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A R T I C L E S

Practical Procedures for the Preparation of *N-tert*-Butyldimethylsilylhydrazones and Their Use in Modified Wolff−Kishner Reductions and in the Synthesis of Vinyl Halides and *gem*-Dihalides

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Abstract: In this work we develop practical chemistry for the preparation of *N-tert*-butyldimethylsilylhydrazone (TBSH) derivatives from carbonyl-containing compounds and show that these products serve as superior alternatives to simple hydrazones in Wolff−Kishner-type reduction reactions, in the Barton vinyl iodide preparation, in the synthesis of vinyl bromides, and in the synthesis of *gem*-diiodides, *gem*-dibromides, and *gem*-dichlorides. In our new procedure for silyl hydrazone synthesis, aliphatic and aromatic ketones and aldehydes are shown to undergo highly efficient coupling (typically >95% yield) to form the corresponding TBSH derivatives when combined with equimolar amounts of 1,2-bis(*tert*-butyldimethylsilyl)-hydrazine (BTBSH) and a catalytic quantity of scandium trifluoromethanesulfonate (typically, 0.01 mol %), neat, or in solvent. Optimized procedures are provided for the use of TBSH derivatives in a Wolff−Kishner-type reduction protocol that proceeds at low temperature (23−100 °C) and in a single reaction flask. Similarly, protocols for the use of TBSH derivatives as precursors to vinyl halides and *gem*-dihalides are described in detail.

Introduction

Hydrazine is widely used as a reagent in synthetic organic chemistry but is probably most frequently associated with the transformation of carbonyl-containing compounds to the corresponding hydrazones.[1] These are intermediates in the Wolff−Kishner reduction[2] as well as many other reactions of synthetic utility, such as the Barton vinyl iodide preparation.[3] The synthesis of hydrazones from carbonyl-containing compounds is frequently problematic, however, and methods that involve hydrazones as intermediates often suffer as a consequence.[1,2b,3,4]

In this work we develop practical chemistry for the preparation of *N-tert*-butyldimethylsilylhydrazones (TBSHs) from carbonyl-containing compounds and show that these products serve as alternatives to hydrazones in transformations that parallel the Wolff−Kishner reduction and the Barton vinyl iodide preparation. The processes that we have developed not only appear to

be more efficient than existing procedures but also employ considerably milder reaction conditions and so may be of value in complex systems as well as in basic synthetic problem solving. We begin with a brief discussion of the primary complication of hydrazone synthesis, hydrazone instability, and summarize prior research leading to the synthesis of *N*-silylhydrazones. We then describe a new strategy for *N*-silylhydrazone synthesis, with a focus on the preparation and utility of *N-tert*-butyldimethylsilylhydrazone (TBSH) intermediates in practical, new methods for the laboratory.

Preparation and Storage of Simple Hydrazones: A Long-Standing Problem in Synthesis. It is well-documented in the literature that the reaction of carbonyl-containing compounds with hydrazine can be complicated by the further transformation of the product hydrazone to the corresponding azine (Scheme 1).[1,2b,3,4] This is particularly true when aldehydes are used as substrates; azine formation can occur both during the initial formation of the hydrazone and subsequently after isolation. A case in point is adamantanecarboxaldehyde hydrazone, which is converted to the corresponding azine within 20 min in solution (ethanol) or upon standing overnight in the solid state.[4f] Similarly, pentanal hydrazone was reported to self-condense so rapidly in solution at room temperature as to make an accurate assessment of its initial purity impossible.[4e] Our own studies in this area only serve to reinforce these conclusions.[5]

Methods to suppress azine formation during the preparation of hydrazones include the use of aprotic solvents such as chloroform,[4d] the incorporation of triethylamine as a cosolvent,[3,4a]

(1) For a review of the applications of hydrazine in organic chemistry, see Roden, B. A. Hydrazine. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd: Chichester, West Sussex, England, 1995; Vol. 4, pp 2680−2684.
(2) (a) Kishner, N. *Zh. Russ. Fiz.-Khim. O-va., Chast. Khim.* **1911**, *43*, 582. (b) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 86.
(3) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.
(4) For discussions on the problems associated with preparing hydrazones, see (a) Grundon, M. F.; Henbest, H. B.; Scott, M. D. *J. Chem. Soc.* **1963**, 1855. (b) Kolbah, D.; Koruncev, D. In *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed.; Müller, E., Ed.; Thieme: Stuttgart, Germany, 1967; Vol. X/2, pp 87−122. (c) Karabatsos, G. J.; Osborne, C. E. *Tetrahedron* **1968**, *24*, 3361. (d) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989. (e) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725. (f) Sanz, D.; Ponce, M. A.; Claramunt, R. M.; Fernández-Castaño, C.; Foces-Foces, C.; Elguero, J. *J. Phys. Org. Chem.* **1999**, *12*, 455.

Scheme 1
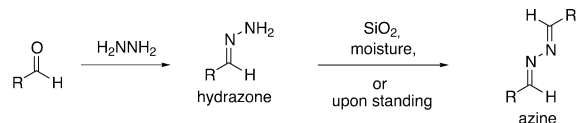
or the inclusion of molecular sieves in the reaction medium.[6] We have confirmed that each of these measures is effective to a degree; however, we have found that, upon concentration, solutions of labile hydrazones prepared by these methods nonetheless undergo rapid azine formation. With care, it may be possible to prepare and even isolate labile hydrazones (Holton and Schecter were able to prepare *p*-anisaldehyde hydrazone in 78% yield by a procedure involving careful concentration at low temperature),[4e] but it is clear that many, if not most, hydrazones should be considered metastable intermediates at best.

Results and Discussion

One solution to the problem of hydrazone instability would be the development of a modified hydrazone derivative that retains or even enhances the synthetic utility of simple hydrazones but offers improved stability with respect to handling and storage. *N*-Silylhydrazones are logical candidates for such an idealized species, and there is substantial precedent for their synthesis.[7]

N-**Silylhydrazones: Background.** *N*-Silylhydrazones are known to form by the direct condensation of carbonyl compounds with monosilylated derivatives of hydrazine.[7] The reaction of pinacolone with *N-tert*-butyldiphenylsilylhydrazine in refluxing *n*-hexane (MgSO$_4$ as desiccant, 65% yield) is exemplary and forms a crystallographically characterizable *N*-silylhydrazone derivative.[7c] As discussed by Bode and Klingebiel,[8] in a practical sense, the transformation is restricted to silylhydrazine derivatives with bulky silyl groups (*N-tert*-butyl-diphenylsilyl,[7c] *N*-di-*tert*-butylmethylsilyl,[7a,b] *N*-triisopropylsilyl[7d]), for silylhydrazines with less hindered silyl groups (*N*-trimethylsilyl,[9] *N*-triethylsilyl,[9] and—of particular importance in the context of this work—*N-tert*-butyldimethylsilylhydrazine[8]) are prone to disproportionation and, thus, are unsuitable as reagents. As the first step in a method for the synthesis of unsymmetrical azines, Justo de Pomar and Soderquist demonstrated that *N*-triisopropylsilylhydrazine condenses in good yield with many aldehydes and some ketones, but sterically hindered ketones such as benzophenone were found to be unreactive toward this bulky reagent, even at reflux in tetrahydrofuran (THF).[7d] In

addition, we have found that the condensation of *N*-triisopropylsilylhydrazine with hydrocinnamaldehyde as substrate (4-Å molecular sieves as desiccant) produces ~8% hydrocinnamaldehyde azine as well as the expected triisopropylsilylhydrazone product (isolated in 82% yield by Kügelrohr distillation). We suspect that the azine is formed from hydrazine, produced by limited hydrolysis of the *N*-triisopropylsilylhydrazine reagent during the condensation, for the *N*-triisopropylsilylhydrazone, once formed, is quite stable toward hydrolysis. This proposal is supported by the observation that exposure of *N*-triisopropylsilylhydrazine to water (1 equiv, 1 M, THF) leads to its partial hydrolysis (~15%) within 1 h at 23 °C (corresponding to roughly two half-lives in the bimolecular condensation with hydrocinnamaldehyde). Our observations are consistent with the fact that the yields of *N*-triisopropylsilylhydrazones formed by the direct condensation of carbonyl compounds with *N*-triisopropylsilylhydrazine do not exceed 86% even in the most favorable cases.[7d] From published reports, it is clear that *N*-trialkylsilylhydrazones are appreciably more stable to storage and handling than simple hydrazones once prepared;[7] however, methods for their synthesis may be limiting. Apart from their use in the preparation of unsymmetrical azines,[7d] *N*-silylhydrazones have not been demonstrated to be of value in synthesis prior to the development of the transformations reported below.[10]

A Highly Efficient and General Procedure for the Synthesis of *N-tert*-Butyldimethylsilylhydrazones (TBSHs); Guidelines for their Purification and Handling. As discussed, complications associated with the synthesis of *N*-silylhydrazones by the direct condensation of carbonyl compounds with a monosilylhydrazine reagent include competitive disproportionation and hydrolysis of the silylhydrazine reagent, as well as general reactivity issues (slow reaction rates). To address the hydrolysis problem, we considered whether it would be possible to use 1,2-bis(*tert*-butyldimethylsilyl)hydrazine (BTBSH) as a reagent, thus forming *tert*-butyldimethylsilanol as a byproduct, rather than water. *tert*-Butyldimethylsilanol is much less nucleophilic than water and can be readily removed in vacuo. The use of BTBSH as a reagent was also considered to address the disproportionation issue but would seem to worsen the problem of poor reactivity. We had planned to address the latter concern by exploring the use of Lewis-acid catalysts in the condensation reaction, which proved successful. In pursing this proposal we have found that TBSHs provide a near-optimum combination of ease and economy of synthesis, as well as desirable reactivity in various useful synthetic transformations (vide infra).

West et al. have shown that BTBSH can be prepared in 70% yield simply by mixing anhydrous hydrazine and *tert*-butyldimethylsilyl chloride in ethyl ether at reflux.[11] We have further simplified this procedure by omitting the solvent. We found that addition of anhydrous hydrazine[12] to solid *tert*-butyldimethylsilyl chloride followed by heating of the resultant slurry

(5) For example, we observed (^{1}H NMR analysis by aliquot dilution in CDCl$_3$) that although *p*-anisaldehyde and hydrazine (1.3 equiv) condensed smoothly in ethanol (complete conversion within 30 min, 23 °C), the product hydrazone was transformed into the corresponding azine over the course of several hours at 23 °C; concentration of ethanolic solutions of the hydrazone before azine formation occurred gave a yellow solid that consisted largely of the azine (but see ref 4e).

(6) (a) Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* **1996**, 273. (b) Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557.

(7) (a) Knipping, K.; Drost, C.; Klingebiel, U.; Noltemeyer, M. *Z. Anorg. Allg. Chem.* **1996**, 1215. (b) Witte-Abel, H.; Drost, C.; Klingebiel, U.; Noltemeyer, M. *J. Organomet. Chem.* **1999**, 341. (c) Gellermann, E.; Klingebiel, U.; Schäfer, M. *Z. Anorg. Allg. Chem.* **2000**, 1131. (d) Justo de Pomar, J. C.; Soderquist, J. A. *Tetrahedron Lett.* **2000**, *41*, 3285.

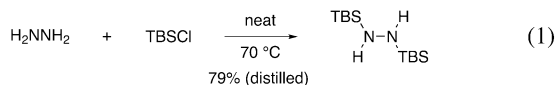(8) Bode, K.; Klingebiel, U. *Adv. Organomet. Chem.* **1996**, *40*, 1.

(9) (a) Wannagat, U.; Kohnen, H. *Angew. Chem.* **1957**, *69*, 783. (b) Wannagat, U.; Liehr, W. *Z. Anorg. Allg. Chem.* **1958**, 129. (c) Bock, H. *Z. Naturforsch. B: Chem. Sci.* **1962**, *17*, 423. (d) Wannagat, U. *Adv. Inorg. Chem. Radiochem.* **1964**, *6*, 225.

(10) Intramolecular cyclization of *N-tert*-butyldiphenylsilylhydrazones derived from *β*-ketoesters has been reported to form *O*-silylpyrazolones at 240 °C (23% yield, see ref 7b,c).

(11) West, R.; Ishikawa, M.; Bailey, R. E. *J. Am. Chem. Soc.* **1966**, *88*, 4648.

(12) Caution! Anhydrous hydrazine has been reported to detonate during distillation if traces of air are present. Hydrazine is also an irritant and a suspected carcinogen. For leading references see ref 1 and (a) Audrieth, L. F.; Ogg, B. A. *The Chemistry of Hydrazine*; Wiley: New York, 1951; pp 94ff. (b) *The Merck Index*, 12th ed.; Budavari, S., O'Neil, M. J., Smith, A., Heckelman, P. E., Kinneary, J F., Eds.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996; p 816. Silylhydrazine reagents should be treated as potential sources of hydrazine; therefore, the appropriate precautions should be taken during their preparation, purification, and handling.

at 70 °C leads to complete reaction within 2.5 h. Cooling to 23 °C induces precipitation of hydrazine hydrochloride; the product is then decanted and distilled at 0.05 Torr (bp 55−65 °C), affording pure BTBSH in 79% yield (3- to 75-g scales; eq 1). BTBSH prepared in this manner and stored at −20 °C under argon has shown no evidence of decomposition nor any loss in purity in over 3 years.

$$H_2NNH_2 \quad + \quad TBSCl \quad \xrightarrow[\text{79\% (distilled)}]{\substack{\text{neat} \\ 70\ °C}} \quad \underset{H}{\overset{TBS}{N}}-\underset{TBS}{\overset{H}{N}} \qquad (1)$$

Although BTBSH shows little propensity to react directly with ketones and aldehydes in the absence of Lewis-acid catalysts, in their presence condensation readily occurs. Among Lewis acids initially screened, scandium triflate [Sc(OTf)$_3$] quickly emerged as a nearly ideal catalyst for the reaction. Condensation of BTBSH with a wide variety of aldehydes and ketones with Sc(OTf)$_3$ as catalyst (0.01 mol %) is remarkably clean, rapid, and efficient at ambient temperature (Table 1). In the case of certain hindered substrates (entries 13 and 15), mild warming (55−100 °C) proved beneficial. Where scale permits, reactions are ideally conducted in the absence of any solvent, but solvents such as ethyl ether, dichloromethane, or chloroform can be used if scale or solubility considerations dictate, without a significant reduction in the yield, although reaction rates are somewhat slower (entries 4, 5, 9, and 11−14; detailed experimental procedures are provided for both neat and solvent-containing reactions). Typically, only a slight excess (1.01−1.05 equiv) of BTBSH is employed in condensation reactions. Substrates containing a free reactive hydroxyl group provide one exception to this guideline (entries 13 and 14), for competitive silylation of these groups occurs. This can be used to advantage, in that both protection and condensation reactions are readily driven to completion by the use of additional equivalents of reagent; thus, *tert*-butyldimethylsilylation of alcohols and phenols occurs concomitantly with TBSH formation. The BTBSH−Sc(OTf)$_3$ reagent combination is a highly effective desiccant that not only consumes any adventitious moisture present in condensation reactions but also can be used to remove the water of hydration in hydrated substrates (entry 14, Table 1). As shown by the data of Table 1, the Sc(OTf)$_3$-catalyzed condensation is tolerant of acid-labile functional groups such as ketals (entries 4, 12, 13, and 15) and is also compatible with the presence of a basic amine (entry 14). The latter property is perhaps not surprising, given that the catalyst must function in the presence of both hydrazine and hydrazone functional groups. The special ability of Sc(OTf)$_3$ to serve as a Lewis-acid activator of carbonyl groups in the presence of amines is, of course, critical to the present application but has been recognized and utilized before in many different contexts.[13]

An essential procedural feature in our protocol for condensation of BTBSH with carbonyl compounds is that the product mixtures be held in vacuo (0.05 Torr, 30−40 °C, 2−12 h depending on scale) to remove *tert*-butyldimethylsilanol formed during the condensation.[14] In addition to removing the *tert*-butyldimethylsilanol byproduct, this step also serves to promote

(13) For a recent review of the use of Sc(OTf)$_3$ in organic synthesis, see Sugiura, M.; Kobayashi, S. Scandium Trifluoromethanesulfonate. In *Encyclopedia of Reagents for Organic Synthesis* [Online]; Paquette, L. A., Ed.; John Wiley & Sons Ltd., 1995−2000.

Table 1. Preparation of *N-tert*-Butydimethylsilylhydrazones

entry	substrate	product	yield (%)
1	**1a**	**2a**	>95
2	**1b**	**2b**	>95
3	**1c**	**2c**	>95
4[a]	**1d**	**2d**	>95
5[a]	**1e**	**2e**	>95
6	**1f**	**2f**	>95
7	**1g**	**2g**	>95
8	**1h**	**2h**	>95
9[b]	**1i**	**2i**	>95
10	**1j**	**2j**	>95
11[c]	**1k**	**2k**	95
12[a]	**1l**	**2l**	>95
13[d]	**1m**	**2m**	93[e]
14[f]	**1n**	**2n**	91[e]
15[g]	**1p**	**2p**	85[e]

[a] Run in CH$_2$Cl$_2$. [b] Run in Et$_2$O. [c] Sc(OTf)$_3$ (0.1 mol %), CHCl$_3$. [d] Sc(OTf)$_3$ (1 mol %), CHCl$_3$, 55 °C. [e] Yield after purification by column chromatography on silica gel (buffered with triethylamine). [f] Sc(OTf)$_3$ (1 mol %), CHCl$_3$, 23 °C. [g] Sc(OTf)$_3$ (0.1 mol %), neat, 100 °C.

the reaction of unreacted BTBSH with any azine that formed during the reaction. We have observed that prior to this step

condensations with aldehydes typically produce ∼1−2% of the corresponding azine, while condensations with ketones produce even less. In the process of removing *tert*-butyldimethylsilanol from the product, azine byproducts are driven to levels that fall below the limits of detection (NMR analysis). One exception is the tetralone substrate of entry 11, where ∼2−3% of the azine is formed during the initial condensation reaction. In this case, the azine crystallizes from the reaction mixture and is not transformed to the product under standard evacuation conditions. Filtration (*n*-hexane as solvent) effectively removes the small amount of azine that is produced in this example. In all cases examined to date, azine formation is an extremely minor competing reaction.

Because catalyst loadings are so low [a typical procedure affording about 10 g of TBSH product contains ∼1−2 mg of entrained Sc(OTf)$_3$], we have found it unnecessary to remove the catalyst for the applications that we have developed to date. Should this prove necessary, we have found that dissolution of the product in *n*-hexane or dichloromethane followed by filtration will remove most or all of the catalyst.

As is typically the case in the preparation of simple hydrazones and their derivatives, TBSHs are formed as mixtures of syn and anti isomers, with the exception of aryl aldehyde substrates (entries 6−8, Table 1), the acetophenone substrate of entry 9, the tetralone substrate of entry 11, and the steroidal example of entry 13, which are formed as single isomers (presumably anti). Ratios of anti to syn products range from 84:16 to 76:24 with aliphatic aldehydes as substrates (entries 1 and 3, respectively) and from 84:16 to 61:39 with aliphatic ketones as substrates (entries 10 and 14, respectively). The individual anti and syn isomers in some cases (entries 14 and 15) can be separated by flash-column chromatography on triethylamine-buffered silica gel. Where these isomers have been separated, when resubjected to the conditions of their formation, these isomers were found to be configurationally stable.[15] It is clear that anti and syn products are formed under kinetic control in these cases and we believe that this is generally so for the TBSH syntheses we have investigated. Anti and syn product ratios are enumerated here for the purposes of completeness, but anti/syn stereoisomerism does not appear to play a role in the applications of TBSHs investigated thus far.

A highly desirable feature of TBSH derivatives is their stability with regard to storage and routine handling in the laboratory. As an illustration, the products of entries 1, 6, and 10 (Table 1), once isolated [each containing entrained Sc(OTf)$_3$], have been stored at −20 °C (argon) for >2 years without evident decomposition or loss in purity, while the TBSH product of entry 7, a low-melting solid, has been stored at ambient temperature under dry nitrogen without decomposition (>2 years). This is not to say that TBSHs require no care in handling. In general, they should be treated as somewhat moisture-sensitive compounds, and unnecessary exposure to water should be avoided. For example, when the TBSH product of entry 7
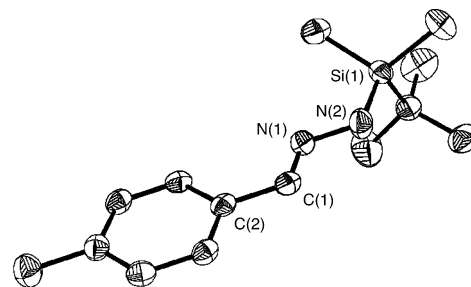

Figure 1. ORTEP diagram of the crystal structure of **2f** (50% thermal ellipsoids). H atoms have been omitted for clarity. Selected bond lengths: Si(1)−N(2), 1.730 Å; N(1)−N(2), 1.365 Å; C(1)−N(1), 1.272 Å. Selected bond angles: N(2)−N(1)−C(1), 118.5°; Si(1)−N(2)−N(1), 121.7°; C(1)−N(1)−N(2)−Si(1), −178.7°.

was allowed to stand open to the atmosphere for several days (100-mg quantity, neat), it was transformed quantitatively into the corresponding azine. As a rule, however, we have found that TBSH derivatives can be prepared and subjected to routine laboratory manipulations such as weighing, rotary evaporation, etc., without special precautions. Sterically encumbered TBSHs (entries 13−15) can be chromatographed in the presence of triethylamine in high yield, but less hindered derivatives cannot be chromatographed without evident decomposition (material loss), although thin-layer chromatography can be used to monitor their transformations (vide infra). TBSHs show good thermal stabilities. In several instances we have distilled TBSHs, obtaining >90% yields of distilled products (e.g., entry 1, bp 115−125 °C, 0.05 Torr; entry 3, bp 80−87 °C, 0.05 Torr; and entry 6, bp 110−120 °C, 0.05 Torr).

Preliminary studies have shown that other silylhydrazone derivatives can be prepared analogously to the method described for TBSH synthesis. For example, we have prepared hydrocinnamaldehyde *N*-triisopropylsilylhydrazone by Sc(OTf)$_3$-mediated condensation of the reagent 1,2-bis(triisopropylsilyl)-hydrazine[16] with hydrocinnamaldehyde (eq 2). The product *N*-triisopropylsilylhydrazone was formed free from contamination by the azine (NMR analysis); separation of the byproduct, triisopropylsilanol, by fractional distillation at 0.05 Torr provided the pure *N*-triisopropylsilylhydrazone in 87% yield (bp 130−134 °C, 4-g scale).

$$\text{(2)}$$
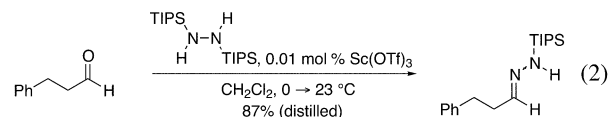
Structural Features of TBSH Derivatives. Crystals suitable for X-ray diffraction precipitated spontaneously during the condensation of *p*-tolualdehyde and BTBSH (entry 6, Table 1); structural analysis was conducted and is summarized in Figure 1. We are aware of X-ray structural information for only one simple aldehyde-derived hydrazone with which to compare our

(14) This is only essential only if it is desired to isolate TBSH derivatives in pure form; as discussed below, Wolff−Kishner-like reductions of TBSH derivatives can be conducted directly, without removal of *tert*-butyldimethylsilanol.

(15) Anti and syn isomers of TBSH **2n** (entry 14, Table 1) were treated separately with Sc(OTf)$_3$ (1 mol %) and TBSOH (3 equiv) in CHCl$_3$ at 23 °C for 12 h, and anti and syn isomers of TBSH **2p** (entry 15, Table 1) were treated separately with Sc(OTf)$_3$ (0.1 mol %) and TBSOH (1 equiv) at 100 °C for 12 h. No isomerization was observed in any case.

(16) 1,2-Bis(triisopropylsilyl)hydrazine is believed to be novel; it was prepared by sequential lithiation and silylation of anhydrous hydrazine. A detailed experimental procedure is provided in the Supporting Information. Bulky bis(trialkylsilyl)hydrazines have previously been prepared by sequential lithiation−silylation protocols, as well as by thermal disproportionation of bulky monosilylhydrazines upon prolonged heating at 220 °C. See ref 8 and (a) Dielkus, S.; Drost, C.; Herbst-Irmer, R.; Klingebiel, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1625. (b) Drost, C.; Klingebiel, U. *Chem. Ber.* **1993**, *126*, 1413. (c) Dielkus, S.; Drost, C.; Herbst-Irmer, R.; Klingebiel, U. *Organometallics* **1994**, *13*, 3985. (d) Bode, K.; Klingebiel, U.; Witte-Abel, H.; Gluth, M.; Noltemeyer, M.; Herbst-Irmer, R.; Schäfer, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *108*, 121.

structural data (fortunately, also from an aromatic aldehyde: 3-cyano-5-(4-pyridyl)pyrid-[1*H*]-2-one-6-carboxaldehyde).[17] In addition, as discussed in the Introduction, Klingebiel and co-workers have previously reported X-ray structural data for the *N-tert*-butyldiphenylsilylhydrazone derivative of the aliphatic ketone pinacolone.[7c] Comparisons among the three structures are instructive. For example, comparison of the TBSH derivative of *p*-tolualdehyde with the prior structure of a simple hydrazone derivative reveals that the silylhydrazone has a shorter C(1)−N(1) bond (1.272 vs 1.297 Å), a longer N(1)−N(2) bond (1.365 vs 1.317 Å), and a C(2)−C(1)−N(1) bond angle that is closer to an idealized trigonal geometry (122.0° vs 116.6°), all of which are consistent with the view that the silylhydrazone derivative has reduced conjugation of the lone pair localized on N(2) with the imine π-system relative to the simple hydrazone. The nitrogen bearing the *tert*-butyldimethylsilyl group appears to be essentially planar, and the N−N−Si bond angle is 121.7°. Silylamines are known to exhibit a high degree of planarity, which has been interpreted as evidence of a partial multiple bond between silicon and nitrogen.[18] To the extent that the lone pair of N(2) in the structure of Figure 1 is involved in multiple bonding with the silicon atom, reduced conjugation with the imine π-bond would be expected[19] and is supported by the structural evidence. Comparisons between the TBSH structure and the prior silylhydrazone structure reveal similar C(1)−N(1) bond lengths (1.272 vs 1.274 Å, respectively) and similar Si−N bond lengths (1.730 vs 1.728 Å), but the TBSH derivative is found to have a shorter N−N bond length (1.365 vs 1.401 Å).[7c]

Applications of TBSH Derivatives in Synthesis. The lability of nitrogen−silicon bonds toward cleavage under a wide range of different reaction conditions suggested that TBSH derivatives might transform as simple hydrazones do in the many known applications of hydrazones in organic synthesis.[20] This supposition has been found to have substantial merit, as illustrated in the applications detailed below.
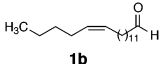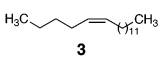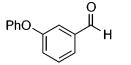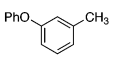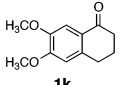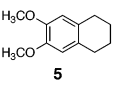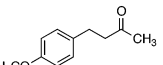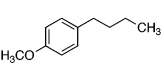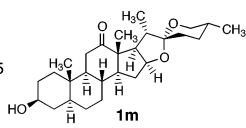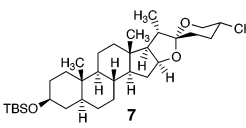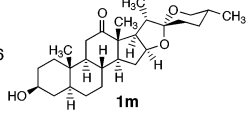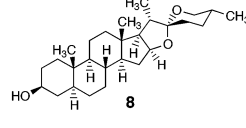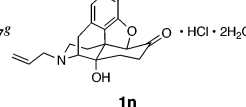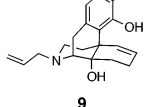
(A) Reduced-Temperature Wolff−Kishner Reductions. The reduction of carbonyl compounds to hydrocarbons via the corresponding hydrazones was first reported by Kishner in 1911[2a] and soon thereafter by Wolff in 1912.[2b] Early procedures described the addition of preformed hydrazones to hot solid potassium hydroxide[2a,21] or their heating with sodium ethoxide in ethanol in a sealed tube at temperatures of 160−200 °C.[2b] Numerous modifications to these procedures have been introduced over the years,[22] but the most commonly employed protocol, reported in 1946 by Huang-Minlon, involves heating of crude hydrazone derivatives with alkali in a high-boiling ethereal solvent such as diethylene glycol, typically at temperatures of 195−200 °C.[23] In addition to the Huang-Minlon procedure, other modifications of the Wolff−Kishner reduction are occasionally employed in synthesis.[24]

In a mechanistic study of the Huang-Minlon modification of the Wolff−Kishner reduction, Szmant et al. found that a minimum temperature of ∼190 °C was necessary to achieve a reasonable rate of reduction.[25] Two independent reports, from Cram et al. in 1962,[26] and from Henbest and co-workers in 1963,[4a] outlined reaction conditions that allowed the Wolff−Kishner reduction to be conducted successfully at temperatures as low as 23 °C. Cram et al. reported that the slow addition of solutions of pure aldehyde- and ketone-derived hydrazones to a solution of potassium *tert*-butoxide in dimethyl sulfoxide at 23 °C afforded reduction products in yields ranging from 64% for camphor hydrazone to 90% for benzophenone hydrazone. Subsequent studies showed that the use of a protic cosolvent such as 2-(2-butoxyethoxy)ethanol[27] or *tert*-butyl alcohol[28] leads to an increase in the rate of reduction under the Cram conditions. Henbest and co-workers reported an alternative procedure in which hydrazones were added in a single portion to a suspension of potassium *tert*-butoxide in toluene at 100−110 °C to effect Wolff−Kishner reduction.[4a] These reduced-temperature modifications of the Wolff−Kishner reduction have not been exploited to any great extent in organic synthesis, presumably due to the necessity to preform and isolate the sensitive hydrazone substrates and, in the case of Cram's conditions, to

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Table 2. Two-Step, One-Flask Wolff−Kishner-type Reduction of Carbonyl Compounds (with Removal of TBSOH)

entry	substrate	T (°C)[b]	product	yield (%)[c]
1	**1b**	23	**3**	99
2	**1g**	100[d]	**4**	96
3	**1k**	100[e]	**5**	92
4	**1j**	23	**6**	93
5	**1m**	23[f]	**7**	91
6	**1m**	100	**8**	95
7[g]	**1n**	23	**9**	78

[a] This step was conducted as detailed in Table 1 (volatile byproducts, including TBSOH, were removed in vacuo prior to reduction). [b] Temperature refers to the Wolff−Kishner step. Standard conditions: 23 °C, KO*t*-Bu (2 M), *t*-BuOH (0.2 M), DMSO, 24 h; 100 °C, KO*t*-Bu (1 M), *t*-BuOH (1 M), DMSO, 24 h. [c] Yield refers to products purified by column chromatography on silica gel. [d] The yield of product after 60 h at 23 °C was 86%. [e] The yield of product after 60 h at 23 °C was 37%. [f] After 48 h. [g] Run as a biphasic mixture with *n*-hexane as a cosolvent.

add the hydrazone over several hours to the reaction mixture in order to minimize the loss of yield that occurs with shorter addition times (due to competitive azine formation).

Although our initial attempts to implement Cram- or Henbest-type reduction conditions with TBSH derivatives as substrates were not terribly encouraging (slow reaction rates), after modification by the addition of *tert*-butyl alcohol as a proton source, outstanding results were achieved. Cram-type conditions (dimethyl sulfoxide) were superior to Henbest-type conditions (toluene), for solubility factors limited conversions in the latter case. In what has proven to be a near optimum two-step, one-flask procedure for carbonyl reduction, we first form the TBSH derivative, according to the protocol described above (including the removal of volatiles at 0.05 Torr, ~30−35 °C), and then add a solution of potassium *tert*-butoxide and *tert*-butyl alcohol in dimethyl sulfoxide directly to the liquid or solid residue in the original reaction vessel (Table 2). Reaction mixtures typically become red in color during the modified Wolff−Kishner reduction, and gas evolution is evident. Whereas reduction proceeds efficiently at 23 °C for most aliphatic substrates,

reduction of aromatic substrates such as 3-phenoxybenzaldehyde (entry 2) and 6,7-dimethoxy-1-tetralone (entry 3) are impractically slow at this temperature but proceed readily at 100 °C.[29] The sterically hindered steroidal substrate **1n** (entry 5) reacts cleanly (>90% yield) but slowly at 23 °C (48 h). Reduction of this substrate is much more rapid at 100 °C, but deprotection of the TBS ether group occurs at this temperature (entry 6).

It is evident that the ability to conduct TBSH synthesis and reduction in a single reaction vessel, without purification of intermediates, is of great convenience operationally. Our studies have shown that yields in the two-step procedure are actually slightly higher when the TBSH intermediate is not purified prior to the reduction step. We have also found that the presence of BTBSH in the reduction step is not deleterious. For example, when 4-(4-methoxyphenyl)-2-butanone TBSH (**2j**) was formed from 2.0 equiv of BTBSH and the unpurified product mixture (following the standard evacuation protocol) was subjected to reduction, the yield of **6** was undiminished relative to a control with only 1.0 equiv of BTBSH. This feature may be beneficial in very small-scale reactions or in other instances where the use of an excess of BTBSH is convenient or necessary.

Reduction of the morphinoid substrate of entry 7 (Table 2) was accompanied by Kishner−Leonard elimination[30] of the phenyl ether bond to provide the phenolic reduction product **9**. This is a relatively common side reaction in standard Wolff−Kishner reductions of hydrazone substrates with α-heteroatomic substituents.[22,30] The TBSH substrate derived from Naloxone (**2n**, Table 1) presented an additional complication due to the cleavage of the silyl aryl ether group that was observed under our standard reduction conditions, but by employing a biphasic solvent system consisting of *n*-hexane and dimethyl sulfoxide, silyl ether cleavage was avoided and the product of reductive elimination (**9**) was precipitated directly from the reaction medium (78% yield). This biphasic solvent system may be useful in other cases where the base lability of the substrate is an issue.

As a further step toward the development of a more streamlined, convenient one-flask carbonyl-reduction procedure, we explored the effect of omitting the evacuation step that serves to remove the *tert*-butyldimethylsilanol byproduct after TBSH formation (and simultaneously converts any azine that has formed to the TBSH product). We found that, with ketone-derived substrates, omission of the evacuation step did not diminish the yield of reduction products relative to procedures that employed the evacuation protocol (entries 3−7, Table 3). In fact, the two processes provided essentially identical yields of products, from which we conclude that the presence of *tert*-butyldimethylsilanol does not fundamentally influence the course of the Wolff−Kishner reduction. In the case of aldehyde-derived substrates (entries 1 and 2), we did observe that omission of the evacuation step led to a small but reproducible diminution in the yield of reduction products (~3−4%), which may be attributable to the presence of ~1−2% azine that would

(29) In some small-scale reductions, conducted at 100 °C and with 0.2 M *tert*-butyl alcohol, the reactions were observed to stall, perhaps as a consequence of the evaporation of *tert*-butyl alcohol. By use of a higher concentration of *tert*-butyl alcohol (1 M) at 100 °C, reproducible results were obtained in both small- and large-scale reactions. We also observed that the use of a lower concentration of potassium *tert*-butoxide (1 M) was effective at 100 °C, providing excellent yields (>90%) of reduction products within 24 h.

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Table 3. Two-Step, One-Flask Wolff−Kishner-type Reduction of Carbonyl Compounds (without Removal of TBSOH)

entry	substrate	T (°C)[b]	product	yield (%)[c]
1	1b	23	3	95
2	1g	100	4	92
3	1k	100	5	91
4	1j	23	6	94
5	1m	23[d]	7	91
6	1m	100	8	96
7[e]	1n	23	9	81

[a] This step was conducted as detailed in Table 1, except that volatile byproducts were not removed in vacuo. *[b]* Temperature refers to the Wolff−Kishner step. Standard conditions: 23 °C, KO*t*-Bu (2 M), *t*-BuOH (0.2 M), DMSO, 24 h; 100 °C, KO*t*-Bu (1 M), *t*-BuOH (1 M), DMSO, 24 h. *[c]* Yield refers to products purified by column chromatography on silica gel. *[d]* After 48 h. *[e]* Run as a biphasic mixture with *n*-hexane as cosolvent.

otherwise have been converted to the corresponding TBSH derivative during the evacuation step.[31]

It is clear that the conditions of carbonyl reduction in the present 2-step procedure are appreciably milder than traditional methods such as the Huang-Minlon modification of the Wolff−Kishner reduction. To make a direct comparison of the efficiencies of the two processes we applied the standard Huang-Minlon Wolff−Kishner reduction conditions (hydrazine hydrate, potassium hydroxide, diethylene glycol, 195 °C) in the reduction of the steroidal ketone **1n**. The reduction product **8** was obtained in 79% yield after column chromatography.[32] Numerous side products were also formed in the reaction. In contrast, the efficiency of reduction of the same substrate (**1n**) by either of our two-step, one-flask procedures (entries 5 and 6, respectively, Tables 2 and 3) exceeded 90%.

(31) It is notable that, under our modified Wolff−Kishner conditions, azines are not observed as byproducts. This stands in contrast to Cram's observations, where azine formation was the principal competing reaction under his modified conditions for Wolff−Kishner reduction.

(32) Willagenin, a C-5 epimer of hecogenin (**1m**), is reduced under the Huang-Minlon conditions in 70% yield: Kenney, H. E.; Wall, M. E. *J. Org. Chem.* **1957**, *22*, 468.

Several features of the new method for the deoxygenation of carbonyl-containing compounds should prove advantageous with respect to traditional Wolff−Kishner protocols. Among these are the benefits of a much reduced reaction temperature and the ease and efficiency with which TBSH derivatives are formed (in contrast to the problems associated with the formation and purification of hydrazones). Other noteworthy features of the new method are the operational convenience of forming and reducing TBSH derivatives in a single reaction vessel and the tolerance of the reduction step to the presence of *tert*-butyldimethylsilanol or excess BTBSH.
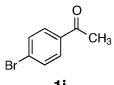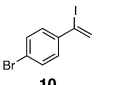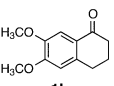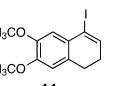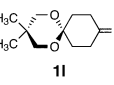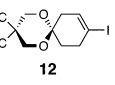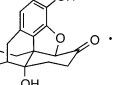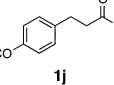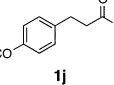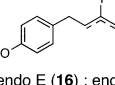
(B) Preparation of Vinyl Iodides. In 1962, Barton et al. described the transformation of ketone-derived hydrazones to vinyl iodides in the presence of iodine and triethylamine.[3] They observed that sterically hindered hydrazones afforded the best yields of vinyl iodides, while less encumbered substrates afforded mixtures of vinyl iodides and *gem*-dihalides. They also observed that omission of triethylamine from the reaction medium led to the exclusive formation of the corresponding azine. A later study by Pross and Sternhell concluded that the use of nearly equal volumes of a basic amine and an ethereal cosolvent provided the highest yield of vinyl iodides relative to the *gem*-diiodide and azine byproducts.[4d] Barton et al. subsequently showed that slow addition of hydrazones to a mixture of iodine and a hindered guanidine base, such as 1,1,3,3-tetramethylguanidine (TMG) or 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) led to further improvement in the formation of vinyl iodides.[33] In their optimized procedure, a solution of hydrazone in ethyl ether or tetrahydrofuran is added over ~30 min to a solution of iodine (2.5 equiv) and a large excess of TMG or BTMG at 23 °C. Yields of vinyl iodides from preformed (and, typically, recrystallized) hydrazone substrates were ~65−85%. This procedure has been frequently employed in fine-chemical synthesis[34] and often provides access to vinyl iodides that would otherwise be difficult to prepare. We anticipated that the merits of TBSH derivatives relative to hydrazones as intermediates might prove advantageous in a modified Barton-type vinyl iodide synthesis.

Our initial attempts to implement Barton's procedure using TBSH derivatives as substrates were highly promising and by minor modifications of the reaction temperature, the rate of addition of the TBSH substrate, and the amount of iodine in the reaction, we found that vinyl iodides could be efficiently prepared from a variety of ketone-derived TBSHs. In the optimized procedure, a solution of an unpurified TBSH deriva-

(33) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605. (b) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147.

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Table 4. Two-Step Synthesis of Vinyl Iodides

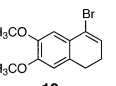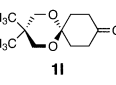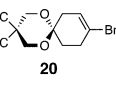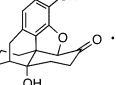| entry	substrate	product(s)	yield (%)[c]
1	1i	10	85
2	1k	11	82
3	1l	12	67[d]
4	1n	tetrasub. (13) : trisub. (14) 57 : 43	84[e]
5	1j	exo (15) : endo E (16) : endo Z (17) 62 : 21 : 17	71
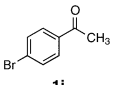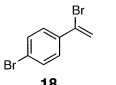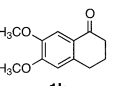
[a] This step was conducted as detailed in Table 1 (volatile byproducts, including TBSOH, were removed in vacuo prior to reduction). [b] Standard conditions: a solution of the TBSH derivative ($\sim$1 M in THF) was added to a solution of I_2 (5 equiv, $\sim$0.5 M in 2:1 THF/TMG) at 0 °C over a period of 2−3 h. [c] Yield refers to products purified by column chromatography on silica gel. [d] The corresponding *gem*-diiodide was also formed (22% yield). [e] The yield of product in this transformation was higher when 8 equiv of I_2 was used; the yield shown reflects this modification.

Table 5. Two-Step Synthesis of Vinyl Bromides

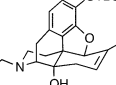| entry	substrate	product(s)	yield (%)[c]
1	1i	18	90
2	1k	19	84
3	1l	20	65[d]
4	1n	21	44[e,f]

[a] This step was conducted as detailed in Table 1 (volatile byproducts, including TBSOH, were removed in vacuo prior to reduction). [b] Standard conditions: a solution of the TBSH derivative ($\sim$1 M in CH_2Cl_2) was added to a solution of Br_2 (2.2 equiv, $\sim$0.25 M in 2:1 CH_2Cl_2/BTMG) at 23 °C over a period of 1 h. [c] Yield refers to products purified by column chromatography on silica gel. [d] The corresponding *gem*-dibromide was also formed (7% yield). [e] The yield of product in this transformation was higher when 8 equiv of Br_2 was used; the yield shown reflects this modification. [f] The isomeric (tetrasubstituted) vinyl bromide is believed to have been formed during the reaction as well but did not survive isolation/purification.

tive (after removal of volatile byproducts in vacuo) is added over 2−3 h to a solution of iodine (5 equiv) in tetrahydrofuran containing excess TMG at 0 °C.[35] As shown by the data of Table 4, use of the modified Barton procedure with several different ketone-derived substrates afforded vinyl iodides in good yields. As in the original Barton procedure, regioisomeric mixtures of vinyl iodide products were obtained where this was possible (e.g., entries 4 and 5, Table 4).[4d,33] The 1,4-cyclohexanedione ketal (**1l**) behaved somewhat differently from other ketones we examined as substrates in that it exhibited a greater propensity to form the corresponding *gem*-diiodide as a byproduct (entry 3, Table 4).

As we had observed in our studies of Wolff−Kishner-type reductions of TBSH derivatives, we found that the highest yields of vinyl iodides were obtained when unpurified TBSHs were used as substrates. For example, the combined yield of vinyl iodides **13** and **14** was 74% when the TBSH derivative of the morphinoid substrate **1n** was purified by column chromatography (triethylamine-buffered silica gel), whereas use of the unpurified TBSH derivative (after removal of volatile byproducts in vacuo) provided **13** and **14** in 84% combined yield (entry 4, Table 4). Yields of vinyl iodides were slightly diminished (4−6%) when we omitted the evacuation step that serves to remove

TBSOH from the TBS intermediates, but the yields were essentially unaffected by the presence of excess BTBSH in the reaction (in contrast, hydrazine is not tolerated in the Barton vinyl iodide synthesis).[33] The primary advantage of the present method for vinyl iodide synthesis relative to the Barton procedure is that it obviates the need for the use of labile hydrazones in the reaction. The ability to employ TBSH derivatives in unpurified form and the tolerance of the vinyl iodide formation to excess BTBSH are also potentially advantageous.

(C) Preparation of Vinyl Bromides. Shortly after Barton's initial publication on the preparation of vinyl iodides from hydrazones, Mori and Tsuneda described the adaptation of Barton's procedure for the synthesis of a steroidal vinyl bromide.[36] They found that treatment of the hydrazone derived from 3β-androsterone hydrazone with *N*-bromosuccinimide (2.5 equiv) in pyridine provided the corresponding vinyl bromide in 47% yield. In a subsequent study, Pross and Sternhell found that molecular bromine was also somewhat effective in the transformation of several ketone-derived hydrazones to the corresponding vinyl bromides (9−46% yield).[37] These procedures have been employed several times in organic synthesis.[38]

When we treated TBSH derivatives with bromine in pyridine according to the protocol for hydrazone bromination,[36] vinyl bromides were obtained in yields comparable to those reported for hydrazones as substrates. By using the hindered guanidine base BTMG, much improved yields of vinyl bromides were obtained (Table 5). In the optimized procedure, a solution of

(35) We found that BTMG was effectively the same as TMG in our modified Barton protocol for the synthesis of vinyl iodides from TBSH derivatives. See ref 33a.

(36) Mori, H.; Tsuneda, K. *Chem. Pharm. Bull.* **1963**, *11*, 1413.
(37) Pross, A.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1437.

an unpurified TBSH derivative in dichloromethane (1 M) is added over 1 h to a solution of bromine (2.2 equiv, ∼0.25 M) in dichloromethane/BTMG (2:1) at 23 °C, providing vinyl bromides in yields of 44−90% (Table 5). As we observed in the preparation of vinyl iodides, omission of the evacuation step after the TBSH synthesis led to diminished yields of vinyl bromides (by ∼8−10%), but excess BTBSH in the reaction was not problematic.

(D) Preparation of *gem*-Dihalides. In their initial report describing the synthesis of vinyl iodides from hydrazones, Barton et al. also showed that aldehyde-derived hydrazones were transformed into *gem*-diiodide products.[3] For example, pival-dehyde hydrazone was reported to react with iodine in ethyl ether containing triethylamine to provide 1,1-diiodoneopentane (no yield was given).[3] In a subsequent study, Pross and Sternhell showed that *gem*-diiodide products predominated under the Barton conditions with a variety of aldehyde-derived hydrazones as substrates; yields of *gem*-diiodides ranged from 38% for benzaldehyde hydrazone to 65% for phenylacetaldehyde hydrazone.[4d] In addition to *gem*-diiodide products, azines and, where feasible, vinyl iodides were formed as well. Despite its limitations, the Barton−Pross−Sternhell procedure has been frequently employed in organic chemistry,[39] due in part to the high value of *gem*-diiodides as precursors to transition-metal alkylidenes in olefination[40] and cyclopropanation reactions.[41]

We found that application of the Barton−Pross−Sternhell procedure to hydrocinnamaldehyde TBSH as substrate provided the corresponding *gem*-diiodide in poor yield (25−35%); however, the yield was readily improved by a procedural modification. In the modified protocol, a solution of the unpurified TBSH derivative (after removal of volatile byprod-ucts) in tetrahydrofuran (∼1 M) is added over 30 min to a mixture of iodine (2.5 equiv, ∼0.5 M) and triethylamine (2.5

equiv, ∼0.5 M) in tetrahydrofuran containing a small amount of methanol (∼2−3 equiv) at −10 °C, affording 1,1-diiodo-3-phenylpropane in 64% yield (eq 3). Application of this protocol to a TBSH derived from the Corey lactone (**1e**, eq 4) provided the expected *gem*-diiodide in 62% yield, suggesting that the new procedure for *gem*-diiodide synthesis may be of general utility.
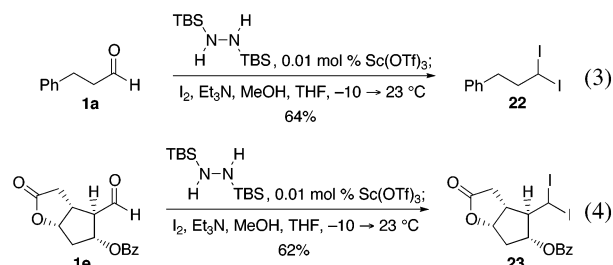
Previously reported attempts to adapt the Barton−Pross−Sternhell procedure for the synthesis of *gem*-dichlorides[37] and mixed *gem*-dihalides[39a,42] have met with limited success, but a recent method described by Takeda et al.[6] provides *gem*-dichlorides[43] from both aldehyde- and ketone-derived hydra-zones in good yields (*gem*-dibromides were prepared by a related procedure).[44] In Takeda's procedure, a solution of a simple hydrazone derivative in methanol is added to a copper(II) halide salt (∼3−6 equiv) in methanol containing triethylamine (∼2−3 equiv) at 0 °C. Yields of *gem*-dihalides formed by this method ranged from 56% for the formation of 4-*tert*-butyl-1,1-dichlo-rocyclohexane to 82% for the formation of the expected *gem*-dibromide product from geranylacetone hydrazone as substrate.

We found that minor modifications of Takeda's protocol for *gem*-dihalide synthesis efficiently provided *gem*-dichloride and *gem*-dibromide products from both aldehyde- and ketone-derived TBSH substrates (eqs 5−8). The most significant deviations from the reported procedure were the use of a lower reaction temperature (−10 °C) and an extended addition time when aldehyde-derived TBSHs were used as substrates. Although we have not conducted an extensive substrate study, from the data at hand it is reasonable to conclude that *gem*-dihalide syntheses with TBSH derivatives as substrates are likely to be more efficient processes in general relative to the corresponding transformations with hydrazones as substrates.
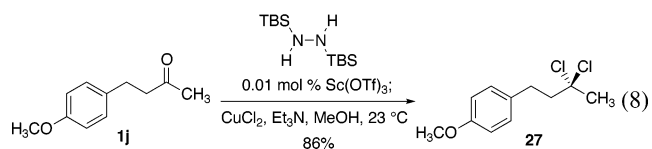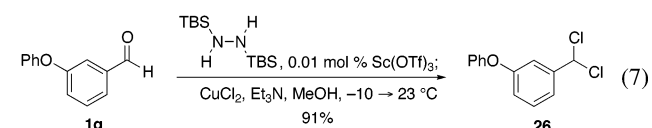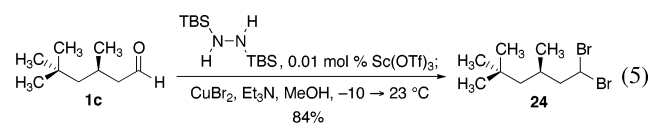
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Conclusion

We have developed a general and highly efficient procedure for the synthesis of TBSH derivatives from carbonyl compounds. The procedure is compatible with a number of different functional groups, proceeds under extremely mild reaction conditions, and provides TBSH products that are of a high degree of purity after removal of volatile byproducts. TBSH derivatives exhibit greatly enhanced stabilities relative to simple hydrazone derivatives. In addition, they are found to be superior substrates in many valuable synthetic transformations that heretofore have employed simple hydrazones as substrates. We have described modified protocols for the use of TBSH derivatives as substrates in a low-temperature Wolff−Kishner-type reduction procedure, a modified Barton vinyl iodide synthesis, and in processes for the synthesis of vinyl bromides, *gem*-diiodides, *gem*-dibromides, and *gem*-dichlorides. We anticipate that the many superior features of TBSH derivatives (stability, efficiency of synthesis, safety concerns,[12] versatility as synthetic precursors) relative to simple hydrazones will lead to their adoption for the laboratory transformations described, as well as in other contexts.

Supporting Information Available: Detailed experimental procedures for TBSHs (compounds **2a**−**2p**), Wolff−Kishner reductions (compounds **3**−**9**), vinyl iodides (compounds **10**−**17**), vinyl bromides (compounds **18**−**21**), and *gem*-dihalides (compounds **22**−**27**), and complete spectroscopic data for all new compounds (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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