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Nickel-catalyzed preparation of stereodefined allylic alcohols using silicon-tethered ynals

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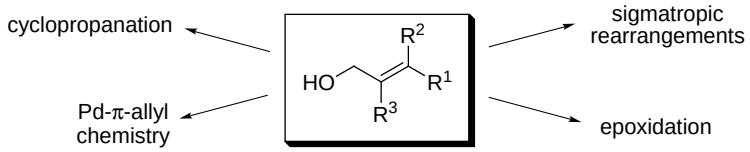
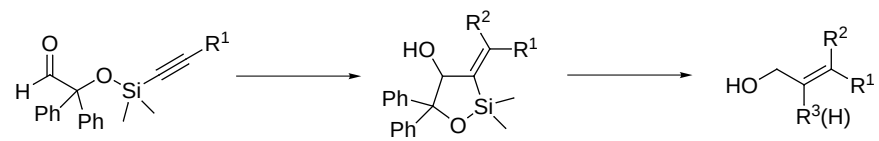
Abstract—The nickel-catalyzed cyclization of silicon-tethered ynals is reported. The silicon heterocycles obtained may be converted into allylic alcohols that possess a stereodefined alkene unit via a cleavage process that involves stereospecific protodesilylation of the vinyl silane functionality. © 2001 Published by Elsevier Science Ltd.

Achiral allylic alcohols and their derivatives are versatile substrates in a variety of asymmetric transformations including Claisen rearrangements and related processes,[1] epoxidations,[2] cyclopropanations,[3] and palladium-catalyzed allylic substitutions (Scheme 1).[4] Despite the impressive utility of these processes, many classes of the requisite allylic alcohols that possess tri- or tetra-substituted alkenes are quite difficult to prepare in an isomerically-pure fashion. Our group has recently reported a method for the preparation of cyclic and acyclic allylic alcohols by nickel-catalyzed cyclizations or couplings of an aldehyde and an alkyne.[5] Given the broad utility of allylic alcohols in the asymmetric processes cited above, we became interested in applying the nickel-catalyzed ynal cyclization in the preparation of achiral allylic alcohols with a high degree of substitution about the alkene moiety. The products obtained would thus be attractive precursors for many asymmetric processes.

The most direct entry to achiral allylic alcohols by the nickel catalysis strategy would involve couplings of alkynes with formaldehyde. Reactions with formaldehyde, however, were much less efficient than the corresponding reactions with aliphatic and aromatic aldehydes. Furthermore, regioselectivities of the alkyne insertion were poor for most substrates. In order to circumvent these limitations, we have examined the temporary silicon-connection method in ynal cyclizations (Scheme 2).[6] This approach enjoys the entropic advantages of the intramolecular variant and generates adducts which may be oxidatively-degraded into the products that would be obtained by formaldehyde couplings. As demonstrated in this study, the cyclic vinylsi-



Scheme 1. Allylic alcohols in asymmetric synthesis.



Scheme 2. Strategy for preparation of allylic alcohols.

Keywords: nickel; silicon heterocycles; alkenes.

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lanes may be cleaved by protodesilylation to afford allylic alcohols with a stereodefined trisubstituted alkene.[7] Furthermore, electrophilic functionalization of the vinylsilane moiety may ultimately provide access to allylic alcohols that possess a stereodefined tetrasubstituted alkene.[8]

The requisite silicon-tethered ynals were most effectively prepared by initial addition of a lithium acetylide to dimethyldichlorosilane to afford chloroalkynylsilanes **1a**–**d**.[9] Chlorosilanes **1a**–**d** and hydroxyaldehyde **2** were then stirred in CH_2Cl_2 at 0°C with Et_3N and catalytic DMAP for 15 min to directly afford ynals **3a**–**d** (Scheme 3). The gem–diphenyl moiety was chosen simply because of the stability and ease of preparation of hydroxyaldehyde **2**,[10] and we expect that other linkages would be equally effective in the subsequent cyclization processes.

With the desired ynals in hand, we examined the efficiency of nickel-catalyzed cyclizations with organozincs according to procedures previously developed in our labs.[5] Organozincs were prepared by treatment of anhydrous zinc chloride in THF with an organolithium or organomagnesium reagent (1.6:1 stoichiometry). A mixture of the organozinc with $Ni(COD)_2$ (10 mol%) was transferred to a THF solution of the ynal and trimethylsilyl chloride. After 1 h at 0°C, trimethylsilyl-protected silicon heterocycles **4a**–**f** were efficiently formed (Scheme 4). Treatment with HF·pyridine selectively deprotected the trimethylsilyl moiety to afford alcohol derivatives **5a**–**f**, whereas treatment with nBu$_4$NF resulted in exhaustive silyl cleavage to afford the corresponding acyclic diols. In the nBu$_4$NF-mediated process, protodesilylation proceeded cleanly to afford the trisubstituted alkene in a stereospecific fashion.[7]

For purposes of obtaining allylic alcohols with a trisubstituted alkene moiety, the most direct and efficient procedure involves treatment of the crude reaction mixture from a nickel-catalyzed cyclization with nBu$_4$NF to afford the 1,2-diol with concomitant protodesilylation of the vinyl silane in a single step (Scheme 4).[11] Treatment of the diol with periodic acid in ether cleanly afforded the expected aldehyde which was directly treated with $NaBH_4/CeCl_3$ to afford the desired allylic alcohols **6a**–**f** in >95:5 isomeric purity. The examples shown demonstrate that aromatic and aliphatic alkynes as well as conjugated enynes participate in the new coupling reaction. Furthermore, aromatic and aliphatic organozincs are tolerated in the cyclization. The formation of compounds **6e** and **6f** demonstrates high selectivity that would undoubtedly be difficult to achieve with methods that involve carbonyl olefination.

In summary, a new method for preparing highly substituted allylic alcohols utilizing temporarily-tethered ynals was developed. Significantly, a high degree of selectivity in the formation of trisubstituted alkenes was observed, thus avoiding the need for tedious separation of alkene stereoisomers. Further investigation of the utility of the silicon heterocycles obtained is in progress.

Acknowledgements

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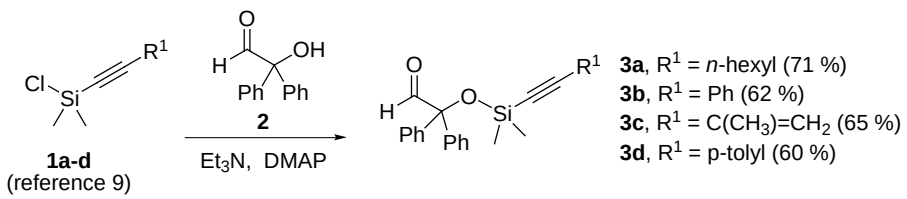
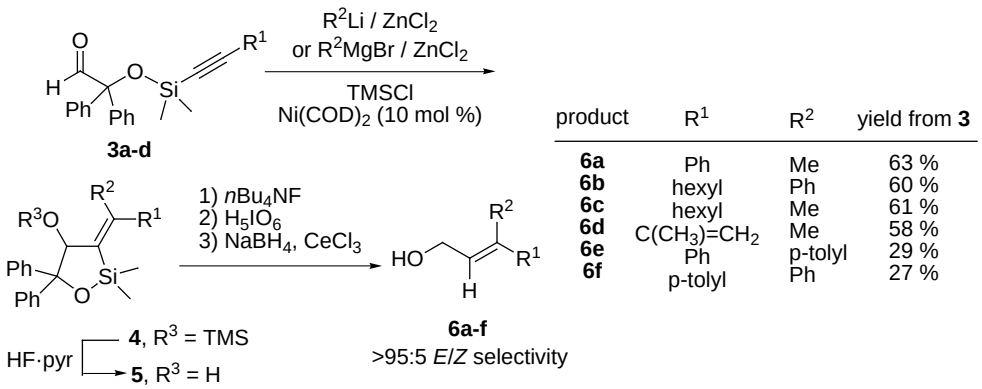


Scheme 3. Cyclization of silicon-tethered ynals.



Scheme 4. Silicon heterocycle formation and oxidative cleavage.

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11. *Preparation of silicon-tethered ynals* **3a–d**. A 0.25 M, CH_2Cl_2 solution of 2,2-diphenyl-2-hydroxyethanal[10] (1.0 equiv.) was cooled to 0°C, and Et_3N (2.5 equiv.), DMAP (10 mol%), and chloroalkynylsilane **1** were added sequentially. The resulting suspension was stirred at 0°C for 15 min, and standard extraction and SiO_2 chromatography afforded pure **3**. *Cyclization of ynals* **3a–d**. The appropriate organolithium or organomagnesium (4.0 equiv.) was added by syringe to a 0.6 M solution of $ZnCl_2$ (2.5 equiv.) in THF at 0°C. After 15 min, a 0.025 M THF solution of $Ni(COD)_2$ (10 mol%) was transferred by cannula to the above mixture, and the resulting solution was immediately transferred to a mixture of ynal **3** (1.0 equiv.) and Me_3SiCl (1.25 equiv.) at 0°C. After consumption of the ynal as judged by TLC analysis (typically 1 h), a standard extractive workup afforded product **4**. The crude product was dissolved in THF (0.1 M) at 0°C and was treated with $n Bu_4NF$ (6.0 equiv.) for 0.25–1.0 h at 25°C. Standard extraction and SiO_2 chromatography afforded the pure diol. *Preparation of allylic alcohols* **6a–f**. A 25°C ether solution of periodic acid (3.0 equiv.) and the allylic diol (1.0 equiv.) was stirred until the starting material was consumed as judged by TLC analysis (typically 0.25–1 h). The mixture was filtered, washed with $NaHCO_3$, and concentrated. The crude material was taken up in ethanol (0.025 M) and was treated with $CeCl_3 \cdot 7H_2O$ (4.0 equiv.) and $NaBH_4$ (4.0 equiv.) for 10 min at 0°C. Standard extraction and SiO_2 chromatography afforded pure **6a–f**.