The Synthetic Utility and Mechanism of the Reductive Deoxygenation of α,β-Unsaturated p-Tosylhydrazones with Sodium Cyanoborohydride

Robert O. Hutchins,* Mark Kacher,[1a] and Louis Rua[1b]

Department of Chemistry, Drexel University, Philadelphia, Pa. 19104

Received October 15, 1974

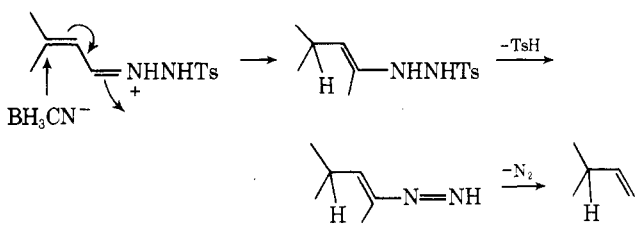
The combination of sodium cyanoborohydride in acidic dimethylformamide–sulfolane provides an effective and convenient system for the reduction of α,β-unsaturated carbonyl tosylhydrazones specifically to the corresponding alkenes with migration of the double bond most probably via a 1,5-sigmatropic rearrangement of an intermediate diazene. Furthermore, the reduction proceeds stereoselectively to furnish the *E* geometric isomer as the predominant product. Applications include (a) conversion of endocyclic to exocyclic double bonds; (b) transformation of alkenes which are conjugated to aromatic rings to unconjugated isomers; (c) deconjugation of certain 1,3-diene systems to 1,4-dienes; (d) synthesis of (*E*)-alkenes. Cyclohexenones and multiply conjugated systems are less successful, giving primarily saturated hydrocarbons in the former case and isomer mixtures in the latter.

During a recent exploration of the reductive deoxygenation of carbonyl tosylhydrazones with $NaBH_3CN$, we observed that α,β-unsaturated systems cleanly afforded alkenes resulting from migration of the double bond from the α,β position to the site formerly occupied by the carbonyl, even in the event that such a migration removed the double bond from conjugation with an aromatic ring.[2] The potential utility of this procedure prompted the present, more thorough investigation of the reaction with respect to synthetic scope and limitations, regio- and stereoselectivity of the alkenes produced, and the mechanistic possibilities.

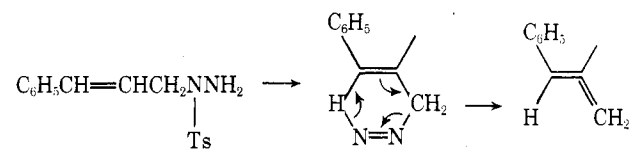
The preparation of the requisite tosylhydrazones and reduction procedure has been described previously and is briefly outlined in the Experimental Section. A variety of α,β-unsaturated tosylhydrazones representing a wide range of structural types were chosen for study and the results are presented in Table I. Synthetically, several features of the reductions are particularly noteworthy. Paramount, the specific formation of the *less* stable positional isomers of alkenes in several examples (entries 1–3, 5, 8–12) appears to offer general and reliable synthetic possibilities such as converting endocylic to exocyclic alkenes (entry 5), moving double bonds out of conjugation with aromatic rings (entries 1–3) and deconjugating certain 1,3-dienes to the 1,4 isomers (entries 8–10). In all such examples the migrations are clean with only a trace, if any, of the unrearranged olefin observed. In addition, the double-bond migration appears to occur stereoselectively to give the trans alkene as the major product, as illustrated by the conversions of benzalacetone and β-ionone (entries 2, 8) predominantly to the corresponding trans alkenes. With α,β,α′,β′-dienones, the procedure proved less successful and led to partial concomitant alkene reduction or mixtures of isomers (entries 13, 14). Furthermore, 9-anthraldehyde tosylhydrazone afforded only 9-methylanthracene (entry 15) with no evidence for products resulting from migration of the conjugate double bond. Cyclohexenones also apparently give anomalous reductions. Thus, isophorone gave principally (in low yield) the saturated hydrocarbon 1,1,3-trimethylcyclohexane in addition to a lesser amount of the alkene (entry 7).[3]

Ostensibly, the most straightforward mechanism for the reductive migration involves initial attack by cyanoborohydride in a 1,4-Michael type addition to give the rearranged tosylhydrazine intermediate, which subsequently decomposes to the alkene as shown in Scheme I.[2] The propensity for cyanoborohydride[4] (and borohydride)[7] to add in a 1,4 fashion to α,β-unsaturated ketones has been noted and $LiAlH_4$ reduces carvone tosylhydrazone to the unsaturated hydrocarbon limonene with preponderant migration of the double bond and initial attack at the conjugate position.[8]

Scheme I



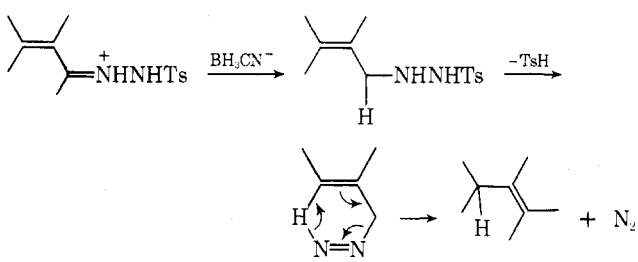
On the other hand, an alternative mechanistic possibility was suggested by the recent report[9] that *N*-allyl-*N*-tosylhydrazines, including cinnamyl tosylhydrazine (**1**), fragment under acidic conditions to the corresponding rearranged alkenes (i.e., **1** affords 3-phenylpropene uncontaminated with the 1 isomer). The mechanism of this tranformation apparently involves initial elimination of *p*-toluenesulfinic acid to the diazene intermediate **2** followed by a 1,5-sigmatropic rearrangement with transfer of hydrogen to the β carbon and π-bond migration. This points to the



1 **2**

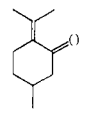
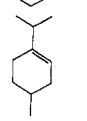
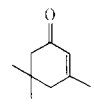
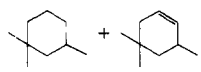
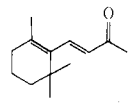
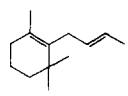
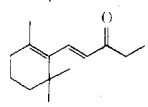
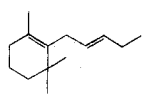
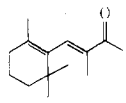
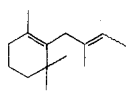
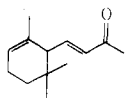
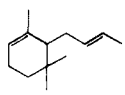
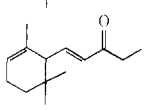
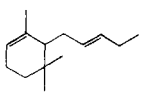
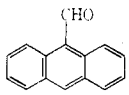
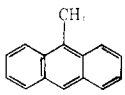
strong possibility that an analogous pathway may operate in the present case, as illustrated in Scheme II. Thus, the

Scheme II



initial step may consist of reduction of the imminium ion to the tosylhydrazine by cyanoborohydride followed by elimination of *p*-toluenesulfinic acid and a subsequent 1,5-sigmatropic shift to the observed rearranged alkene. Evidence for this latter mechanism was provided by the observation that the tosylhydrazine **1** gave 3-phenylpropene under the reaction conditions used successfully for reduction of tosylhydrazones (entry 16), again with no evidence for the un-

Table I
Reduction of Conjugated Carbonyl Compounds with Sodium Cyanoborohydride

Entry	Tosylhydrazone	Time,[a] hr	Product	Yield,[b] % (isolated)
1	$C_6H_5CH{=}CHCHO$	3.0	$C_6H_5CH_2CH{=}CH_2$	98
2	(E)-$C_6H_5CH{=}CHCOCH_3$	2.5	$C_6H_5CH_2CH{=}CHCH_3$	68.5[d] (54)[e]
3	p-$CH_3OC_6H_4CH{=}CHCOCH_3$	3.0	p-$CH_3OC_6H_4CH_2CH{=}CHCH_3$	67 (57)
4	$C_6H_5CH{=}CHCOC_6H_5$	4.0	$C_6H_5CH_2CH{=}CHC_6H_5$	60
5		2.0 4.0[c]		79 (84)
6		6.0		(70)
7		2.0		36 (19)[f]
8		3.0[c]		85 (65–70)
9		3.0[c]		(63–76)
10		5.0[c]		(45)
11		5.0[c]		(81)
12		6.0[c]		(77)
13	$(C_6H_5CH{=}CH)_2CO$	4.0	$C_6H_5CH_2CH{=}CH(CH_2)_2C_6H_5$	45 (38)
14	$[C_6H_5(CH{=}CH)_2]_2$	5.0	$C_6H_5(CH{=}CH)_2(CH_2)_3CH{=}CHC_6H_5$ + other isomers	(ca. 54)
15		7.0		(70)
16	$C_6H_5CH{=}CHCH_2\underset{\text{TS}}{\overset{|}{N}}NH_2$	3.0[c]	$C_6H_5CH_2CH{=}CH_2$	79

[a] Solutions were 0.2 M in tosylhydrazone, 0.8 M in $NaBH_3CN$ in 1:1 DMF–sulfolane, acidified with concentrated HCl to pH < 3.8 (Bromocresol Green indicator). [b] Yields were determined by GLC using internal standards and detector response factors; isolated yields are for purified products. [c] An additional portion of Bromocresol Green and concentrated HCl added after half the specified time. [d] Composed of 61.5% E and 7.0% Z geometric isomers. [e] Composed of 47.8% E and 6.2% Z geometric isomers. [f] NMR indicated an approximate ratio of 9:1 with the alkane predominant.

rearranged alkene. Apparently, the sigmatropic shift is considerably more facile than collapse to the unrearranged isomer.[10] This pathway also explains the reluctance of isophorone tosylhydrazone to give the rearranged products. Inspection of models reveal that the requisite correct positioning of the diazene over the ring is geometrically difficult, especially because of the blocking axial 5-methyl group.[11]

In summary, the reductive deoxygenations of α,β-unsaturated carbonyl tosylhydrazones offer a convenient, clean, and synthetically useful tactic for preparing such otherwise difficult olefins as exocyclic alkenes, unconjugated arenes, and 1,4-dienes. The double-bond migration occurs predominantly to give the more stable E isomer. The procedure is less successful with cyclohexenones. The probable mechanism involves a diazene intermediate which transfers hydrogen to the β carbon with concomitant π-bond migration via a 1,5-sigmatropic rearrangement.[12]

Experimental Section

Materials. $NaBH_3CN$ was obtained from Alfa Inorganics and used without purification. Sulfolane and DMF were distilled from CaH_2 and stored over 4A molecular sieves. The ketones and aldehydes were commercial materials which were purified before use. GLC analyses were performed on a Hewlett-Packard Model 5250B instrument equipped with a Disc Integrator using either 10% OV-1 or 10% Carbowax 20M on 80–100 Chromosorb W (AW-DMCS) columns. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Elemental analyses were determined by A. Bernhardt, West Germany, or Chemalytics, Inc., Tempe, Ariz. Drying of organic solvents was accomplished with anhydrous $MgSO_4$. In all cases, the nmr and ir spectra were consistent with the assigned structures.

Tosylhydrazone Formation. The carbonyl compound and a

Table II
Carbonyl Tosylhydrazones[a]

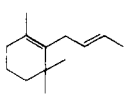
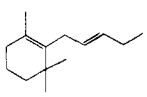
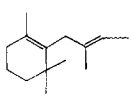
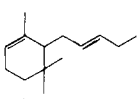
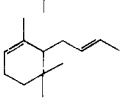
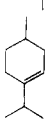
Tosylhydrazone	Yield, %	Mp, °C	Registry no.
β-Ionone	80	169–171	53941-08-5
1-Methyl-β-ionone	91	130–131	53941-09-6
3-Methyl-β-ionone	77	149–151	53941-10-9
α-Ionone	83	188–189 dec	53941-11-0
1-Methyl-α-ionone	80	144–146 dec	53941-12-1
1,5-Diphenyl-1,4-pentadien-3-one	94	145–148	538-58-9
(+)-Pulegone	33	145–147	89-82-7
1,9-Diphenyl-1,3,6,8-nonatetraene	68	143–150	622-21-9
9-Anthraldehyde	52	183–184	642-31-9

[a] Other tosylhydrazones listed in ref 2. All new tosylhydrazones gave satisfactory elemental analyses the results of which have been provided to the Editor.

lutions were diluted with water and the cyclohexane solutions analyzed by GLC to determine yields. For preparative-scale reactions, the aqueous phase was extracted twice with cyclohexane, and the combined cyclohexane solution was washed with water, dried, and concentrated on a rotary evaporator. Purification was accomplished by distillation at reduced pressure or recrystallization. All new products exhibited expected spectral characteristics and provided satisfactory elemental analyses (Table III).

As a representative preparative application, the reduction of (*E*)-1-phenylbuten-3-one to 1-phenyl-2-butene is described. A solution of the tosylhydrazone (6.29 g, 20 mmol), $NaBH_3CN$ (5.02 g, 80 mmol), and a few milligrams of Bromocresol Green in 100 ml of 1:1 DMF–sulfolane was heated to 105° and concentrated HCl was added dropwise cautiously until the pH was <3.8 as indicated by a color change from blue to tan. Approximately 40 ml of cyclohexane was added and the reaction mixture was heated with stirring for 1 hr. A few milligrams of Bromocresol Green and a few drops of concentrated HCl were added to maintain the pH below 3.8 and heating was continued for 1.5 hr; then the solution was diluted with 150 ml of water and the layers were separated. The aqueous phase was extracted twice with cyclohexane, and the cyclohexane solution was washed with three portions of water, dried, and concentrated. The residue was flash distilled at 2.8 mm (Kugelrohr apparatus) to

Table III[a]
Physical Data for New Alkene Products

Alkene	Bp, °C (mmHg)	$n^{25}D$	NMR data, Hz[c] (60 MHz, $CDCl_3$)	Registry no.
	58 (0.35)[b]	1.4810[b]	57, s (6 H), $(CH_3)_2C$ 93, broad s (3 H), $CH_3C{=}C$ 163, ind. m (2 H), $(C{=}C)_2CH_2$ 321, m (2 H), $HC{=}CH$[d]	53941-13-2
	76 (0.45)	1.4790	59, s (6 H), $(CH_3)_2C$ ca. 60, ind. t (3 H), CH_3CH_2 164, ind. m (2 H), $(C{=}C)_2CH_2$ 322, m (2 H), $HC{=}CH$	53941-14-3
	61 (0.15)	1.4811	53, 56, two s (6 H), $(CH_3)_2C$ 89, s (ca. 3 H), $CH_3C{=}C$ ca. 95, 96, ind. s and d (ca. 6 H); $CH_3C{=}C$, $CH_3CH{=}C$ 160, ind. m (2 H), $(C{=}C)_2CH_2$ 315, m (1 H), $HC{=}C$[d]	53941-15-4
	*e*	1.4775	53, 56, two s (6 H), $(CH_3)_2C$ 100, broad s (6 H), $CH_3C{=}C$ 322, m (3 H), $HC{=}C$, $HC{=}CH$	53941-16-5
	68 (0.35)	1.4760	52–65, singlets and ind. t (9 H), $(CH_3)_2C$, CH_3CH_2 ca. 321, m (3 H), $HC{=}CH$, $HC{=}C$	53941-17-6
	*e*	1.4510	59, d, J = 6 Hz (6 H), $(CH_3)_2C$ ca. 58, ind. d (3 H), CH_3CH 326, broad m (1 H), $HC{=}C$	619-52-3

[a] Alkene products gave satisfactory elemental analyses the results of which have been provided to the Editor. [b] Lit. bp 91.5–93° (11 mm), $n^{18}D$ 1.4795 (ref 12). [c] Downfield from Me_4Si standard. [d] No signals attributable to conjugated alkene protons were observed. [e] Flash distilled at reduced pressure.

10% molar excess of *p*-toluenesulfonylhydrazine in absolute ethanol (ca. 2 ml per gram of carbonyl compound) were heated on a steam bath until a clear solution resulted (15 min). Cooling afforded crystalline products in good to excellent yields (Table II). Recrystallization was accomplished from ethanol or aqueous acetone.

Reduction Procedure. For analytical reductions, the carbonyl tosylhydrazone, a fourfold molar excess of $NaBH_3CN$, and a small amount of Bromocresol Green were dissolved in a 1:1 mixture of sulfolane and DMF such that the solutions were 0.2 *M* in tosylhydrazone and 0.8 *M* in $NaBH_3CN$. The mixtures were heated at 100–105° and concentrated HCl was added cautiously dropwise until a color change was indicated by the indicator (tan). An internal standard and 5–10 ml of cyclohexane were added and the solutions were heated for the appropriate periods indicated in Table I. For several cases, an additional portion of Bromocresol Green and concentrated HCl were added (Table I). After completion, the solutions were diluted with water and the cyclohexane solutions analyzed by GLC to determine yields. For preparative-scale reactions, the aqueous phase was extracted twice with cyclohexane, and the combined cyclohexane solution was washed with water, dried, and concentrated on a rotary evaporator. Purification was accomplished by distillation at reduced pressure or recrystallization. All new products exhibited expected spectral characteristics and provided satisfactory elemental analyses (Table III).

As a representative preparative application, the reduction of (*E*)-1-phenylbuten-3-one to 1-phenyl-2-butene is described. A solution of the tosylhydrazone (6.29 g, 20 mmol), $NaBH_3CN$ (5.02 g, 80 mmol), and a few milligrams of Bromocresol Green in 100 ml of 1:1 DMF–sulfolane was heated to 105° and concentrated HCl was added dropwise cautiously until the pH was <3.8 as indicated by a color change from blue to tan. Approximately 40 ml of cyclohexane was added and the reaction mixture was heated with stirring for 1 hr. A few milligrams of Bromocresol Green and a few drops of concentrated HCl were added to maintain the pH below 3.8 and heating was continued for 1.5 hr; then the solution was diluted with 150 ml of water and the layers were separated. The aqueous phase was extracted twice with cyclohexane, and the cyclohexane solution was washed with three portions of water, dried, and concentrated. The residue was flash distilled at 2.8 mm (Kugelrohr apparatus) to obtain 1.42 g (54%) of 1-phenyl-2-butene. Analysis by GLC (10 ft 10% Carbowax 20M column, 150°) indicated the product to be composed of ca. 47.8% *E* and 6.2% *Z*[13] geometric isomers.

Registry No.—(*E*)-1-Phenylbuten-3-one tosylhydrazone, 53941-18-7; (*E*)-1-phenyl-2-butene, 935-00-2; (*Z*)-1-phenyl-2-butene, 15324-90-0; sodium cyanoborohydride, 25895-60-7.

References and Notes

(1) (a) Undergraduate Research Participant, 1972–1973; (b) NDEA Fellow, 1971–1974.
(2) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(3) Reference 2 contains an error. The product indicated from isophorone tosylhydrazone was 3,3,5-trimethycyclohexene instead of mostly the

saturated hydrocarbon. This problem arose from the unknown extreme difficulty in separating the two compounds by GLC. NMR spectroscopy confirmed the predominance of the latter. Presumably, 3,5-dimethyl-2-cyclohexen-1-one tosylhydrazone also furnishes the corresponding saturated hydrocarbon in major amount instead of the reported 3,5-dimethylcyclohexene. 4-Cholesten-3-one tosylhydrazone afforded a complex mixture of hydrocarbons and alkenes. Anyway, the procedure does not appear very synthetically useful with cyclohexenones.

(4) Borch and coworkers (ref 5) obtained cyclopentanol upon cyanoborohydride reduction of 2-cyclopentenone. However, a more thorough investigation of the reduction of cholestenone-type systems (ref 6) indicated the major products usually to be the allylic alcohols, leaving the double bonds unmolested.

(5) R. F. Borch, M. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

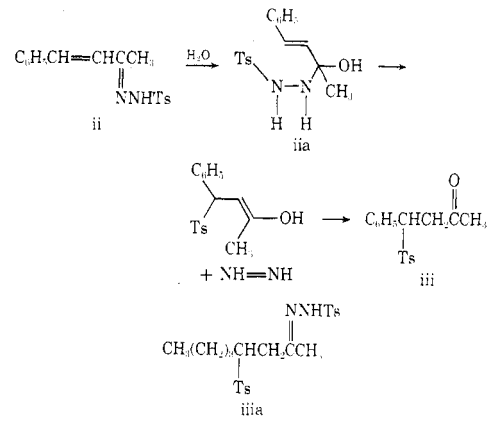
(6) M.-H. Boutique, R. Jacquesy, and Y. Petit, *Bull. Soc. Chim. Fr.*, 3062 (1973).

(7) See, for example, H. C. Brown and H. M. Hess, *J. Org. Chem.*, **38**, 2206 (1969).

(8) I. Elphimoff-Felkin and M. Verrier, *Tetrahedron Lett.*, 1515 (1968).

(9) T. Sato and I. Homma, *Bull. Chem. Soc. Jpn.*, **44**, 1885 (1971).

(10) This general type of sigmatropic migration has also been suggested (ref 9) to account for the transformation of certain α,β-unsaturated tosylhydrazone intermediates (i.e., ii) to β-tosyl ketones (i.e., iii) by thermolysis in aqueous acetic acid as indicated. We also observed a similar occurrence upon attempted preparation of (*E*)-3-octen-2-one tosylhydrazone. The only isolatable product was the corresponding β-ketotosylhydrazone iiia. Evidently, rearrangement of the intermediate analogous to iia is very facile for this example; further reaction of the β-tosyl ketone with *p*-toluenesulfonylhydrazine would produce the observed product. The reason this example chose to rearrange while all other α,β-unsaturated ketones gave the normal tosylhydrazones is not obvious.



(11) Sato and Homma (ref 9) also noted the failure of 3-methyl-2-cyclohexenone tosylhydrazone to rearrange to the corresponding β-tosyl ketone and offered a similar explanation.

(12) Analogous sigmatropic rearrangements of intermediate diazenes may also account for the production of rearranged alkenes often encountered in Wolff–Kishner reductions of α,β-unsaturated aldehydes and ketones. See, for example, R. Fischer, G. Lardelli, and O. Jegar, *Helv. Chim. Acta*, **34**, 1577 (1951).

(13) An authentic sample of the *Z* isomer was prepared from the epoxide via the procedure of Vedejs; cf. E. Vedejs and P. Fuchs, *J. Am. Chem. Soc.*, **93**, 4070 (1971).

Reaction of Lithium Aluminum Hydride with Hindered Phenols. New Stereoselective Reducing Agents

Howard Haubenstock

Richmond College of the City University of New York, Staten Island, New York 10301

Received June 26, 1974

A study involving the reaction of lithium aluminum hydride ($LiAlH_4$) with hindered phenols and alcohols is described. This has resulted in the preparation of a new series of stereoselective reagents for the reduction of substituted cyclohexanones. The most highly selective reagent was formed by the reaction of $LiAlH_4$ with 2 molar equiv of 2,6-di-*tert*-butylphenol followed by 1 molar equiv of neopentyl alcohol. Several experiments involved the reaction of lithium borohydride with hindered phenols in which different results were obtained.

Lithium aluminum alkoxyhydrides have proven to be useful selective reagents in the reduction of organic compounds.[1] The preparation of these reagents by the reaction of lithium aluminum hydride ($LiAlH_4$) with alcohols has been found to be a generally useful and convenient procedure.[1,2] These reagents are of interest not only because of their ease of preparation and useful applications,[1] but also because of their possible role as intermediate species in the reduction of carbonyl compounds with $LiAlH_4$.[3] The stereoselective reducing properties of lithium aluminum alkoxyhydrides and the stabilities of these species (to disproportionation) have recently been discussed.[4] It was also found that the hindered reagent formed from the reaction of 3 mol of di-*tert*-butyl ketone with 1 mol of $LiAlH_4$ reduced 3,3,5-trimethylcyclohexanone to 98% of the trans–axial alcohol.[4] However, this moderately hindered ketone is quite sensitive to stereoselective reduction by bulky reagents,[3,5,6] and a better test substrate for a selective reducing agent is an unhindered ketone such as 4-*tert*-butylcyclohexanone (**1**). Reduction of **1** with the above reagent (in 92 vol % THF, 8% ether) gave 76% of axial *cis*-4-*tert*-butylcyclohexanol (*cis*-**2**). This reagent is thus seen to be more highly stereoselective than other aluminum alkoxyhydrides previously used. For example, reduction of **1** with lithium aluminum tri-*tert*-butoxyhydride gave only 10% of *cis*-**2**.[5a,b,8] Lithium aluminum trimethoxyhydride is generally more highly stereoselective than the tri-*tert*-butoxyhydride owing to its relatively high degree of association;[5c] but it affords only 41% of *cis*-**2** on reduction of **1**.[5a]

In view of the apparent relationship between steric bulk and stereoselectivity of the reagent[3,4] it was thought to be of interest to prepare highly sterically hindered lithium aluminum triaryloxyhydrides by the reaction of $LiAlH_4$ with phenols. It would be of considerable interest to have highly stereoselective reagents easily prepared from relatively inexpensive starting materials. It should be noted that other procedures, most of which do not involve aluminum compounds, have been reported for the synthesis of axial alcohols, in particular the use of lithium tri-*sec*-butylborohydride,[9] potassium triisopropoxyborohydride,[10] iridium tetrachloride–trimethyl phosphite,[11] isobornyloxyaluminum dichloride,[12] and lithium dimesitylborohydride bis(dimethoxyethane).[13]

A study of the stereoselectivities of lithium aluminum triaryloxyhydrides in the reduction of the ketone **1** was undertaken. The general procedure (see Experimental Section for details) involved the addition of a solution of the phenol in tetrahydrofuran (THF) to a standardized solution of $LiAlH_4$ (commercially available in THF or diethyl ether) with measurement of hydrogen evolution. This was followed by addition of **1**. After hydrolysis of the reaction mixture, the concentrated product mixture was analyzed