Asymmetric Synthesis of 1,1-Disubstituted Tetralins and Dihydronaphthalenes by Diastereoselective Addition of Lithiosilanes to Chiral Naphthalenes

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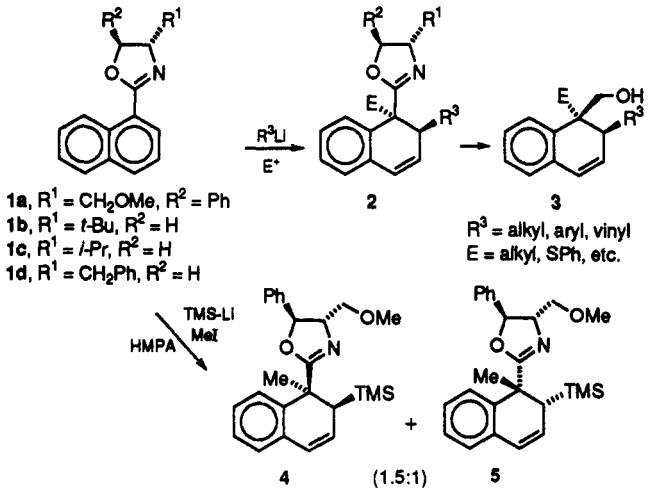
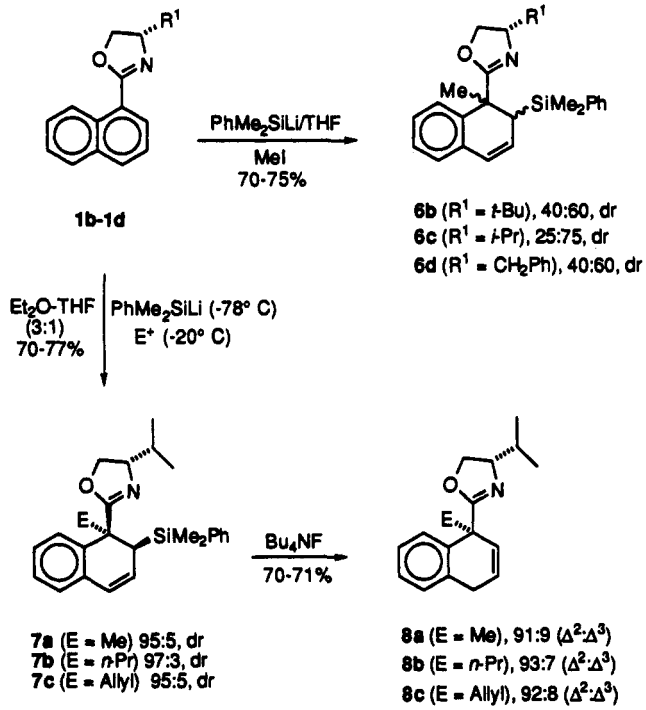
Summary: Highly diastereoselective additions of lithiosilanes to chiral naphthalenes can be performed in ether/THF. Trapping of the resulting azaenolate, followed by protodesilylation, allows access to 1,1-disubstituted tetralins or dihydronaphthalenes in good yields and high enantiomeric excess.

A recent report by Shibasaki[1] et al. describing an asymmetric route to the title compounds using an intramolecular Heck reaction has prompted us to describe our own results to reach these important substances. Our route, using stoichiometric reagents, was based on earlier studies[2] wherein a variety of organolithium reagents were added to naphthalenes bearing a chiral oxazoline (**1a–d**).



The diastereoselective addition followed by trapping the intermediate azaenolate gave the disubstituted adducts **2** in greater than 95% de. Removal of the chiral auxiliary led to a series of tetralins **3** as well as more complex systems related to aphidocolins, scopadulcic acids, and kaurenes.[3] However, the major limitation encountered during this work was the lack of specificity when we attempted to add the trimethylsilyl group to **1a–1c**. The products **4** and **5** were obtained in a 1.5:1 ratio due to poorly selective diastereofacial addition of the lithiosilane. This poor selectivity was attributed to the presence of HMPA required to generate TMS-Li from hexamethyldisilane.[4] The well-known lithium-ion-coordinating ability of HMPA presumably interfered with the required coordination of the silyllithium reagent to the chiral oxazoline.

It became apparent that without a highly stereoselective addition of the lithiosilanes there could be no ready access to quaternary benzyl systems such as **2** (R^3 = H) after a desilylation step. Therefore, we attempted to avoid the HMPA-containing process by employing the Fleming procedure[5] to generate lithiodimethylphenylsilane from lithium wire and the corresponding silyl chloride. Unfortunately, utilizing this reagent with **1** under conditions reported earlier,[2] gave good yields, but disappointing diastereoselectivities of adducts **6b–6d**. Varying the temperature of addition (−78 to −100 °C) also had little effect on the diastereomeric ratios (dr).[6]



In an attempt to maximize the complexation of the silyllithium reagent to the chiral oxazoline, providing some rigidity and order to the transition state, we chose to reduce the solvent polarity by introduction of ether. Thus, when an ether–THF (3:1) mixture was employed and the silyllithium reagent was added at −78 °C, followed by addition of an electrophile at −20 °C, the diastereoselective

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(1) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477.

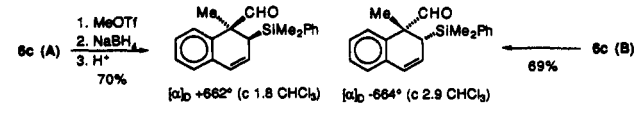
(2) (a) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611. (b) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.

(3) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607. For a review on the recent advances in the synthetic utility of oxazolines, see: Gant, T. G.; Meyers, A. I. *Tetrahedron Rep.*, in press.

(4) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063.

(5) Fleming, I.; Newton, T. W.; Roessier, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.

(6) Both diastereomers of **6c** were readily separated by radial chromatography (silica gel 60, PF_{254} containing gypsum), and the oxazoline was removed as shown below. Both diastereomers of **6c** (A, B) gave their respective optical antipodes which confirmed that the additions to **1** were pure *trans* in nature—only the initial diastereofacial addition differed.



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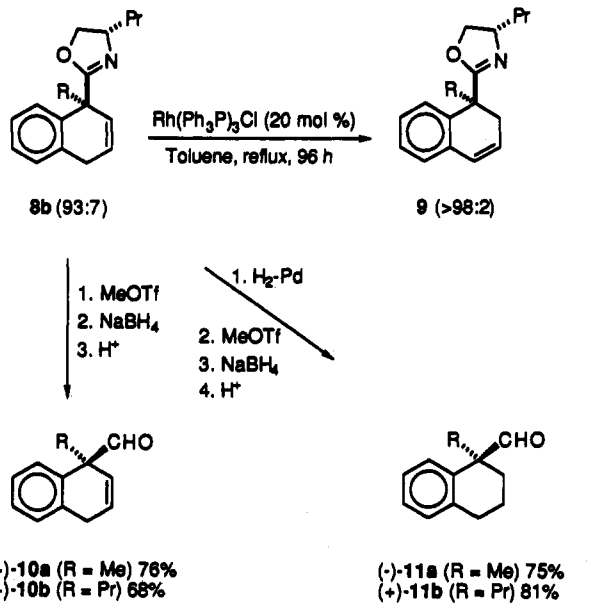
addition proceeded at very high levels. The ratio of diastereomers **7a–c** was 95–98% to 2–5%, and they were readily purified to a single product in 70–77% yield. The use of the ether–THF mixture was, therefore, the key to successful access to the adducts **7**.

In order to remove the silyl group from **7**, which had served its purpose as a "surrogate proton", we found that tetrabutylammonium fluoride in aqueous THF (20 °C, 1.5 h) provided a mild method.[7] The products **8a–c** were obtained in good yield but were contaminated with 7–9% of an isomeric olefin found to be the conjugated Δ^3-isomer **9**.[8] It was observed, however, that the Δ^2-double bond in **8** could be readily isomerized to the Δ^3-isomer by treatment with Wilkinson's catalyst in refluxing toluene. Thus, either isomer **8** or **9** was accessible for further synthetic use. In this regard the diastereomerically pure tetralins **8a** and **8b** were subjected to the previously described[2] procedure involving quaternization (MeOTf), reduction ($NaBH_4$), and hydrolysis (oxalic acid) furnishing the quaternary substituted aldehydes **10a** and **10b** in good overall yields. Alternatively, the silylated oxazolines **7a** and **7b** were treated sequentially with TBAF and H_2-Pd-C to produce the corresponding saturated oxazolines in 77–83% yields. The latter were then transformed, as above, to give the saturated quaternary substituted tetralins **11a** and **11b** in >99% enantiomeric excess.

In summary, the route described for reaching chiral nonracemic 1,1-disubstituted tetralins or dihydronaphthalenes is one of efficiency and convenience and competes well with the recently described asymmetric catalytic process.[1]



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Supplementary Material Available: Experimental details and spectral data for **7a–c**, **8a–c**, **9**, **10a,b**, and **11a,b** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Acid-catalyzed protodesilylation of **7** failed to provide any useful yields of **8**.

(8) The isomerization may be due to the acidic workup utilized to separate the oxazoline **8** from the silyl side products but only to a very minor extent. This aspect is currently under further scrutiny.

(9) Physical data for these and other compounds as well as experimental procedures are given in the supplementary material.