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The Stereoselective Reductions of Ketones to the Most Thermodynamically Stable Alcohols Using Lithium and Hydrated Salts of Common Transition Metals

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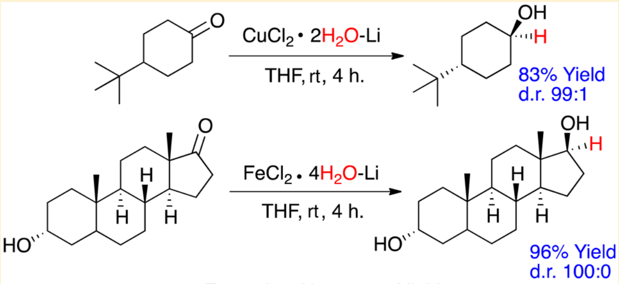
Ⓢ *Supporting Information*

ABSTRACT: A simple method is presented for the highly stereoselective reductions of ketones to the most thermodynamically stable alcohols. In this procedure, the ketone is treated with lithium dispersion and either $FeCl_2{\cdot}4H_2O$ or $CuCl_2{\cdot}2H_2O$ in THF at room temperature. This protocol is applied to a large number and variety of ketones and is both more convenient and efficient than those commonly reported for the diastereoselective reduction of five- and six-membered cyclic ketones.



45 Examples, Up to 99% Yield,
Excellent Stereoselectivity,
Most Thermodynamically Stable Alcohol

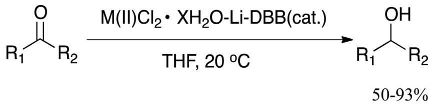
INTRODUCTION

One of the most widely used and valuable functional group transformations in synthetic organic chemistry is the reduction of unsaturated substrates, specifically ketones in order to obtain the corresponding alcohols. Interesting alternatives to the catalytic hydrogenation of ketones, which employs high hydrogen pressure or hazardous reducing agents, include metal-mediated reductions by electron- or hydride-transfer.[1] Most of the published results for the stereoselective reduction of cyclic ketones consist of using metal hydrides or complex reducing agents.[2] In general, for six-membered rings, bulky reducing agents favor the approach to the carbonyl group via an equatorial trajectory, giving the thermodynamically less stable axial alcohol.[3] Several valuable protocols have been devised for the synthesis of the more stable equatorial alcohols;[4] however, a simple, consistently high-yielding method is unavailable.

We now present a new, simple, and effective methodology to accomplish the diastereoselective reduction of mono- and poly cyclic ketones under very mild conditions to afford the thermodynamically more stable alcohol product. This method was developed during our investigation of the protocol by Yus and co-workers[5] for the reduction of unsaturated groups. Their procedure makes use of the hydrates of transition-metal salts $FeCl_2{\cdot}4H_2O$, $NiCl_2{\cdot}2H_2O$, or $CuCl_2{\cdot}2H_2O$ in the presence of lithium metal and catalytic amounts of *p*,*p*′-di-*tert*-butyl biphenyl (DBB) (Scheme 1). The role of the latter additive is to pick up an electron from the Li to form an aromatic radical-anion, which then transfers the electron to another component of the solution, thus acting as an electron-transfer agent.

In a publication that will soon appear in *The Journal of Organic Chemistry*, we reveal that the reductive lithiation of alkyl phenyl thioethers and alkyl chlorides, previously done only in the presence of aromatic electron-transfer agents, surprisingly does not actually require the use of such reagents when the Li is supplied in the form of a dispersion in mineral oil. This led us to investigate whether or not the same is true of the ketone reductions performed by Yus[1,6,7] in the presence of the hydrates of transition-metal salts. We restricted our studies to the commercially available copper and iron salts and did not examine the commercially unavailable[8] and toxic nickel salts. It turns out that in the reduction of ketones by our procedure, the aromatic electron-transfer agent is indeed not required. Furthermore, most surprisingly, in some important cases, the reported diastereoselectivity is just the opposite in the presence of such agents.[1] We have not been able to reproduce some of these reported stereoselectivity results.

Scheme 1. Yus's Reduction of Carbonyl Compounds[a]



[a] M = Cu, Ni or Fe, X = 2 or 4.

RESULTS AND DISCUSSION

Yus and co-workers employ an 8:1 molar ratio of lithium sand to $CuCl_2{\cdot}2H_2O$[7] and an 8:1 molar ratio of lithium powder to $FeCl_2{\cdot}4H_2O$.[1] There is no mention as to why they use different types of lithium or what their lithium sources are. We were able

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to use a 4:1 molar ratio of lithium dispersion, (25 wt% in mineral oil) containing 0.1% sodium, to $CuCl_2{\cdot}2H_2O$ and in the case of the more highly hydrated $FeCl_2{\cdot}4H_2O$, a 6:1 molar ratio to achieve the diastereoselective reduction of cyclic ketones in moderate to excellent yields. An important advantage of this dispersion is that it can be weighed and transferred to the designated flask open to the air without the lithium reacting. The mineral oil that coats the lithium metal can then be removed under argon by rinsing with hexanes so that the lithium remains unreacted under argon until the solvent and the substrate are added.

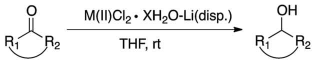
In the reduction of 4-*tert*-butylcyclohexanone, **1**, (Table 1, entries 1 and 3), in which the bulky *tert*-butyl group is locked in the equatorial position and is remote from the carbonyl reaction center, the resulting product was the thermodynamically more stable equatorial alcohol, *trans*-4-*tert*-butylcyclohexanol, **8**.[9] This result resembles those obtained with the most common metal hydrides ($LiAlH_4$, $NaBH_4$, or $LiBH_4$)[10] or the complex reducing agents of Caubére's group.[11] Lithium metal in liquid ammonia afforded only the *trans* isomer, although in a much lower yield (57%).[12] More recently, Cha and co-workers performed the reduction of **1** with 1.1 equiv of Al-methanesulfonyldiisobutylalane ($DIBAO_3SCH_3$) at room temperature to obtain 99% (as determined by GC after 72 h) of the more stable *trans*-alcohol in a ratio of 94:6 eq/ax.[4g] Their procedure not only requires the preparation of the $DIBAO_3SCH_3$ reagent but also a significantly longer reaction time in order to achieve a diastereoselectivity similar to that obtained in our present work. Using the deuterated salt $CuCl_2{\cdot}2D_2O$, prepared from anhydrous $CuCl_2$ and D_2O, instead of the hydrated one, furnished the corresponding alcohol, **9**, deuterated at the 1-position (entry 2).

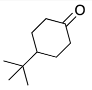
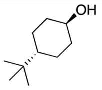
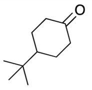
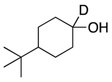
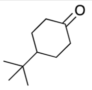
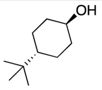
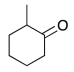
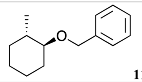
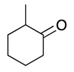
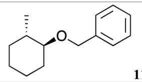
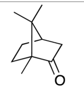
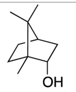
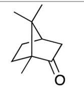
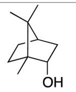
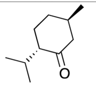
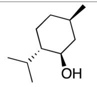
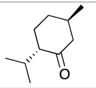
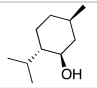
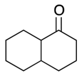
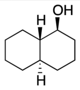
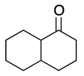
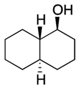
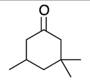
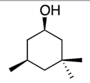
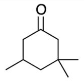
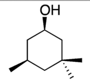
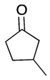
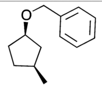
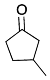
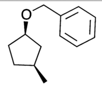
In the case of the more hindered ketone, 2-methylcyclohexanone, **2**, (Table 1, entries 4 and 5), the thermodynamically more stable equatorial alcohol, *trans*-2-methylcyclohexanol, **10**, was produced after only 10 min. The crude alcohol was protected as a benzyl ether,[13] **11**, in order to ease the isolation and purification of the product. The diastereoselectivity of **10** surpasses that observed with common reducing systems ($LiAlH_4$, $NaBH_4$, 9-BBN)[14] or $BH_3{\cdot}THF$.[1] The metal-ammonia reduction of **2** affords nearly exclusive formation of the equatorial alcohol; however, a significantly lower yield (63%) was collected after 100 min.[4a] In the work by Cha et al., a longer reaction time, when compared to our procedure, was employed in their reduction of **2** with Al-trifluoromethanesulfonyldiisobutylalane ($DIBAO_3SCF_3$) to produce 94% (as determined by GC after 1 h.) of the more stable *trans*-alcohol in a ratio of 91:9 eq/ax.[4h]

Interestingly, the reduction of (±)-camphor, **3**, (Table 1, entries 6 and 7) required 2 equiv of the metal(II) salts and a longer reaction time (24 h) leading to ratios of 96:4 and 95:5 of the more stable *endo*-borneol, **12**, to *exo*. Yus reported that, for the same reaction time and equivalents, the reduction of **3** yielded 55% of **12** (*endo*/*exo* 85:15) with $CuCl_2{\cdot}2H_2O$ and 62% of **12** (*endo*/*exo* 90:10) with $FeCl_2{\cdot}4H_2O$.[1] Thus, a higher yield and diastereoselectivity was obtained under our conditions, that is, in the absence of an aromatic electron-transfer reagent.

In the reduction of (−)-menthone, **4**, (Table 1, entries 8 and 9) the alcohol that is so favorably produced, (−)-menthol, **13**, is capable of an all-equatorial configuration. Solodar and co-workers obtained less of **13**, 74% (−)-menthol to 26% mixture of *neo*-, *iso*-, and *neoiso*-menthol, in their stereoselective

Table 1. Stereoselective Reduction of Cyclic Ketones with either $CuCl_2{\cdot}2H_2O$−Li(disp.) or $FeCl_2{\cdot}4H_2O$−Li(disp.)



Entry	Ketone[a]		Metal (II)	Equiv	Rxn. Time (h.)	Product[b]		%Yield[c]	d.r.[d]
1		**1**	Cu	1.5	4		**8**	83	99:1
2		**1**	Cu	1.5	4		**9**	78[e]	-
3		**1**	Fe	1.5	4		**8**	77	100:0
4		**2**	Cu	1.5	10 min.		**11**	80[f]	92:8[g]
5		**2**	Fe	1.5	10 min.		**11**	99[f]	95:5[g]
6		**3**	Cu	2	24		**12**	65	96:4
7		**3**	Fe	2	24		**12**	78	95:5
8		**4**	Cu	1.5	4		**13**	86	94:6
9		**4**	Fe	1.5	4		**13**	99	95:5
10		**5**[h]	Cu	1.5	2		**14a**	82	92:5:3[i]
11		**5**[h]	Fe	1.5	2		**14a**	95	94:4:2[i]
12		**6**	Cu	2	1		**15**	26	100:0
13		**6**	Fe	1.5	1		**15**	70	100:0
14		**7**	Cu	1[j]	5 min.		**17**	63[f]	60:40[k]
15		**7**	Fe	1[l]	5 min.		**17**	70[f]	60:40[k]

[a] 1.0 mmol scale. [b] The structure of the major diastereoisomer is shown. [c] Isolated yield after chromatography purification. [d] Diastereomeric ratio determined by ^{1}HNMR. [e] $CuCl_2{\cdot}2D_2O$ was used instead of $CuCl_2{\cdot}2H_2O$, deuterium incorporation ≥85% (^{1}HNMR). [f] Isolated yields of benzyl-ether product. [g] Diastereomeric ratio of *trans*-2-methylcyclohexanol to *cis*. [h] Commercially available unknown mixture of *cis* and *trans* from a chemical supplier. [i] Diastereomeric ratio of (±)-*trans, cis*- to (±)-*trans, trans*-[20] to (±)-*cis, trans*-[21] decahydro-1-naphthol determined by ^{1}HNMR. [j] 3:1 ratio of lithium dispersion to $CuCl_2{\cdot}2H_2O$. [k] Diastereomeric ratio of *cis*-3-methylcyclopentanol to *trans*. [l] 5:1 ratio of lithium dispersion to $FeCl_2{\cdot}4H_2O$.

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reduction of **4** with 3 equiv of lithium metal and 1 equiv of water in ether at ambient temperature.[15]

When our methodology was applied to a mixture of *cis*- and *trans*-1-decalone, **5**, (Table 1, entries 10 and 11), the major diastereomeric product, (±)-*trans*,*cis*-decahydro-1-naphthol, **14a**, was that which would result from the reduction of pure *trans*-1-decalone, despite the starting material containing a mixture of isomers. Presumably, the *trans*-isomer of **5** reacts faster than the *cis*-isomer. The (±)-*cis*,*cis*-decahydro-1-naphthol was not produced in either reduction reaction. Houk and co-workers observed only 60% of **14** after 24 h. by $NaBH_4$ reduction of *trans*-1-decalone.[16] Alternatively, Yus et al. isolated the less thermodynamically stable axial alcohol, (±)-*trans*,*trans*-decahydro-1-naphthol, with their $M(II)Cl_2 \cdot XH_2O$−Li-DBB reduction of *trans*-1-decalone.[1]

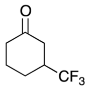
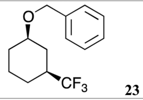
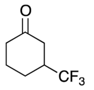
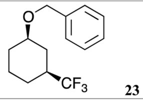
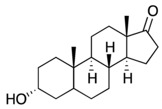
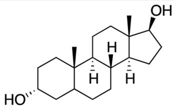
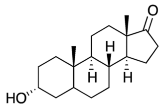
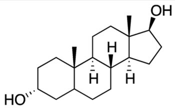
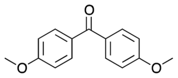
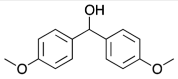
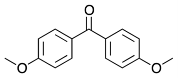
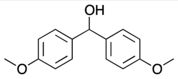
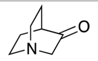
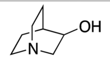
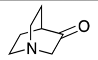
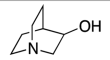
In the case of 3,3,5-trimethylcyclohexanone, **6**, (Table 1, entries 12 and 13), a significantly higher yield of the thermodynamically stable equatorial alcohol, *cis*-3,3,5-trimethylcyclohexanol, **15**, was isolated with the $FeCl_2 \cdot 4H_2O$ in comparison to the $CuCl_2 \cdot 2H_2O$. Furthermore, 2 equiv of $CuCl_2 \cdot 2H_2O$ were required to reduce **6** to an isolable amount. More recently, Cha and co-workers performed the reduction of **6** with their $DIBAO_3SCF_3$ to obtain the more stable *cis*-alcohol in a ratio of 98:2 eq/ax after 72 h,[4h] that is with less diastereoselectivity than in our reduction after only 1 h.

Examination of the conformation of 3-methylcyclopentanone shows that the 3-methyl group prefers to occupy a pseudo-equatorial position[17] of an envelope conformation.[18] Under our conditions, the reduction of 3-methylcyclopentanone, **7**, (Table 1, entries 14 and 15) led to 3-methylcyclopentanol, in only 5 min, with an excess of the *cis*-isomer, **16a**. The $LiAlH_4$ reduction of **7** also provides a 60:40 *cis* to *trans* ratio of 3-methylcyclopentanol.[19] Similar to the case of **2**, the reduction product was protected as a benzyl ether to afford **17**.

In order to further assess the reduction capability of our method in the presence of various functional groups, other than alkyl substituents, we have successfully reduced ketones containing a trifluoromethyl group, a hydroxyl group, a methoxy group, and a tertiary amine (Table 2). 3-(Trifluoromethyl)cyclohexanone, **18**, was reduced to the more thermodynamically stable *cis*-3-(trifluoromethyl)-cyclohexanol, **22**, in excellent diastereoselectivity (Table 2, entries 1 and 2). The crude alcohol was protected as a benzyl ether, **23**, in order to ease the isolation and purification of the product. To the best of our knowledge, the only other reduction of **18** occurred with microorganisms, in which **18** was reduced with *Streptomyces* C53 in 94% in a ratio of 55:45 *cis*-3-(trifluoromethyl)cyclohexanol to *trans* after 24 h.[22]

The hindered steroidal ketone, 3α-hydroxy-5α-androstan-17-one, **19**, was diastereoselectively reduced to 5α-androstane-3α,17β-diol, **24** (Table 2, entries 3 and 4). The free 3α-hydroxy group did not affect the ketone reduction. Satoh and co-workers[23] indicated that the reduction of **19** with $NaBH_4$ alone is difficult; therefore, they employed a large excess of $NaBH_4$ (10 equiv) and $PdCl_2$ in their reduction of **19** to obtain **24** in 96% yield.

Table 2. Reduction of Ketones Containing Various Functional Groups with either $CuCl_2 \cdot 2H_2O$−Li(disp.) or $FeCl_2 \cdot 4H_2O$−Li(disp.)

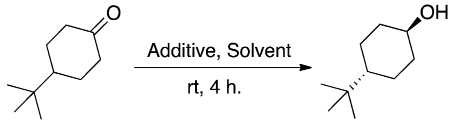
Entry	Ketone[a]	Metal (II)[b]	Rxn. Time (h.)	Product[c]	%Yield[d]	d.r.[e]
1	 **18**	Cu	1	 **23**	70[f]	95:5[g]
2	 **18**	Fe	1	 **23**	85[f]	97:3[g]
3	 **19**	Cu	4	 **24**	75	100:0
4	 **19**	Fe	4	 **24**	96	100:0
5	 **20**	Cu	2	 **25**	83	-
6	 **20**	Fe	2	 **25**	60	-
7	 **21**	Cu	24	 **26**	65	-
8	 **21**	Fe	24	 **26**	65	-

[a] 1.0 mmol scale in THF at room temperature. [b] 1.5 equiv $CuCl_2 \cdot 2H_2O$ or $FeCl_2 \cdot 4H_2O$. [c] The structure of the major diastereoisomer is shown. [d] Isolated yield after chromatography purification. [e] Diastereomeric ratio determined by ^{1}HNMR. [f] Isolated yields of benzyl-ether product. [g] Diastereomeric ratio of *cis*-3-(trifluoromethyl)cyclohexanol to *trans*.

The reduction of 4,4′-dimethoxybenzophenone, **20**, (Table 2, entries 5 and 6) yielded bis(4-methoxyphenyl)methanol, **25**, in moderate or good yield depending on whether the iron or copper salt was employed. There have been many reports of biological reductions[24] and asymmetric hydrogenations[25] of 3-quinuclidinone, **21**, and/or the hydrochloride salt of **21**. As shown in Table 2 (entries 7 and 8), **21** was reduced to 3-quininuclidinol, **26**, in moderate yield under our mild reduction conditions.

Further experiments were performed on the reduction of 4-*tert*-butylcyclohexanone, **1**, in order to determine the effect of variables such as solvent, the presence or absence of the copper salt, and the state of hydration (Table 3). When the solvent was

Table 3. Effects of Some Reaction Variables on the Stereoselective Reduction of 4-*tert*-Butylcyclohexanone



1 **8**

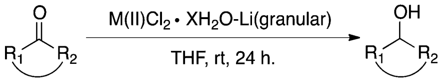
entry	additive	solvent[a]	% yield[b]	d.r.[c]
1	$CuCl_2 \cdot 2H_2O$	THF	83	99:1
2	$CuCl_2 \cdot 2H_2O$	hexanes	54	100:0
3	$CuCl_2$ (anhydrous)	THF	28	98:2
4	–	THF	26	95:5
5	water (1.1 equiv)	THF	42	99:1
6	water (2.2 equiv)	THF	48	94:6

[a] 1.0 mmol scale. [b] Isolated yield after chromatography purification. [c] Diastereomeric ratio determined by ^{1}HNMR.

changed from THF to hexanes, the reduction of **1** with $CuCl_2 \cdot 2H_2O$ produced approximately 30% lower yield of **8** (Table 3, entry 2) presumably because, unlike THF, hexanes cannot complex the lithium metal or the intermediate carbonyl radical-anion. In the absence of a proton donor source from the hydrate of the Cu (II) salt, as in entries 3 and 4, a considerably lower yield of **8** was isolated. Because some of the reduction product was observed in these cases, the carbonyl radical-anion intermediate most likely reacts with atmospheric moisture to form the alkoxy radical, which would then be further reduced to an alkoxide ion.[9] This is evident when both 1.1 equiv and a stoichiometric amount of water were introduced into the reaction mixture and the yields of **8** increases (entries 5 and 6); however, these yields remain significantly lower than those achieved in the presence of the metal(II) hydrate salts. When the reaction mixture was quenched with D_2O, rather than water, there was no change in the amount of **8**. This further supports the fact that the hydrogen at the 1-position of the reduction product alcohol indeed comes from the hydrate of the metal(II) salt and not from the THF solvent.

In order to determine if commercially available granular lithium behaved in a manner similar to that of lithium dispersion, the Li source was changed to granular lithium (0.5% sodium), which presumably has less surface area due to the large chunks of granular metal. A slight excess of the granular lithium, in comparison to the amount of lithium dispersion, was employed because the granular Li metal is not stored in mineral oil, therefore, can react with moisture in the air upon transferring to the desired flask. Furthermore, a longer reaction time (24 h) was necessary to achieve the diastereoselective reduction of cyclic ketones in moderate to excellent yields (Table 4). Thus, the increase in the surface area of the Li metal, from the granular to the dispersion, apparently somewhat enhances the rate of electron transfer for the reduction of ketones, despite the granular lithium having five times the amount of sodium compared to the lithium dispersion.[26] The diastereoselectivities remained the same as, or very similar to, those observed with the lithium dispersion reduction conditions shown in Table 1. The only major discrepancy in going from the dispersion to the granular was in the case of **6** (Table 4, entry 8), in which a significantly lower yield of **15** was isolated with the $FeCl_2 \cdot 4H_2O$, regardless of whether the equivalents of the Fe (II) salt employed were increased or decreased. This result remains puzzling, and perhaps a better understanding of the reduction mechanism would provide an explanation.

Table 4. Stereoselective Reduction of Cyclic Ketones with Granular Lithium and Either $CuCl_2 \cdot 2H_2O$ or $FeCl_2 \cdot 4H_2O$



entry	ketone[a]	metal(II)	equiv	product[b]	% yield[c]	d.r.[d]
1	**1**	Cu	1.5	**8**	86	96:4
2	**1**	Fe	1.5	**8**	85	100:0
3	**3**	Cu	2	**12**	44	100:0
4	**3**	Fe	1	**12**	64	90:10
5	**4**	Cu	1.5	**13**	99	93:7
6	**4**	Fe	1.5	**13**	99	94:6
7	**6**	Cu	1.5	**15**	56	100:0
8	**6**	Fe	1.5	**15**	31	100:0

[a]1.0 mmol scale. [b]The structure of the major diastereoisomer is shown. [c]Isolated yield after chromatography purification. [d]Diastereomeric ratio determined by ^{1}HNMR.

In a blank reaction, Yus and co-workers attempted to reduce an alkyne, 1-ethynylcyclohexanol, to the corresponding alkane in the absence of an arene electron carrier catalyst, and the yield of 1-ethylcyclohexanol decreased from 70% to <5%.[27] It was thus determined that the role of the arene was crucial for the reaction to proceed, and therefore, an arene electron-transfer catalyst, either naphthalene or DBB, has been included in Yus's metal reduction reaction conditions.[1,5−7] In order to determine the significance of an arene electron-transfer catalyst in our work, 10 mol% of DBB was added to the $CuCl_2 \cdot 2H_2O$-granular lithium reduction of various substrates (Table 5). The ratio of the starting material (SM) to the product was determined by ^{1}HNMR and compared to the ratio obtained from the reduction of the same substrates in the absence of the DBB (Table 5). The reduction conditions were repeated with the Fe (II) salt. As shown in Table 5, DBB did not affect the rate of the reduction or the diastereoselectivity observed under either the $CuCl_2 \cdot 2H_2O$ or the $FeCl_2 \cdot 4H_2O$ reaction conditions. Surprisingly, Yus et al. isolated the less thermodynamically stable alcohol, *cis*-2-methylcyclohexanol, with their $M(II)Cl_2 \cdot XH_2O$−Li-DBB reduction of **2**,[1] which is the opposite of what we observed in our reduction of **2** in the presence of a catalytic amount of DBB (Table 5, entries 5 and 6). We are unable to explain this discrepancy.

Table 5. Stereoselective Reduction of Cyclic Ketones with Granular Lithium and Either $CuCl_2 \cdot 2H_2O$ or $FeCl_2 \cdot 4H_2O$ in Presence or Absence of DBB after 4 h

entry	ketone[a]	metal(II)	dbb	product[b]	ratio SM/ product[c]	d.r.[d]
1	**1**	Cu	Yes	**8**	2:1	90:10
2	**1**	Cu	No	**8**	2:1	95:5
3	**1**	Fe	Yes	**8**	17:1	100:0
4	**1**	Fe	No	**8**	19:1	100:0
5	**2**	Cu	Yes	**10**	–[e]	91:9
6	**2**	Fe	Yes	**10**	–[e]	98:2
7	**4**	Cu	Yes	**13**	12:1	100:0
8	**4**	Cu	No	**13**	8:1	100:0
9	**4**	Fe	Yes	**13**	9:1	100:0
10	**4**	Fe	No	**13**	14:1	100:0
11	**6**	Cu	Yes	**15**	4:1	96:4
12	**6**	Cu	No	**15**	1.5:1	94:6
13	**6**	Fe	Yes	**15**	7:1	97:3
14	**6**	Fe	No	**15**	2:1	97:3

[a]1.0 mmol scale in THF at room temperature. [b]The structure of the major diastereoisomer is shown. [c]Ratio determined by ^{1}HNMR. [d]Diastereomeric ratio determined by ^{1}HNMR. [e]Ratio not provided because the reduction of **2** was not performed with granular lithium in the absence of DBB, therefore, the ratio would be ambiguous.

CONCLUSION

It was found that the reductions of monocyclic and bicyclic six-membered ring ketones using lithium and either $FeCl_2 \cdot 4H_2O$ or $CuCl_2 \cdot 2H_2O$ in the presence of DBB, the system promulgated by Yus and collaborators,[1,7] are just as effective in the absence of the latter electron-transfer agent provided that the lithium is a dispersion in mineral oil or the commercially available granular form. Under our very mild conditions, the reduction is highly stereoselective, affording the most thermodynamically stable alcohol in moderate to excellent yields, even in the presence of various functional groups. The procedure presented here is more efficient than the most commonly reported reduction protocols due to the use of only commercially available reagents at room temperature and a shorter reaction time in most cases. The source of the carbinol proton is the hydrate of the transition-metal salts. It is most surprising and inexplicable that in two important cases, that of 2-methylcyclohexanone and *trans*-1-decalone, Yus et al. obtained the opposite diastereoselectivity, that is the least thermodynamically stable alcohol products, under their reduction conditions;[1] although we have not been able to reproduce their results. The $FeCl_2{\cdot}4H_2O$−Li and $CuCl_2{\cdot}2H_2O$−Li reducing systems developed here should become the default protocol for the kind of ketone reductions studied here and should have significant mechanistic implications.

Since our laboratory will soon shut down, we hope that others will study the scope and mechanism of this new fascinating reduction procedure.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out under a positive pressure of dry argon gas in oven-dried (120 °C) flasks and standard precautions against moisture were taken. An ice bath was used to obtain 0 °C. Flash chromatography was performed with silica gel (32−63 μm). Thin-layer chromatography (TLC) was performed on glass supported (0.25 mm) silica plates. Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; aqueous solution of $KMnO_4$; solution of *p*-anisaldehyde (PAA); iodine (I_2). Commercial solvents and reagents were used as received with the following exceptions: 3-quinuclidinone was used after neutralization of 3-quinuclidinone hydrochloride, tetrahydrofuran (THF) was distilled over sodium metal in the presence of benzophenone as indicator, and hexanes was freshly distilled over CaH_2. Lithium dispersion (25 wt % in mineral oil) was commercially available from a chemical supplier. Toward the end of the work described here, a chemical supplier discontinued offering lithium dispersion; however, recipes for its preparation are available.[28] Furthermore, granular lithium, commercially available from a chemical supplier, is only slightly less effective than the dispersion. ^{1}H and ^{13}C NMR spectra operating at 300 or 400 MHz for ^{1}H and 75 MHz for ^{13}C at 22 °C unless otherwise noted. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of $CHCl_3$ triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hz.

$CuCl_2{\cdot}2H_2O$ and Lithium Dispersion Reduction (Tables 1 and 2). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (82 mg, 3.0 mmol; 0.17 g, 6.0 mmol; or 0.22 g, 8.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.17 g, 1.0 mmol; 0.26 g, 1.5 mmol; or 0.34 g, 2.0 mmol) was added at once followed by the dropwise addition of a solution of the ketone substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for the allotted amount of time (see Table) and then was cooled in an ice-water bath and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

$FeCl_2{\cdot}4H_2O$ and Lithium Dispersion Reduction (Tables 1 and 2). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.14 g, 5.0 mmol; 0.25 g, 9.0 mmol; or 0.33 g, 12 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate (0.20 g, 1.0 mmol; 0.30 g, 1.5 mmol; or 0.40 g, 2.0 mmol) was added at once followed by the dropwise addition of a solution of the ketone substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for the allotted amount of time (see Table) and then was cooled in an ice-water bath and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

$CuCl_2{\cdot}2H_2O$ and Lithium Dispersion Reduction of 1 in Hexanes (Table 3, entry 2). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed four times with hexanes (3 mL). Hexanes (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.20 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol) in hexanes (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then was cooled in an ice-water bath and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded *trans*-4-*tert*-butylcyclohexanol, **8** (83 mg, 54% yield).

$CuCl_2$ (anhydrous) and Lithium Dispersion Reduction of 1 in THF (Table 3, entry 3). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Copper(II) chloride anhydrous (0.20 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 4 h and then was cooled in an ice−water bath and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 4-*tert*-butylcyclohexanol, **8** (44 mg, 28% yield) with a *trans* to *cis* ratio of 98:2.

Lithium Dispersion Reduction of 1 in THF (Table 3, entry 4). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (67 mg, 2.4 mmol). The lithium was washed three times with hexanes (2 mL) and once with THF (2 mL). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. A solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol), in THF (0.5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 4-*tert*-butylcyclohexanol, **8** (40 mg, 26% yield) with a *trans* to *cis* ratio of 95:5.

Lithium Dispersion Reduction of 1 in Wet THF (Table 3, entry 5). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.11 g, 4.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with nonanhydrous THF (3 mL). Nonanhydrous THF (3.5 mL) was added to the lithium, water (0.02 mL, 1.1 mmol) was added to the lithium, and the mixture was stirred at room temperature. A solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol), in nonanhydrous THF (0.5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 4-*tert*-

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butylcyclohexanol, **8** (65 mg, 42% yield) with a *trans* to *cis* ratio of 99:1.

Lithium Dispersion Reduction of 1 in Wet THF (Table 3, entry 6). A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.14 g, 5.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with nonanhydrous THF (3 mL). Nonanhydrous THF (3.5 mL) was added to the lithium, water (0.04 mL, 2.2 mmol) was added to the lithium, and the mixture was stirred at room temperature. A solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol), in nonanhydrous THF (0.5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded 4-*tert*-butylcyclohexanol, **8** (75 mg, 48% yield) with a *trans* to *cis* ratio of 94:6.

$CuCl_2$·$2H_2O$ and Granular Lithium Reduction (Table 4). A 25 mL round-bottom flask was charged with granular lithium (63 mg, 9.0 mmol or 83 mg, 12 mmol). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.26 g, 1.5 mmol or 0.34 g, 2.0 mmol) was added at once followed by the dropwise addition of a solution of the ketone substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 24 h, cooled in an ice-water bath, and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

$FeCl_2$·$4H_2O$ and Granular Lithium Reduction (Table 4). A 25 mL round-bottom flask was charged with granular lithium (56 mg, 8.0 mmol or 83 mg, 12 mmol). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate (0.20 g, 1.0 mmol or 0.30 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of the ketone substrate (1.0 mmol) in THF (0.5 mL). The reaction mixture was stirred at room temperature for 24 h, cooled in an ice-water bath, and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product.

$CuCl_2$·$2H_2O$, DBB, and Granular Lithium Reduction (Table 5). A 25 mL round-bottom flask was charged with granular lithium (63 mg, 9.0 mmol). THF (3 mL) was added to the lithium, and the mixture was stirred at room temperature. Copper(II) chloride dihydrate (0.26 g, 1.5 mmol) was added at once followed by a solution of DBB (27 mg, 0.10 mmol) in THF (0.5 mL). A solution of the ketone substrate (1.0 mmol) in THF (0.5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

$FeCl_2$·$4H_2O$, DBB, and Granular Lithium Reduction (Table 5). A 25 mL round-bottom flask was charged with granular lithium (83 mg, 12 mmol). THF (3 mL) was added to the lithium, and the mixture was stirred at room temperature. Iron(II) chloride tetrahydrate (0.30 g, 1.5 mmol) was added at once followed by a solution of DBB (27 mg, 0.10 mmol) in THF (0.5 mL). A solution of the ketone substrate (1.0 mmol) in THF (0.5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

trans-4-tert-Butylcyclohexanol ***8***.[21] White solid (0.13 g, 83% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 3.52 (tt, J = 10.8, 4.2 Hz, 1H), 2.00 (d, J = 10.5 Hz, 2H), 1.78 (d, J = 10.2 Hz, 2H), 1.57 (br, 1H), 1.26–1.10 (m, 2H), 1.06–0.96 (m, 3H), 0.85 (s, 9H); ^{13}CNMR ($CDCl_3$) δ (ppm): 71.1, 47.1, 35.9, 32.2, 27.6, 25.5.

1-Deutero-4-tert-butylcyclohexan-1-ol ***9***. A 25 mL round-bottom flask was charged with 25 wt % lithium dispersion in mineral oil (0.17 g, 6.0 mmol). The lithium was washed three times with hexanes (3 mL) and once with THF (3 mL). THF (3.5 mL) was added to the lithium, and the mixture was stirred at room temperature. $CuCl_2$·$2D_2O$ (prepared from anhydrous $CuCl_2$ and D_2O; 0.26 g, 1.5 mmol) was added at once followed by the dropwise addition of a solution of 4-*tert*-butylcyclohexanone, **1** (0.15 g, 1.0 mmol), in THF (0.5 mL). The reaction mixture was stirred at room temperature for 4 h, cooled in an ice-water bath, and quenched with water. The mixture was filtered through a Celite pad and washed with diethyl ether. The filtrate was further extracted with diethyl ether; the extract was dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (EtOAc/hexanes) afforded pure product **9** (0.12 g, 78% yield) as a white residue in a D to H ratio of 85:15. ^{1}HNMR ($CDCl_3$) δ (ppm): 2.15 (br, 1H), 1.96 (d, J = 12.0 Hz, 2H), 1.74 (d, J = 9.6 Hz, 2H), 1.22–1.14 (m, 2H), 1.06–0.92 (m, 3H), 0.81 (s, 9H); ^{13}CNMR ($CDCl_3$) δ (ppm): 71.0, 70.8, 70.6, 70.3, 47.1, 35.9 (d, J = 8.2 Hz), 32.2, 27.6, 25.5 (d, J = 7.5 Hz); FTMS (+p ESI) calcd for $C_{10}H_{20}{}^2HO$ 158.16497; found 158.16455.

trans-2-Methylcyclohexanol ***10***.[21] Crude oil. ^{1}HNMR ($CDCl_3$) δ (ppm): 3.10 (td, J = 9.6, 4.2 Hz, 1H), 1.95–1.91 (m, 1H), 1.74–1.57 (m, 4H), 1.30–1.16 (m, 4H), 0.99 (d, J = 6.4 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 76.6, 40.4, 35.6, 33.8, 25.8, 25.3, 18.7.

Benzyl trans-2-Methylcyclohexyl Ether ***11***.[29] A 10 mL round-bottom flask was charged with 60 wt % sodium hydride in mineral oil (80 mg, 2.0 mmol). The sodium hydride was washed three times with hexanes (2 mL) and once with THF (2 mL). THF (4 mL) was added to the flask, and the mixture was cooled to 0 °C. A solution of the crude alcohol, **10** (~0.19 g) in THF (0.25 mL) was added dropwise. Tetrabutylammonium iodide (60 mg, 0.16 mmol) was added to the reaction mixture at once followed by the dropwise addition of benzyl bromide (0.20 mL, 1.7 mmol). The ice-water bath was removed, and reaction mixture was stirred at room temperature for 24 h and quenched with water. The product was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (hexanes) afforded pure product **11** as a colorless oil (0.16 g, 80% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.34–7.21 (m, 5H), 4.63 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 2.89 (td, J = 9.4, 4.5 Hz, 1H), 2.14–2.11 (m, 1H), 1.75–1.69 (m, 2H), 1.61–1.44 (m, 2H), 1.26–1.21 (m, 4H), 1.01 (d, J = 6.3 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 139.3, 128.2, 127.6, 127.3, 83.6, 70.6, 38.4, 33.9, 31.1, 25.6, 25.0, 18.9; TOF MS (EI$^+$) calcd for $C_{14}H_{20}O$ 204.1514; found 204.1551; IR (film) 697, 735, 926, 986, 1028, 1072, 1096, 1160, 1205, 1250, 1303, 1355, 1453, 1496, 2856, 2927, 3031, 3064 cm^{-1}.

Endoborneol ***12***.[30] White solid (0.10 g, 65% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 4.00 (dd, J = 10.0, 1.6 Hz, 1H), 2.27 (ddd, J = 15.8, 4.4, 3.8 Hz, 1H), 1.92–1.85 (m, 1H), 1.77–1.69 (m, 1H), 1.63–1.61 (m, 2H), 1.28–1.21 (m, 2H), 0.94 (dd, J = 10.0, 3.4 Hz, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 77.3, 49.4, 48.0, 45.1, 39.0, 28.2, 25.9, 20.2, 18.6, 13.3.

(−)-Menthol ***13***.[31] White solid (0.13 g, 86% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 3.41 (td, J = 10.0, 3.6 Hz, 1H), 2.17 (pent, J = 5.7 Hz, 1H), 1.96 (d, J = 11.4 Hz, 1H), 1.64 (t, J = 13.2 Hz, 2H), 1.45 (m, 2H), 1.15–1.08 (m, 1H), 0.94–0.90 (m, 9H), 0.81 (d, J = 6.9 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 71.4, 50.0, 45.0, 34.5, 31.6, 25.7, 23.0, 22.1, 21.0, 16.0.

(±)-trans,cis-Decahydro-1-naphthol ***14***.[32] White solid (0.13 g, 82% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 3.18 (ddd, J = 15.2, 9.8, 4.2 Hz, 1H), 2.12 (d, J = 7.6 Hz, 1H), 1.98–1.94 (m, 1H), 1.88 (br, 1H), 1.78–1.62 (m, 4H), 1.51 (d, J = 10.0 Hz, 1H), 1.34–1.19 (m, 4H), 0.97–0.87 (m, 5H); ^{13}CNMR ($CDCl_3$) δ (ppm): 74.9, 50.4, 41.1, 35.7, 33.5, 33.4, 28.9, 26.3, 26.1, 24.0. The three isomers could not be separated; therefore, the following data concern the mixture of these three compounds: TOF MS (ES$^+$) calcd for $C_{10}H_{17}O$ 153.1279; found

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153.1284; IR (film) 823, 839, 915, 953, 1020, 1040, 1059, 1141, 1238, 1358, 1448, 1641, 2853, 2919, 3369 cm^{-1}.

cis-3,3,5-Trimethylcyclohexanol ***15***. White solid (37 mg, 26% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 3.72 (tt, J = 11.2, 4.5 Hz, 1H), 2.21 (br, 1H), 1.91 (d sextet, J = 15.6, 1.8 Hz, 2H), 1.67−1.51 (m, 2H), 1.26 (d pent, J = 6.0, 1.8 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.73 (q, J = 10.0 Hz, 2H); ^{13}CNMR ($CDCl_3$) δ (ppm): 67.8, 48.2, 47.6, 44.6, 33.1, 32.2, 27.2, 25.7, 22.3; TOF MS (ES$^+$) calcd for $C_9H_{17}O$ 141.1279; found 141.1265; IR (film) 1026, 1080, 1365, 1460, 1641, 2922, 2925, 2951, 3412 cm^{-1}.

cis-3-Methylcyclopentanol ***16a***.[18] Crude oil. ^{1}HNMR ($CDCl_3$) δ (ppm): 4.29 (tt, J = 10.0, 6.2 Hz, 1H), 2.27−2.13 (m, 1H), 2.04−1.09 (m, 6H), 1.06 (d, J = 6.4 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 73.7, 44.1, 35.4, 32.9, 32.2, 21.0.

trans-3-Methylcyclopentanol ***16b***.[18] Crude oil. ^{1}HNMR ($CDCl_3$) δ (ppm): 4.36 (pent, J = 2.8 Hz, 1H), 2.27−2.13 (m, 1H), 2.04−1.09 (m, 6H), 0.99 (d, J = 6.4 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 73.7, 44.3, 35.2, 32.4, 31.8, 20.6.

Benzyl cis-3-Methylcyclopentyl Ether ***17***. A 10 mL round-bottom flask was charged with 60 wt % sodium hydride in mineral oil (40 mg, 1.0 mmol). The sodium hydride was washed three times with hexanes (2 mL) and once with THF (2 mL). THF (1.8 mL) was added to the flask, and the mixture was cooled to 0 °C. A solution of the crude alcohol, **16** (~90 mg) in THF (0.5 mL), was added dropwise. Tetrabutylammonium iodide (40 mg, 0.10 mmol) was added to the reaction mixture at once followed by the dropwise addition of benzyl bromide (0.13 mL, 1.1 mmol). The ice-water bath was removed, and reaction mixture was stirred at room temperature for 24 h and quenched with water. The product was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (Et_2O/hexanes) afforded pure product **17** as a colorless oil (0.12g, 63% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.33−7.26 (m, 5H), 4.45 (d, J = 4.2 Hz, 2H), 3.98 (q, J = 5.7 Hz, 1H), 2.19−2.08 (m, 1H), 1.94−1.68 (m, 4H), 1.36−1.20 (m, 2H), 1.04 (d, J = 6.6 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 139.0, 128.2, 127.5, 127.3, 80.9, 70.8, 41.3, 32.9, 32.4, 32.2, 20.9; TOF MS (AP$^+$) calcd for $C_{13}H_{19}O$ 191.1436; found 191.1434; IR (film) 649, 699, 733, 908, 1028, 1068, 1095, 1205, 1376, 1496, 2868, 2955, 3032, 3066, 3089 cm^{-1}.

cis-3-(Trifluoromethyl)cyclohexanol ***22***.[22] Crude oil. ^{1}HNMR ($CDCl_3$) δ (ppm): 3.61 (tt, J = 10.8, 4.2 Hz, 1H), 2.20−2.15 (m, 1H), 2.11−1.86 (m, 4H), 1.43−1.12 (m, 4H); ^{13}CNMR ($CDCl_3$) δ (ppm): 132.7, 129.0, 125.3, 121.6, 69.3, 40.9 (q, J = 27.0 Hz), 34.7, 34.0 (q, J = 2.2 Hz), 24.0 (q, J = 2.2 Hz), 22.7.

Benzyl cis-3-(Trifluoromethyl)cyclohexyl Ether ***23***. A 10 mL round-bottom flask was charged with 60 wt % sodium hydride in mineral oil (57 mg, 1.4 mmol). The sodium hydride was washed three times with hexanes (2 mL) and once with THF (2 mL). THF (1.7 mL) was added to the flask, and the mixture was cooled to 0 °C. A solution of the crude alcohol, **22** (~0.16 g) in THF (0.5 mL), was added dropwise. Tetrabutylammonium iodide (35 mg, 0.095 mmol) was added to the reaction mixture at once followed by the dropwise addition of benzyl bromide (0.14 mL, 1.2 mmol). The ice-water bath was removed, and reaction mixture was stirred at room temperature for 24 h and t quenched with water. The product was extracted with diethyl ether; the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel (Et_2O/hexanes) afforded pure product **23** as a colorless oil (0.18g, 70% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.36−7.27 (m, 5H), 4.57 (s, 2H), 3.34−3.33 (m, 1H), 2.31 (d, J = 11.5 Hz, 1H), 2.13−2.02 (m, 2H), 1.88 (m, 2H), 1.33−1.23 (m, 4H); ^{13}CNMR ($CDCl_3$) δ (ppm): 138.6, 128.4, 127.8, 127.5, 127.5, 76.0, 70.0, 41.0 (q, J = 26.2 Hz), 31.8, 31.1 (d, J = 1.2 Hz), 24.4 (d, J = 2.5 Hz), 22.8; ^{19}FNMR ($CDCl_3$) δ (ppm): −73.6 (d, J = 5.0 Hz); TOF MS (AP$^+$) calcd for $C_{14}H_{17}OF_3$ 258.1232; found 258.1251; IR (film) 698, 736, 1028, 1089, 1122, 1173, 1213, 1253, 1278, 1320, 1360, 1454, 1496, 2867, 2945, 3031, 3065 cm^{-1}.

5α-Androstane-3α,17β-diol ***24***.[33] White solid (0.22g, 75% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 4.04 (m, 1H), 3.63 (t, J = 8.4 Hz, 1H), 2.11−1.99 (m, 1H), 1.79 (d, J = 12.3 Hz, 1H), 1.69−0.89 (m, 22H), 0.79 (s, 3H), 0.73 (s, 3H); ^{13}CNMR ($CDCl_3$) δ (ppm): 82.0, 66.5, 54.5, 51.1, 43.0, 39.2, 36.8, 36.2, 35.9, 35.6, 32.2, 31.6, 30.5, 29.0, 28.4, 23.4, 20.4, 11.2, 11.1; TOF MS (EI$^+$) calcd for $C_{19}H_{31}O_2$ 291.2324; found 291.2347.

bis(4-Methoxyphenyl)methanol ***25***.[34] White solid (0.20 g, 83% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.24 (d, J = 8.4 Hz, 4H), 6.83 (d, J = 8.4 Hz, 4H), 5.70 (s, 1H), 3.75 (s, 6H), 2.44 (br, 1H); ^{13}CNMR ($CDCl_3$) δ (ppm): 158.8, 136.4, 127.7, 113.7, 75.2, 55.2.

3-Quinuclidinol ***26***.[25a] White solid (83 mg, 65% yield). ^{1}HNMR ($CDCl_3$) δ (ppm): 3.81 (t, J = 4.0 Hz, 1H), 3.31 (br, 1H), 3.10 (qd, J = 14.1, 8.3, 5.7, 2.0 Hz, 1H), 2.94−2.84 (m, 1H), 2.76−2.55 (m, 4H), 1.98−1.87 (m, 1H), 1.78 (q, J = 3.0 Hz, 1H), 1.71−1.61 (m, 1H), 1.50−1.29 (m, 2H); ^{13}CNMR ($CDCl_3$) δ (ppm): 67.4, 58.0, 47.4, 46.3, 28.4, 24.8, 18.9.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01232.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Moglie, Y.; Alonso, F.; Vitale, C.; Yus, M.; Radivoy, G. *Tetrahedron* **2006**, *62*, 2812−2819.

(2) (a) Brown, H. C.; Varma, V. *J. Org. Chem.* **1974**, *39*, 1631−1636. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597. (c) Hayashi, T.; Kikuchi, S.; Asano, Y.; Endo, Y.; Yamada, T. *Org. Process Res. Dev.* **2012**, *16*, 1235−1240 and references cited therein.

(3) (a) Ourisson, G.; Rassat, A. *Tetrahedron Lett.* **1960**, *1*, 16−19. (b) Brown, H. C.; Varma, V. *J. Am. Chem. Soc.* **1966**, *88*, 2871. (c) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534−2536. (d) Kim, S.; Ahn, K. H.; Chung, Y. W. *J. Org. Chem.* **1982**, *47*, 4581−4582. (e) Yoon, N. M.; Kim, K. E.; Kang, J. *J. Org. Chem.* **1986**, *51*, 226−229. (f) Brown, H. C.; Nazer, B.; Cha, J. S.; Sikorski, J. A. *J. Org. Chem.* **1986**, *51*, 5264−5270. (g) Cha, J. S.; Yoon, M. S.; Kim, Y. S.; Lee, K. W. *Tetrahedron Lett.* **1988**, *29*, 1069−1070. (h) Cho, S. D.; Lim, H. J.; Kim, H. J.; Cha, J. S. *Bull. Korean Chem. Soc.* **2002**, *23*, 1695−1696 and references cited therein..

(4) (a) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486−6492. (b) Maruoka, K.; Sakurai, M.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 3853−3856. (c) Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 5201−5204. (d) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378−6385. (e) Denis, C.; Laignel, B.; Plusquellec, D.; Marouille, J-Y. L.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53−56. (f) Cha, J. S.; Park, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1051−1052. (g) Cha, J. S.; Noh, M. Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 840−844. (h) Cha, J. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 219−224.

(5) Reviews: (a) Alonso, F.; Yus, M. *Chem. Soc. Rev.* **2004**, *33*, 284−293. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009−4091.

(6) Alonso, F.; Yus, M. *Tetrahedron* **1998**, *54*, 1921−1928.

(7) Alonso, F.; Vitale, C.; Radivoy, G.; Yus, M. *Synthesis* **2003**, *2003*, 443−447.

(8) $NiCl_2 \cdot 2H_2O$ is prepared from commercially available $NiCl_2 \cdot 6H_2O$ by heating *in vacuo* (ca. 0.5 Torr) at 100 °C in Kugelrohr for 2 h: Alonso, F.; Yus, M. *Tetrahedron Lett.* **1996**, *37*, 6925−6928.

(9) According to Huffman and Charles, in the metal-ammonia reduction of ketones, the π^* LUMO presumably accepts an electron from the lithium metal (or solvated electron) and becomes a radical-anion. This radical-anion has several competitive reaction paths open: (1) dimerization to the pinacol coupled diol product; (2) protonation of the radical-anion to give an alkoxide radical; and (3) reduction of the radical-anion to the vicinal dianion. Protonation of the radical-anion to the alkoxy radical, which would then be further reduced to an alkoxide ion, results in protonation from the least hindered side of the carbonyl atom. Reduction of the radical-anion to the dianion gives a tetrahedral species, which should give rise to approximately an equilibrium mixture of products, in which the thermodynamically stable isomer predominates.[4a]

(10) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, 1991; p 56.

(11) Brunet, J. J.; Mordenti, L.; Caubére, P. *J. Org. Chem.* **1978**, *43*, 4804−4808.

(12) Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594−599.

(13) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535−3536.

(14) Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Synthesis. Recent Advances and Practical Applications*; Abdel-Magid, A. F., Ed.; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; p 21.

(15) Solodar, J. *J. Org. Chem.* **1976**, *41*, 3461−3464.

(16) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018−5027.

(17) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546.

(18) Fuchs, B.; Haber, R. G. *Tetrahedron Lett.* **1966**, *7*, 1323−1328.

(19) Haber, R. G.; Fuchs, B. *Tetrahedron Lett.* **1966**, *7*, 1447−1451.

(20) Chênevert, R.; Courchesne, G.; Jacques, F. *Tetrahedron: Asymmetry* **2004**, *15*, 3587−3590.

(21) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nat. Chem.* **2010**, *2*, 478−483.

(22) Arnone, A.; Bernardi, R.; Blasco, F.; Cardillo, R.; Resnati, G.; Gerus, I. I.; Kukhar, V. P. *Tetrahedron* **1998**, *54*, 2809−2818.

(23) Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, *10*, 1029−1030.

(24) (a) Isotani, K.; Kurokawa, J.; Itoh, N. *Int. J. Mol. Sci.* **2012**, *13*, 13542−13553. (b) Wang, Y.; Li, J.; Wu, Q.; Zhu, D. *J. Mol. Catal. B: Enzym.* **2013**, *88*, 14−19. (c) Isotani, K.; Kurokawa, J.; Suzuki, F.; Nomoto, S.; Negishi, T.; Matsuda, M.; Itoh, N. *Appl. Environ. Microbiol.* **2013**, *79*, 1378−1384. (d) Kolet, S. P.; Jadhav, D. D.; Priyadarshini, B.; Swarge, B. N.; Thurlasiram, H. V. *Tetrahedron Lett.* **2014**, *55*, 5911−5914. (e) Hou, F.; Miyakawa, T.; Kataoka, M.; Takeshita, D.; Kumashiro, S.; Uzura, A.; Urano, N.; Nagata, K.; Shimizu, S.; Tanokura, M. *Biochem. Biophys. Res. Commun.* **2014**, *446*, 911−915 and references cited therein..

(25) (a) Arai, N.; Akashi, M.; Sugizaki, S.; Ooka, H.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2010**, *12*, 3380−3383. (b) Matsumura, K.; Arai, N.; Hori, K.; Saito, T.; Sayo, N.; Ohkuma, T. *J. Am. Chem. Soc.* **2011**, *133*, 10696−10699. (c) Slade, A. T.; Lensink, C.; Falshaw, A.; Clark, G. R.; Wright, L. J. *Dalton Trans.* **2014**, *43*, 17163−17171 and references therin..

(26) The sodium initiates the radical pathway and increases the rate of electron transfer. (a) *Organometallics in Organic Synthesis*, Schlosser, M., Ed.; Wiley: New York, 1994. (b) Kamienski, C.; Esmay, D. *J. Org. Chem.* **1960**, *25*, 1807−1808.

(27) Alonso, F.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 149−152.

(28) Yakovleva, M.; Gao, Y.; Fitch, K. B.; Palepu, P. T.; Li, Y.; Woltermann, C. J. *Method of Forming a Lithium Dispersion and Stabilized Lithium Metal Powder*. U. S. Patent EP 2186151 B1, December 4, 2013.

(29) Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716−7730.

(30) Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem. - Eur. J.* **2009**, *15*, 1713−1722.

(31) Atta-ur-Rahman; Yaqoob, M.; Farooq, A.; Anjum, S.; Asif, F.; Choudhary, M. I. *J. Nat. Prod.* **1998**, *61*, 1340−1342.

(32) Maio, G. D.; Mascia, M. G.; Vecchi, E. *Tetrahedron* **2002**, *58*, 3313−3318.

(33) (a) Świzdor, A.; Panek, A.; Milecka-Tronina, N. *Steroids* **2014**, *82*, 44−52. (b) Hunter, A. C.; Khuenl-Brady, H.; Barrett, P.; Dodd, H. T.; Dedi, C. *J. Steroid Biochem. Mol. Biol.* **2010**, *118*, 171−176.

(34) Denegri, B.; Kronja, O. *J. Org. Chem.* **2007**, *72*, 8427−8433.

■ NOTE ADDED AFTER ASAP PUBLICATION

Updated experimental procedures with the correctly calculated *J*-values for the isolated compounds on August 21, 2015.