Stereoinversion

DOI: 10.1002/anie.201308803

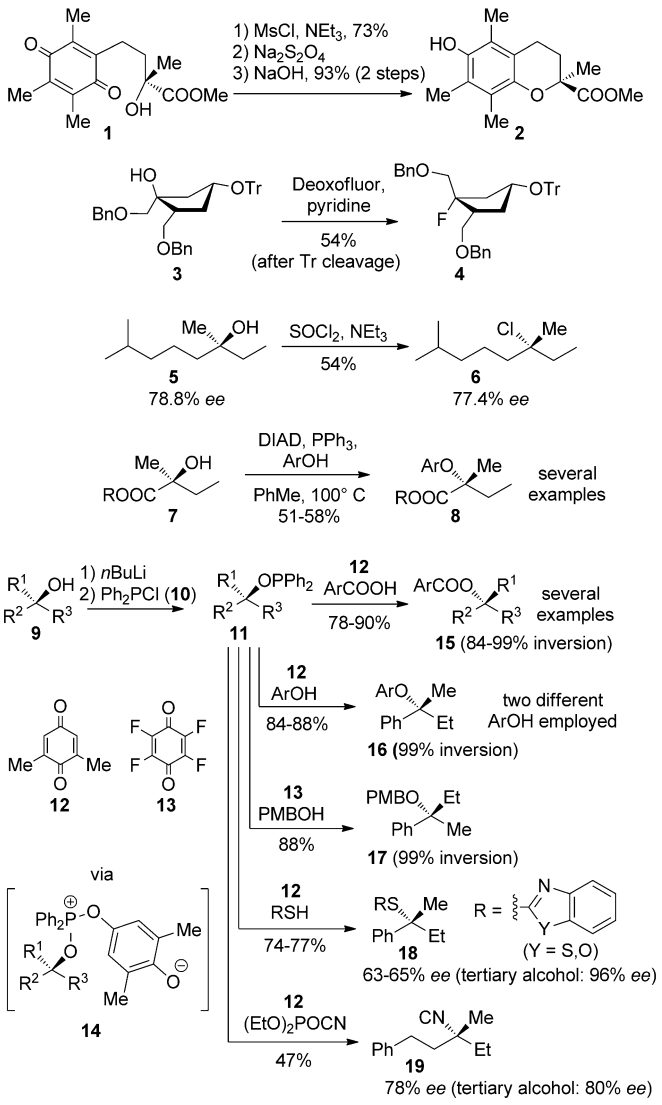
Tertiary Alcohols as Substrates for S_N2-Like Stereoinversion

*Andreas F. B. Räder and Konrad Tiefenbacher**

isocyanides · nucleophilic substitution · stereoinversion · tertiary alcohols

According to organic chemistry textbooks, the bimolecular nucleophilic substitution reaction (S_N2) is limited to primary and secondary substrates. In the case of stereogenic secondary carbon electrophiles, a clean stereoinversion can be observed due to the selective backside attack of the nucleophile. On tertiary electrophiles, based on steric arguments, only the S_N1 mechanism is applicable, resulting in a loss of stereochemical information at the affected carbon center. However, an inspection of the primary literature reveals that there are several exceptions to this rule.

We herein focus on examples where a formal S_N2 reaction was successfully realized on asymmetrically substituted tertiary alcohols (Scheme 1). Cohen and co-workers, building on earlier work,[1] demonstrated that an intramolecular cyclization of quinone **1** was feasible with inversion at the tertiary center.[2] Mesylation of the hydroxy group, reduction of the quinone unit, and base-promoted cyclization furnished chromane **2** in excellent yield. Samuelsson and co-workers successfully converted tertiary cyclopentanol **3** into the fluorinated compound **4**.[3] The Müller group introduced a chlorine substituent at tetrahydrolinalool (**5**) with nearly complete inversion.[4] Shi and co-workers demonstrated that a Mitsunobu reaction, utilizing phenols as nucleophiles, was successful with a substrate in which a tertiary hydroxy group is adjacent to an ester group (**7**→**8**).[5] Mukaiyama et al. utilized chlorodiphenylphosphine (**10**) and quinones **12** or **13** to activate tertiary alcohols in situ via intermediate **14** and displaced the phosphanyloxy group with a variety of nucleophiles. Employing aryl carboxylic acids, phenols, and 4-methoxybenzyl alcohol they were able to achieve excellent degrees of inversion of configuration (**15**–**17**).[6] The use of thiol nucleophiles was explored with a single chiral tertiary alcohol substrate and only modest degrees of inversion were obtained (**18**).[7] The Mukaiyama group also presented a single example with cyanide as a reaction partner which gave good degrees of inversion, albeit in modest yield (**19**).[8] Although several examples have been described in the literature, the scope is rather narrow or has remained unexplored. Especially limiting is the range of nucleophiles, restricted mainly to oxygen species.



Scheme 1. Examples of nucleophilic substitutions on tertiary hydroxy groups which exhibit good degrees of stereoinversion. PMB: *para*-methoxybenzyl.

The Shenvi group recently reported on the successful use of trimethylsilyl cyanide (TMSCN) as an N-nucleophile and demonstrated the wide scope of this transformation, which consists of two steps (Figure 1 a).[9] First, the tertiary alcohol is

[*] M. Sc. A. F. B. Räder, Prof. Dr. K. Tiefenbacher
Department Chemie, Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
E-mail: konrad.tiefenbacher@tum.de

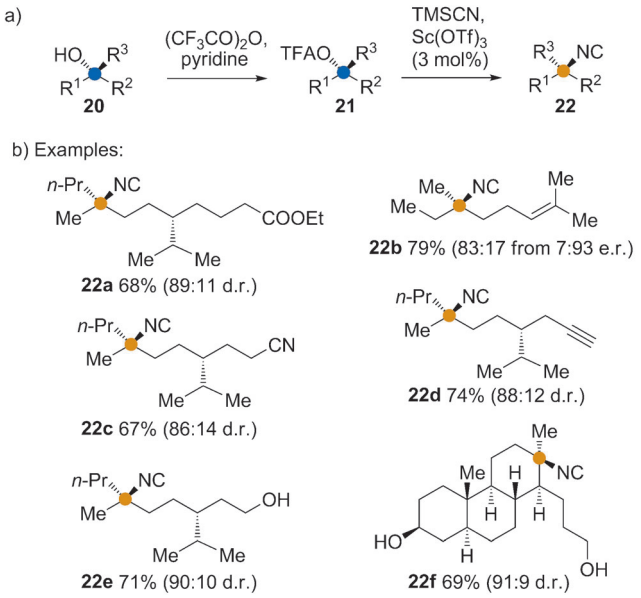


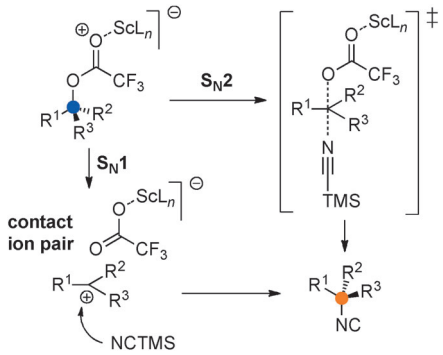
Figure 1. a) Two-step conversion of tertiary alcohols into isocyanides with inversion of configuration. b) Selected examples of reaction products.

converted into the trifluoroacetate **21**. After an aqueous workup, the crude trifluoroacetate is treated with catalytic amounts of scandium(III) triflate (3 mol%) and an excess of TMSCN to yield the tertiary isocyanide **22** in generally good yields and with good stereoselectivities. Several acyclic and cyclic terpene-derived tertiary alcohols were successfully converted (for examples see Figure 1b). The method had initially been applied in the total synthesis of a marine diterpene.[10]

The described method displays a very good functional-group tolerance. The presence of alkene, alkyne, ester, nitrile, or dihydroquinone moieties does not affect the stereoselectivity (Figure 1b), although with Lewis basic functional groups, higher catalyst loadings were necessary due to decreased reaction rates. Even more interesting is the fact that unprotected primary and secondary hydroxy groups are not affected under the reaction conditions! They are converted into the respective trifluoroacetates but these are just spectators in the displacement step: after liberation of the alcohol functionality by treatment with triethylamine in methanol, the products containing a primary or secondary hydroxy group (**22e** and **22f** in Figure 1b) were obtained in good yields. It was further demonstrated that the obtained tertiary isocyanides can be transformed to a variety of functional groups. Hydrolysis with aqueous HCl provides chiral *tert*-alkyl amines, while hydrolysis under milder conditions provides formamides. Alternatively the isocyanide can also be transformed to an isothiocyanate.

The authors also describe some limitations to the inversion of tertiary hydroxy groups. Cyclohexanols proved to be problematic substrates as axial tertiary hydroxy groups reacted with stereoretention. This was attributed to the conformational freedom of the monocyclic ring system, since with the more rigid decalin the expected stereoinversion was observed. Another limitation concerns highly congested tertiary alcohols with branched substituents: they gave only low diastereoselectivities under the described conditions.

The mechanism of the reaction has not been fully established, but the authors present two alternatives. The high degree of stereoinversion could stem from a genuine S_N2 mechanism. Alternatively and more likely a S_N1 mechanism would be operational where the cationic intermediate is present as a contact ion pair, thereby efficiently shielding one face of the reactive species from attack of the nucleophile (Scheme 2).



Scheme 2. Possible reaction mechanism explaining the observed stereoinversion. L = ligand (OTf or TMSCN).

In summary, the Shenvi group reported the first robust method to convert tertiary alcohols into isocyanides with inverted configuration. Especially interesting is the fact that tertiary hydroxy groups are converted selectively in the presence of unprotected primary and secondary hydroxy groups, completely reversing the classical S_N2 reactivity. This work will increase interest in the area of stereoinversion at tertiary electrophiles which hopefully will result in an expansion of the chemical toolbox available to organic chemists.

Received: October 9, 2013
Published online: December 4, 2013

[1] P. Schudel, H. Mayer, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *46*, 333.
[2] N. Cohen, R. J. Lopresti, C. Neukom, *J. Org. Chem.* **1981**, *46*, 2445.
[3] J. Wachtmeister, A. Mühlman, B. Classon, B. Samuelsson, *Tetrahedron* **1999**, *55*, 10761.
[4] P. Müller, J.-C. Rossier, *J. Chem. Soc. Perkin Trans. 2* **2000**, 2232.
[5] Y.-J. Shi, D. L. Hughes, J. M. McNamara, *Tetrahedron Lett.* **2003**, *44*, 3609.
[6] a) T. Mukaiyama, T. Shintou, K. Fukumoto, *J. Am. Chem. Soc.* **2003**, *125*, 10538; b) T. Shintou, T. Mukaiyama, *J. Am. Chem. Soc.* **2004**, *126*, 7359.
[7] T. Mukaiyama, K. Ikegai, *Chem. Lett.* **2004**, *33*, 1522.
[8] K. Masutani, T. Minowa, Y. Hagiwara, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1106.
[9] S. V. Pronin, C. A. Reiher, R. A. Shenvi, *Nature* **2013**, *501*, 195.
[10] S. V. Pronin, R. A. Shenvi, *J. Am. Chem. Soc.* **2012**, *134*, 19604.

