et_2O/hexane) afforded two separable aldol diastereomers as a colorless oil (combined yield 0.57 g, 76%). *Diastereomer 1:* R_f=0.23; IR (thin film) 3461, 2956, 2926, 2871, 1704, 1463; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (m), 4.73 (dt, J=8.4, 2.8 Hz, 1H), 2.21 (m), 1.89 (m), 1.48 (m), 1.31 (h, J=7.2 Hz), 0.96 (t, J=6.8 Hz), 0.91 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 142.5, 140.1, 128.1, 66.4, 42.8, 39.3, 39.2, 29.3, 28.6, 28.4, 27.6, 27.6, 20.1, 13.9, 9.4. *Diastereomer 2:* R_f=0.10; IR (thin film) 3417, 2956, 2926, 2872, 1705, 1462; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (mq, J=33.0, 8.8, 1.8 Hz, 1H), 4.81 (bt, J=9.0 Hz, 1H), 2.90 (bs, 1H), 2.41 (m, 6H), 1.94 (dd, J=22.1, 1.9 Hz, 3H), 1.76 (bm, 5H), 1.48 (bm, 8H), 1.32 (m, 8H), 0.91 (mt, J=7.3, 6.8 Hz, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 144.4, 139.9, 67.2, 53.5, 39.2, 39.1, 31.4, 29.6, 29.4, 29.3, 27.6, 20.8, 20.4, 20.3, 13.9, 9.4; LREIMS (*m/z*, rel. int.) 443(1), 425(3), 304(12),

248(5), 201(2), 192(2), 177(35), 159(18), 140(28), 121(50), 107(9), 97(23), 84(30), 70(66), 55(70); HREIMS calcd for (M−Bu, ^{116}Sn) $C_{21}H_{39}O_2Sn$ 439.1967, found 439.1953.

6-Benzyloxy-4-ethyl-5-hydroxy-3-hexanone (Table 2, entry 7). General method **B** was employed using the following quantities: toluene (2.5 mL), copper hydride $[CuH(PPh_3)]_6$ (8.0 mg, 0.004 mmol, 2.5 mol% Cu), tetramethyldisiloxane (0.25 mL, 1.4 mmol, 1.2 equiv.), *trans*-4-hexen-3-one (0.13 mL, 1.17 mmol), benzyloxyacetaldehyde (0.20 mL, 1.4 mmol, 1.2 equiv.), and 1.0 M $TiCl_4$ (1.4 mL, 1.4 mmol, 1.2 equiv.). Flash chromatography (8:2 hexanes/EtOAc) afforded a colorless oil (combined yield 0.23 g, 79%). IR (thin film) 3466, 2968, 2935, 2875, 1708, 1497, 1456, 1377, 1092, 737, 699. *Diastereomer 1:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.55 (d, J=11.6 Hz, 1H), 4.52 (d, J=11.6 Hz, 1H), 3.92 (p, J=5.7 Hz, 1H), 3.51 (dd, J=9.7, 4.4 Hz, 1H), 3.49 (dd, J=9.7, 5.5 Hz, 1H), 3.11 (d, J=7.0 Hz, 1H), 2.69 (dt, J=8.6, 5.9 Hz, 1H), 2.52 (m, 2H), 1.62 (m, 3H), 1.00 (t, J=7.3 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 137.7, 128.7, 128.1, 128.0, 73.8, 73.0, 71.9, 54.8, 38.2, 22.6, 12.1, 7.4. *Diastereomer 2:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.52 (d, J=12.0 Hz, 1H), 4.51 (d, J=12.0 Hz), 3.97 (p, J=3.3 Hz, 1H), 3.50 (m, 1H), 3.39 (m, 1H), 3.15 (d, J=7 Hz, 1H), 2.75 (m, 1H), 2.50 (m, 2H), 1.62 (m, 3H), 1.01 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 137.6, 128.7, 128.1, 128.0, 73.7, 72.2, 70.9, 55.6, 38.1, 21.3, 12.1, 7.5; LRFABMS (NBA) 251(33), 233(11), 143(100), 115(18), 107(16); HRFABMS (NBA) calcd for $C_{15}H_{23}O$ (M+H) 251.1647, found 251.1648.

2-Benzyl-3-hydroxy-5-methyl-1-phenyl-1-hexanone (Table 2, entry 8). General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (24 mg, 0.012 mmol, 5 mol% Cu), phenylsilane (0.20 mL, 1.6 mmol, 1.1 equiv.), *trans*-chalcone (0.31 g, 1.5 mmol), isovaleraldehyde (0.26 g, 2.4 mmol, 1.6 equiv.), neat $BF_3{\cdot}Et_2O$ (0.30 mL, 2.4 mmol, 1.6 equiv.). Purification by flash chromatography (1:10 Et_2O/hexane) afforded two separable aldol diastereomers (combined yield 0.317 g, 73%). *Diastereomer 1:* R_f=0.27, colorless oil; IR (thin film) 3481, 3063, 3028, 2955, 2869, 1676; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J=7.9, 1.1 Hz, 2H), 7.56 (bt, J=7.2 Hz, 1H), 7.43 (t, J=7.5 Hz, 2H), 7.23 (m, 4H), 7.16 (m, 1H), 3.87 (h, J=4.1 Hz, 1H), 3.74 (h, J=3.9 Hz, 1H), 3.20 (d, J=9.2 Hz, 1H), 3.11 (dd, J=7.5, 4.6 Hz, 2H), 1.8 (m, 1H), 1.44 (m, 1H), 1.19 (m, 1H), 0.83 (dd, J=18.8, 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 139.2, 137.7, 133.7, 129.3, 128.9, 128.7, 128.4, 126.6, 70.8, 52.7, 45.3, 36.6, 25.0, 23.6, 22.0. *Diastereomer 2:* R_f=0.20; white solid, mp=64–66°C; IR (KBr) 3460, 3062, 3078, 2956, 2869, 1673; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J=8.2, 1.0 Hz, 2H), 7.59 (t, J=7.6 Hz, 1H), 7.44 (t, J=7.8 Hz, 2H), 7.25 (dd, J=11.9, 7.2 Hz, 4H), 7.19 (m, 1H), 4.14 (h, J=3.4 Hz, 1H), 3.89 (p, J=4.3 Hz, 1H), 3.25 (m, 2H), 2.86 (d, J=33.2 Hz, 1H), 1.95 (h, J=5.8 Hz, 1H), 1.72 (m, 1H), 1.39 (m, 1H), 1.03 (dd, J=8.7, 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 139.2, 139.8, 137.6, 133.4, 129.2, 129.2, 128.7, 128.6, 128.5, 126.3, 70.3, 53.8, 44.1, 33.8, 24.9, 23.7, 22.0; LRCIMS (CH_4) (*m*/*z*, rel. int.) 279(10), 211(39), 119(8), 105(35), 91(30), 69(23), 51(32), 49(100), 45(9), 43(31); HREIMS calcd for (M+H) $C_{20}H_{25}O_2$ 297.1854, found 297.1850.

2-(3-Cyclohexenyl-hydroxymethyl)-4,4-dimethylcyclohexanone [Scheme 2, (a)]. General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (88.0 mg, 0.045 mmol, 18 mol% Cu), dimethylphenylsilane (0.34 mL, 2.22 mmol, 1.5 equiv.), 4,4-dimethyl-2-cyclohexenone (0.20 mL, 1.5 mmol), (1,2,3,6)-tetrahydrobenzaldehyde (0.94 mL, 1.7 mmol, 1.1 equiv.), and neat $BF_3{\cdot}Et_2O$ (0.24 mL, 1.7 mmol, 1.1 equiv.). Purification by flash chromatography (1:8 Et_2O/hexane) afforded two separable aldol diastereomers as white solids (combined yield 0.28 g, 80%). IR (neat) 3512, 3455, 3021, 2925, 1703. *Diastereomer 1:* R_f=0.11; mp=62–63°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (m, 2H), 3.66 (p, J=7.5 Hz, 1H), 3.51 (d, J=4.1 Hz, 1H), 2.61 (p, J=7.5 Hz, 1H), 2.50 (dt, J=14.1, 6.3 Hz, 1H), 2.28 (dq, J=14.3, 2.7, 2.0 Hz, 1H), 2.09 (bm, 4H), 1.86 (bd, J=17.1 Hz, 1H), 1.96 (bm, 5H), 1.42 (t, J=13.3 Hz, 1H), 1.23 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.2, 127.2, 126.6, 75.0, 49.0, 43.1, 40.0, 39.3, 35.1, 31.6, 30.8, 26.7, 25.9, 24.7, 24.3. *Diastereomer 2:* R_f=0.05 (mixture of diastereomers); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (m, 2H), 3.93 (d, J=3.3 Hz, 1H), 3.86 (d, J=3.3 Hz, 1H), 2.71 (dd, J=12.8, 3.3 Hz, 1H), 2.64 (dd, J=12.8, 5.6 Hz, 1H), 2.51(m, 4H), 2.35 (bd, J=17.8 Hz, 1H), 2.25 (m, 1H), 2.05 (bs, 2H), 1.85 (m, 1H), 1.69 (m, 2H), 1.55 (m, 1H), 2.21 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.0, 128.2, 126.8, 126.2, 125.3, 72.4, 72.3, 48.0, 47.8, 39.8, 38.9, 38.2, 34.8, 34.6, 31.7, 30.5, 29.0, 27.6, 25.7, 24.8, 24.7, 24.6, 24.4; LRCIMS (CH_4) combined diastereomers (*m*/*z*, rel. int.) 237(3), 219(29), 201(14.8), 167(4), 155(10), 139(20), 127(100), 109(45), 93(77), 81(18), 59(22); HRCIMS (CH_4) calcd for $C_{15}H_{25}O_2$ 237.1854, found 237.1864.

2-(4-Nitrobenzylhydroxy)-4,4-dimethylcyclohexanone [Scheme 2, (b)]. General method **A** was employed using the following quantities: copper hydride $[CuH(PPh_3)]_6$ (98.0 mg, 0.05 mmol, 18 mol% Cu), dimethylphenylsilane (0.35 ml, 2.28 mmol, 1.5 equiv.), 4,4-dimethyl-2-cyclohexenone (0.19 mL, 1.5 mmol), 4-nitrobenzaldehyde (0.34 g, 2.2 mmol, 1.5 equiv.), and neat $BF_3{\cdot}Et_2O$ (0.23 mL, 1.8 mmol, 1.2 equiv.). Purification by flash chromatography (1:2 Et_2O/hexane) afforded two separable aldol diastereomers as white solids (combined yield 0.98 g, 68%); IR (KBr) 3406, 3109, 3056, 2952, 2857, 1693, 1515, 1349. *Diastereomer 1:* R_f=0.17, mp=144–146°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 5.46 (d, J=4.67 Hz, 1H), 5.31 (bt, J=3.9 Hz, 1H), 3.53 (s, 1H), 2.81 (ddd, J=13.2, 5.5, 2.1 Hz, 1H), 2.49 (m, 1H), 2.14 (dt, J=15.3, 3.8 Hz, 1H), 1.65 (t, J=13.5 Hz, 1H), 1.59 (m, 1H), 1.26 (ddd, J=13.1, 5.8, 2.7 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 210.1, 153.2, 146.2, 127.1, 127.2, 122.9, 68.3, 52.0, 38.2, 37.7, 37.4, 31.6, 29.8, 24.1. *Diastereomer 2:* R_f=0.11, mp=146–148°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H), 5.48 (1H), 1.60 (m, 1H), 1.43 (dt, J=13.6, 4.7 Hz, 1H), 1.30 (dd, J=13.2, 5.0 Hz, 1H), 5.07 (bt, J=4.9 Hz, 1H), 2.97 (dt, J=13.7, 5.5 Hz, 1H), 2.57 (td, J=14.1, 5.5 Hz, 1H), 2.07 (dd, J=14.3, 5.2 Hz, 1H), 1.12 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ

211.0, 151.6, 146.4, 128.1, 122.9, 69.9, 52.5, 42.1, 38.2, 31.2, 30.3, 24.2; LRCIMS (CH_4) (*m/z*, rel. int.) 237(3), 219(29), 201(15), 167(4), 155(10), 139(20), 127(100), 109(45), 93(77), 81(18), 59(22); HRCIMS (CH_4) calcd for (M+H) $C_{15}H_{20}O_4N$ 278.1392, found 278.1388.

3-Benzyl-5-benzyloxy-4-hydroxy-2-pentanone (Scheme 3). General method **B** was employed using the following quantities; copper hydride $[CuH(PPh_3)]_6$ (7.2 mg, 0.004 mmol, 2.2 mol% Cu), polymethylhydroxysilane (PMHS; 0.08 mL, 1.25 mmol, 1.25 equiv.), *trans*-4-phenyl-3-buten-2-one (0.148 g, 1.0 mmol), benzyloxyacetaldehyde (0.18 mL, 1.3 mmol, 1.3 equiv.), and 1.0 M $TiCl_4$ (1.3 mL, 1.3 mmol, 1.3 equiv.). Purification by flash chromatography (1:4 EtOAc/hexanes) afforded aldol diastereomers as a yellow oil (combined yield 0.24 g, 81%). R_f=0.20; IR (thin film) 3438, 3032, 2923, 2866, 2253, 1703, 1643, 1454, 1362, 1102, 909, 732, 650; ^{1}H NMR (400 MHz, $CDCl_3$) [Note: integrations not given for combined diastereomers as signals overlap] δ 7.30 (m), 7.15 (m), 4.51 (m), 4.02 (m, 1H), 3.89 (m, 1H), 3.52 (m), 3.44 (m), 3.27 (bm, 1H), 3.08 (m, 3H), 2.88 (m, 3H), 2.75 (bm, 1H), 1.93 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 212.3, 139.4, 138.8, 137.8, 129.1, 128.8, 128.0, 126.7, 126.6, 73.7, 72.8, 71.8, 71.0, 56.9, 55.5, 35.6, 34.5, 32.8; LRFAB (NBA) (*m/z*, rel. int.) 299(52), 281(8), 219(10), 191(50), 165(10), 115(22); HRFAB (NBA) (M+H) calcd for $C_{19}H_{22}O_3$ 299.3762, found 299.1648.

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