Highly Efficient Methodology for the Reductive Coupling of Aldehyde Tosylhydrazones with Alkyllithium Reagents

Andrew G. Myers* and Mohammad Movassaghi

Division of Chemistry and Chemical Engineering
California Institute of Technology
Pasadena, California 91125

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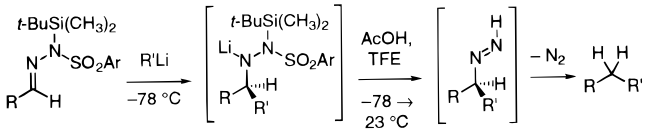
Aldehyde tosylhydrazones are nearly ideal synthetic intermediates; they are readily available, stable, and frequently crystalline compounds that can be stored indefinitely, whereas the parent aldehydes cannot, being susceptible to autoxidation, self-condensation, and hydration.[1] In this work, we describe a new and efficient process for the construction of C−C σ bonds by the reductive coupling of aldehyde tosylhydrazones with alkyllithium reagents.

In an earlier study we reported that aldehyde tosylhydrazones are readily *N*-*tert*-butyldimethylsilylated, in quantitative yield, and that the resultant derivatives undergo 1,2-addition of vinyllithium reagents to form olefinic products in a process involving, ultimately, [3,3]-sigmatropic elimination of dinitrogen from an allylic diazene intermediate.[2] In this work, we show that saturated (sp^3-hybridized) alkyllithium reagents (typically, 1.2 equiv) add to *N*-*tert*-butyldimethylsilyl aldehyde tosylhydrazones at −78 °C and that the resultant adducts can be made to extrude dinitrogen in a free-radical process,[3] leading to a net reductive coupling reaction that often proceeds with remarkable overall efficiency (Scheme 1, Table 1). These features distinguish the present methodology from the important precedents of Vedejs et al., who reported the reductive coupling of (nonsilylated) aldehyde tosylhydrazones with alkyllithium reagents (≥3 equiv, 20−61% yield) by an anionic fragmentation pathway,[4a] and of Bertz, who described the coupling of nonepimerizable aldehyde tosylhydrazones with cuprate reagents, also by anionic fragmentation.[4b]

Sequential treatment of aldehyde tosylhydrazones (0.2 M in tetrahydrofuran, THF) with triethylamine (1.3 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.2 equiv) at −78 °C followed by the addition of methanol (1.3 equiv), dilution with hexanes, and immediate washing of the cold reaction solution with saturated aqueous sodium bicarbonate solution, and then brine, drying over magnesium sulfate, and concentration affords the silylated tosylhydrazones in quantitative yield.[2] Because of their propensity to hydrolyze upon exposure to silica gel, these intermediates are used directly in the coupling reactions, without purification. Entry 8 (Table 1) is illustrative of a typical coupling protocol: a solution of (2*S*)-1-lithio-2-methyl-3-phenylpropane (0.378 mmol, 1.2 equiv) in diethyl ether (1.0 mL) at −78 °C was added to a solution of *N*-*tert*-butyldimethylsilyl (2*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal tosylhydrazone (147 mg, 0.315 mmol) in THF (1.5 mL) at −78 °C. After 15 min, acetic acid (1.25 equiv) was added, followed by trifluoroethanol (TFE, 5.0 mL), and the resulting solution was warmed to 23 °C to induce diazene formation and elimination of dinitrogen. The reaction was complete within 8 h at 23 °C. After extractive isolation and chromatography on silica gel, the coupled product was obtained as a colorless oil (133 mg, 95%). ^{1}H and ^{13}C NMR analysis showed that the coupled product was a single diastereomer, demonstrating that epimerization of the aldehyde-derived stereocenter did not occur throughout the sequence of tosylhydrazone formation, silylation, and coupling. Entries 6, 7, and 9−12 of Table 1 were also shown to proceed without detectable epimerization, reinforcing the potential utility of the method for asymmetric synthesis using "α-chiral" aldehydes.[5] Recent advances in the preparation of (stereochemically) complex primary alkyllithium reagents further extend the potential of the method in asymmetric synthesis, as illustrated by entries 6, 8, and 10.[6]

Scheme 1



Prior studies support the pathway shown in Scheme 1 as the likely sequence for the present coupling chemistry: 1,2-addition of the alkyllithium reagent and protonation of the adduct followed by elimination of *p*-toluenesulfinic acid, protodesilylation, and loss of dinitrogen.[2] That the latter step proceeds by a radical pathway was established unequivocally by trapping of the intermediate free radical with TEMPO, by intramolecular radical cyclization experiments (see the Supporting Information), and by the observation of fragmentation within the substrate of entry 13.[7]

A particularly noteworthy feature of the coupling chemistry described is the overall efficiency of the process (Table 1), a sequence initiated by 1,2-addition of the alkyllithium reagent. The latter step is no doubt facilitated relative to additions to the anionic intermediates formed from nonsilylated tosylhydrazones[4] by the fact that the silylated tosylhydrazone is a neutral species; however, the X-ray crystal structure of *N*-*tert*-butyldimethylsilyl 1-naphthaldehyde tosylhydrazone (Figure 1) suggests that there may be other beneficial factors associated with *N*-silylation as well. The sulfonamide nitrogen is found to be nearly planar, a common feature within silylated amines but not within sulfonylhydrazones.[8] The bulky *tert*-butyldimethylsilyl group is adjacent to the imino lone pair, while the arenesulfonyl group is syn coplanar with the aldimine hydrogen atom. This places one of the sulfonyl oxygens in a nearly ideal orientation to direct the addition of an organolithium reagent to the imine group. The least basic organometallic reagent observed to add efficiently to a silylated tosylhydrazone is the amide enolate of entry 5 (addition at −20

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(2) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208.

(3) (a) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193. (b) Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1971**, *93*, 1992. (c) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572. (d) Myers, A. G.; Movassaghi, M.; Zheng, B. *Tetrahedron Lett.* **1997**, *38*, 6569.

(4) (a) Vedejs, E.; Stolle, W. T. *Tetrahedron Lett.* **1977**, 135. (b) Bertz, S. H. *Tetrahedron Lett.* **1980**, *21*, 3151. For other examples of reductive coupling of aldehyde tosylhydrazones with organometallic reagents, see: (c) Vedejs, E.; Dolphin, J. M.; Stolle, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 249. (d) Chandrasekhar, S.; Takhi, M.; Yadav, J. S. *Tetrahedron Lett.* **1995**, *36*, 307. (e) Chandrasekhar, S.; Takhi, M.; Yadav, J. S. *Tetrahedron Lett.* **1995**, *36*, 5071.

(5) For preparations of "α-chiral" aldehydes and alkyl iodides used in entries 6−8 and 10, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457.

(6) Noncommercial alkyllithiums were generated either by lithium−iodide exchange (Table 1 entries 1, 2, 6, and 8−10) or by deprotonation (Table 1 entries 4 and 5): (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406. (c) For a review of *ortho*-metalation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(7) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

(8) (a) Hedberg, K. *J. Am. Chem. Soc.* **1955**, *77*, 6491. (b) Ebsworth, E. A. V.; Murray, E. K.; Rankin, D. W. H.; Robertson, H. E. *J. Chem. Soc., Dalton Trans.* **1981**, 1501. (c) Anderson, D. G.; Rankin, D. W. H.; Robertson, H. E.; Gundersen, G.; Seip, R. *J. Chem. Soc., Dalton Trans.* **1990**, 161. (d) Mitzel, N.; Schier, A.; Schmidbaur, H. *Chem. Ber.* **1992**, *125*, 2711. (e) Mitzel, N. W.; Reide, J.; Schier, A.; Paul, M.; Schmidbaur, H. *Chem. Ber.* **1993**, *126*, 2027.

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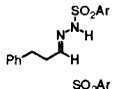
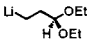
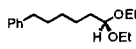
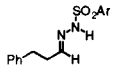
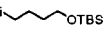
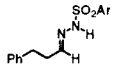
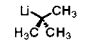
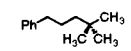
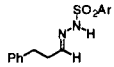
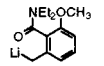
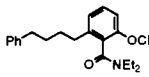
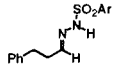
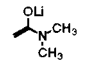
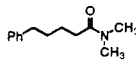
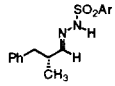
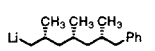
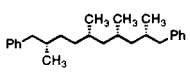
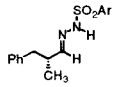
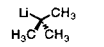
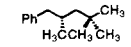
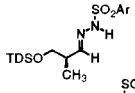
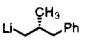
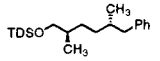
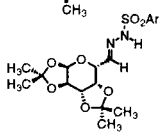
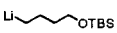
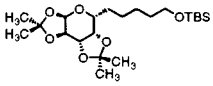
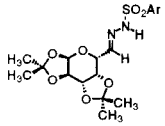
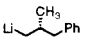
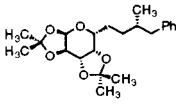
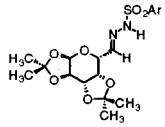
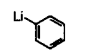
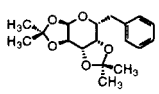
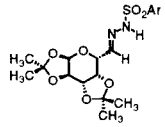
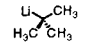
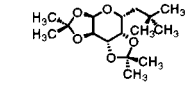
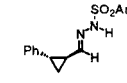
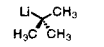
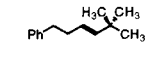
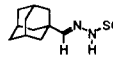
Table 1. Reductive Coupling of Aldehyde Tosylhydrazones with Alkyllithiums

Entry	Substrate[a]	Alkyllithium[b]	Product	Yield[c]
1				89
2				88
3				91
4				95
5				97
6				94[d]
7				94[d]
8				95[d]
9				96[d]
10				92[d]
11				78[d]
12				87[d]
13				83
14				95
15				81
16				94

[a]Ar=$C_6H_4CH_3$ in all entries but 14, where Ar=2,4,6-triisopropylbenzene. [b]1.2 equiv of alkyllithium was used in all entries but 4 and 5, where 1.5 and 1.1 equiv were used, respectively. [c]Isolated yields. [d]Products found to be single diastereomers (≥ 95% de by ^{1}H and ^{13}C NMR analysis); in the case of entry 7 the product was shown to be 98% ee.

°C); lithium acetylides and Grignard reagents examined thus far have been found to react not at all or very slowly.

Although hindered alkyllithium reagents such as *tert*-butyllithium readily undergo reductive coupling with a range of silylated aldehyde tosylhydrazones (see entries 3, 7, 12, and 13), the efficiency of alkyllithium addition to the imino carbon apparently diminishes when the tosylhydrazone component becomes excessively hindered, as in the case of 1-adamantanecarboxaldehyde tosylhydrazone, where competitive *ortho*-lithiation of the tolyl group occurs upon attempted addition of *n*-butyllithium.[9] The use of triisopropylbenzenesulfonyl (trisyl) hydrazones[10] in such cases alleviates this problem, but does necessitate that the addition reactions be conducted at somewhat warmer temperatures (0 °C, entry 14). The facility of enolization (see the Supporting Information) precludes the extension of the present methodology to silylated ketone tosylhydrazones.

Figure 1.

Where possible, [3,3]-sigmatropic elimination of dinitrogen is preferred over radical fragmentation of the intermediate monoalkyl diazene.[3c] Such is believed to be the case for aryllithium adducts (entry 11) and intermediates arising from aromatic aldehyde substrates (entries 15 and 16). The isonaphthalene product of entry 15 is sufficiently stable to be isolated, but the isotoluene intermediates of entries 11 and 16 are not, undergoing isomerization in situ to form the indicated aromatic products. Rearomatization is believed to involve protonation of the isotoluene ring, a proposal supported by the greater rate (and efficiency) of rearomatization of the electron-rich substrate of entry 16 versus that of entry 11.

Carbon−carbon σ bonds that link saturated centers are seldom targeted for retrosynthetic disconnection in current practice, largely because of the paucity of reliable methodology to accomplish such bond formations directly. Indirect sequences, such as C−C π bond formation followed by hydrogenation, are much more commonly employed for fragment assembly about a C−C σ bond. The methodology described herein offers an alternative to such two-step sequences and, further, provides an efficient construction of σ bonds to quaternary and aromatic centers, not possible by olefination−hydrogenation routes. The compatibility of the present methodology with "α-chiral" aldehydes, sterically hindered alkyllithiums and aldehydes, and the mild reaction conditions and overall efficiency of the transformation make this coupling chemistry a potentially powerful addition to existing carbon−carbon (sp^3−sp^3) bond-forming processes.

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Supporting Information Available: Experimental details and analytical data for the products of Table 1, procedures for preparation of aldehyde tosylhydrazones, X-ray data, and other supporting data referenced (22 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(9) *ortho*-Lithiation is followed by N → C silyl transfer (see the Supporting Information).

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