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1,4-Hydrogen Radical Transfer as a New and Versatile Tool for the Synthesis of Enantiomerically Pure 1,2,3-Triols

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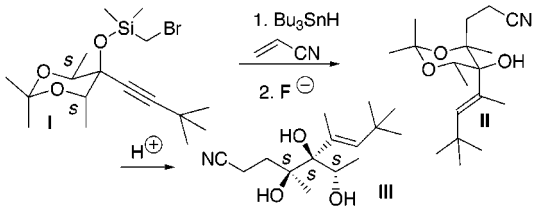
ABSTRACT



1,4-Hydrogen radical transfers can now be reliably envisaged in radical synthetic chemistry as demonstrated by the formation of the cyano derivative II from I. Due to related sequences involving this new translocation process, followed by a highly diastereoselective trapping of the resulting anomeric radical, access to intriguing enantiopure 1,2,3-triols such as III is available.

The principle of remote functionalization through radical hydrogen transfers is well-established. Generally, on the basis of very reactive heteroatomic radicals,[1] they have, for instance, served in the chlorination of steroids.[2] Highly reactive carbon-centered radicals (vinyl and aryl)[3] have also been utilized to provide useful radical translocations. Curran has notably defined the concept of protection and radical translocation (PRT) groups such as 2-*O*-(2-bromoaryl)-dimethylsilyl ethers,[4] aryl amides,[5] and 2-bromo-4-methoxyphenyl ether,[6] which due to their dual role, have proved very versatile in numerous synthetic applications.

For enthalpic and entropic reasons, 1,5- and 1,6-H transfers are generally the most widely encountered hydrogen transfers in these sequences.[7] In sharp contrast, the 1,4-H transfer has been observed less frequently, sometimes as a side reaction[8] and most often as a theoretical curiosity.[9] To the best of our knowledge, it has never been implemented in any synthetic sequence. Herein, we describe the first versatile use of a

† Fax: 33-1-44-27-73-60.

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(4) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900−5902.

(5) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343−7366.

(6) Curran, D. P.; Xu, J. *J. Am. Chem. Soc.* **1996**, *118*, 3142−3147.

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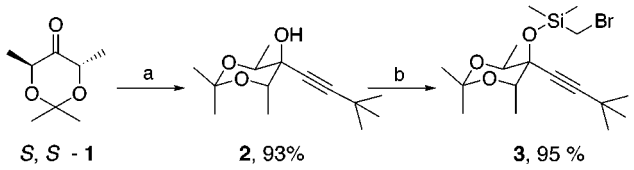
1,4-H transfer followed by a highly diastereoselective intermolecular trapping of the resulting radical as a means for the functionalization of 1,3-dioxane substrates and notably the preparation of highly substituted enantiomerically pure 1,2,3-triol derivatives.

To assess the synthetic potential associated with the 1,4-H translocation strategy, we studied the behavior of bromomethyldimethylsilyl ether **3**, easily obtained from the alkylation of the C_2-symmetric *S,S*-ketone **1**, described by Enders,[10] with the lithium *tert*-butylacetylide in the presence of $CeCl_3$,[11] followed by a classical silylation step of the resulting alcohol **2** (Scheme 1).

Scheme 1



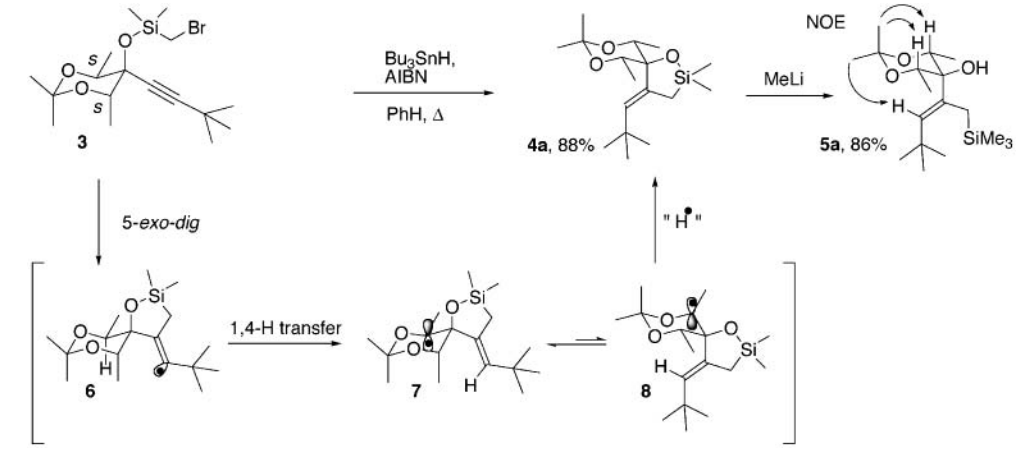
a) Me_3CCCLi, $CeCl_3$, THF ; b) $ClMe_2SiCH_2Br$, Imidazole, DMF.

When precursor **3** was submitted to radical reaction conditions,[12] only *meso* **4a** was isolated in 88% yield. Alternatively, a one-pot MeLi treatment of the cyclization crude product provided **5a** in 86% overall yield from **3**. The relative stereochemistry of **5a** was determined by NOE measurements. This epimerization was rationalized by the following sequence. After an initial 5-*exo*-*dig* cyclization, the protected vinyl radical **6** undergoes a completely chemoselective and diastereoselective 1,4-H transfer to the α-oxygenated position of the ring, at the expense of a statistically more favorable 1,5-H transfer involving a methyl group. This generates anomeric radical **7**, which as demonstrated by Giese[13] on mannosyl derivatives benefits from a 2-fold stabilization: a planar arrangement of the singly occupied p-orbital (SOMO) with the p-type lone pairs of the ring oxygen atom and delocalization of the SOMO into the σ^*-LUMO of the adjacent axial C−O bond. As a consequence, intermediate **7** would retain a chair conformation. Examination of the molecular models reveals, however, that no stannane reduction of **7** *syn* to the axial C−O bond is possible. Moreover, the α-face also appears to be very sterically hindered because of two axial methyl groups and the vinylic moiety. A simple chair−chair interconversion gives rise to **8** which can be reduced from the β-face through axial attack.[14] This results in a neat inversion of configuration to produce the *meso* derivative **4a** (Scheme 2).

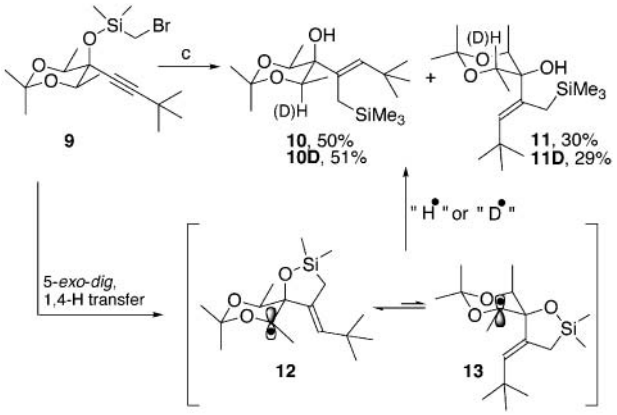
To confirm the high efficiency of the 1,4-H transfer and to gain a better insight into the controlling elements of the diastereoselectivity, we examined the behavior of the *meso* precursor **9**.[15] The radical cyclization of **9** provided two products: the *meso* compound **10** in 50% yield and the minor disymmetric product **11** in 30% yield (Scheme 3). Labeling with tin deuteride indicated complete deuterium incorporation at the α-oxygenated position (**10D** and **11D**), confirming complete 1,4-H transfer. In this case, the reduction of the resulting radical is not completely diastereoselective. A major reduction pathway involving **12** occurs, creating *meso* **10**. As in the previous case, after a chair−chair interconversion, conformer **13** can be considered and would be responsible for the formation of **11**. While radical **8** appears to be much more prone to reaction with tin hydride than **7**, only subtle steric effects allow a distinction between radicals **12** and **13**. Radical **12** displays an axial methyl group, and steric hindrance from the vinyl proton may also intervene. Radical **13** possesses two methyl groups in the axial position. This slightly more contributing steric bias must account for the less favored formation of **11**.

Having established the reliability of the 1,4-H transfer in this series, we applied it for the synthesis of enantiopure substrates. A single diastereoselective trapping of intermediate radical **8** should provide access to various enantiopure 1,2,3-triols. Our initial trial was accomplished with Bu_3SnD, giving a consistent yield (85%) of **5aD** (Scheme 4). Radical **8** could also add to activated olefins (Table 1, entries 2 and 3) to furnish diastereomerically, and thus enantiomerically, pure adducts **4b** and **5c** (see below for a proof of the

Scheme 2



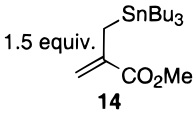
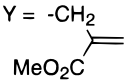
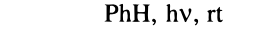
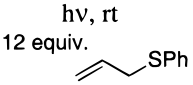
Scheme 3



c) 1. Bu_3SnH or Bu_3SnD, AIBN, PhH, Δ ; 2. MeLi.

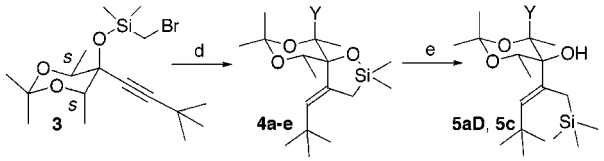
enantiomeric purity). Cyanide **4b** is a nice crystalline solid, and its relative stereochemistry was confirmed by an X-ray analysis.[16] However, a major issue in these reactions was the stannane competitive reduction of **8**. To overcome this side reaction, we focused on hydride-free reaction conditions

Table 1. Functionalization of the 1,3-Dioxane Moiety of **3**

Entry	Conditions	Product	Yield %
1	Bu_3SnD, AIBN, PhH, Δ	**5aD**, Y = D	85[a]
2	Bu_3SnH, AIBN, PhH, Δ, 15 equiv.	**4b**, Y = CH_2CH_2CN	52[b]
3	Bu_3SnH, AIBN, PhH, Δ, 15 equiv. 	**5c**, Y = $CH_2CH_2SO_2Ph$	36[a,c]
4	AIBN, PhH, Δ, 1.5 equiv.  **14**	**4d**, Y = 	32[d]
5	Bu_3SnH, AIBN, PhH, hν, rt, 15 equiv. 	**4b**	56[e]
6	AIBN, PhH, hν, rt, 12 equiv. 	**4e**, Y =	61[f]

[a] Overall yield from **3**. [b] *meso* adduct **4a** was isolated (24%). [c] *meso* adduct **5a** was isolated (23%). [d] In addition, diastereomeric cyclopropanes **15** (20%) were formed. [e] 86% yield based on recovery of **3**. [f] 72% yield based on recovery of **3** and *meso* adduct **4a** was isolated (23%).

Scheme 4



d) see Table 1; e) MeLi.

and we examined the behavior of **3**, with stannyl acrylate **14**. Two adducts, the expected compound **4d** (32%) and hexasubstituted cyclopropanes **15**,[17] as a 2:1 mixture of diastereomers, were obtained. The formation of **15** presumably originates from a 3-*exo-trig* cyclization of radical **7**, followed by addition to **14**. This example adds to the rather limited list of radical cyclopropanations.[18] Once again steric factors can be invoked. Probably due to its bulkiness, the reaction of stannyl acrylate **14** with **8** is slow. No reduction is possible in these conditions, and the 3-*exo-trig* cyclization appears to be the only option.

Photochemical reaction conditions proved also rewarding. A cleaner reaction was obtained with acrylonitrile (entry 5),

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(11) For a recent review, see: Liu, H.-J.; Shia, K.-S.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803−3830.

(12) For a review on this chemistry, see: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854.

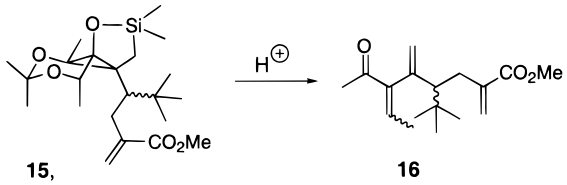
(13) a) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H. G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896−898. (b) Korth, H. G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1453−1459. (c) For a recent discussion of this, see: Martin, J.; Jamarillo G.; L. M.; Wang, P. G. *Tetrahedron Lett.* **1998**, *39*, 5927−5930.

(14) For examples of selective axial trapping of closely related radicals, see: (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 8**,** 969−980. (b) Sugimura, T.; Goto, S.-i.; Koguro, K.; Futagawa, T.; Misaki, S.; Morimoto, Y.; Yasuoka, N.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 505−508. (c) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (d) Rychnovsky, S. C.; Skalitzky, D. J. *Synlett* **1995**, 555−556. (e) ref 3c.

(15) Precursor **9** was obtained after silylation (91%) of the corresponding *meso* alcohol, obtained after complete equatorial alkylation of the symmetric ketone (85%), see: Polo, C.; Ramos, V.; Torroba, T.; Rodríguez, M. L.; Bossis, R.; Marcaccini, S.; Pepino, R. *Heterocycles* **1991**, *32*, 1757−1762.

(16) Crystallographic data for **4b** have been deposited at the Cambridge Crystallographic Data Centre (File CCDC 145900).

(17) Hexasubstituted cyclopropanes **15** showed some instability in acidic medium ($CDCl_3$ solvent of a NMR tube) and rearranged to acyclic substrate **16**.



15, 2 dias. 2 : 1. **16**

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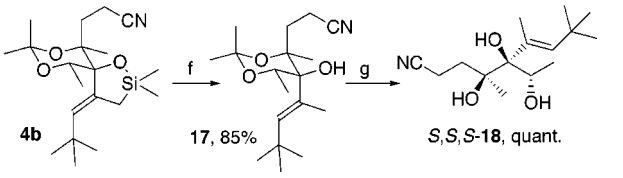
since very little of **4a** (<5%) was isolated and 56% of **4b** was obtained. These conditions also allowed the allylation of radical **8**, which could not be achieved by using the plain tributylallystannne in refluxing conditions. Photolysis of **3** in the presence of 12 equiv of allyl phenyl sulfide resulted in the formation of allylated adduct **4e** in 61% yield, at 85% conversion (entry 6). A non-negligible amount of *meso* adduct **4a** (23%) was observed in this reaction, and we suspect the allyl sulfide to also play the role of a hydride source.

Finally, triol *S*,*S*,*S*-**18** was synthesized from **4b** in two steps including a protodesilylation and a ketal cleavage in acidic medium in 85% overall yield (Scheme 5). The optical purity

Scheme 5



f) Bu_4NF on SiO_2, DMF, 60°C; g) AcOH, H_2O, 60°C.

of **18** was probed by condensing the secondary alcoholic functionality of **18** on the (*R*)- and (*S*)-Mosher chlorides. For each diastereomer, no trace of the other diastereomer was detected by ^{19}F NMR.

In conclusion, we have shown that an enantiopure C_2-symmetric 1,3-dioxane moiety is readily functionalized through the use of a new radical sequence combining the previously unexploited 1,4-H transfer and a highly diastereoselective trapping of the resulting anomeric radical. A variety of organic functionalities could be appended, setting two adjacent enantiopure quaternary centers,[19] and opening an access to intriguing enantiopure 1,2,3-triols. Further studies are now directed toward the synthesis of biologically relevant polyol systems.

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Supporting Information Available: Spectral data, experimental procedures, ^{19}F of Mosher esters of **18**, and X-ray data for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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