

Dondoni.⁴⁴ 2-TST is a metalated heterocycle that was prepared in Dondoni's laboratory and employed as a synthetic auxiliary. 2-TST undergoes rapid and spontaneous carbodesilylation reactions with various C-electrophiles for instance ketenes, acyl chlorides, aldehydes, and heteroaryl cations producing the corresponding 2-substituted thiazoles in good yields. Reaction with chiral aldehydes has been shown to occur with good *anti*-diastereoselectivity to produce compounds, which upon conversion of thiazole to formyl group furnishing aldehydes, possess one extra carbon atom. There are two main properties of the thiazole ring that have render this methodology effective: i) its tolerance to a wide range of reaction conditions allowing for elaboration of the substrate in which it has been introduced and ii) easy transformation into the formyl group under almost neutral conditions, thus leaving stereocenters untouched as well as acid- or base-sensitive functionally groups present in the molecule. After the addition of 2-TST, a sequence of simple and high-yielding transformations, namely OH-protection, *N*-methylation, reduction and finally hydrolysis, can be conveniently carried out to yield the desired aldehyde, as shown below.

Chemists at Hoffman-La Roche applied this methodology toward the large scale synthesis of the HIV protease inhibitor saquinavir (Ro 31-8959), a drug that was later approved by the USFDA in 1995 for the treatment of AIDS. As part of this work, they employed 2-TST to produce a starting material comprising the chiral aldehyde for the hydroxyethylamine isosteric dipeptide intermediate, shown below. With the mono-protected nitrogen atom on the amino aldehyde, the desired *anti*-alcohol was formed as a minor product, the ratio of major:minor being 3:2. The target aldehyde was obtained in low overall yield, and as a result, the approach had to be abandoned in favor of another approach.⁴⁵ Yet the potential of this approach is well reflected due to its operational simplicity. Interestingly, Dondoni et al. later demonstrated that the *anti*-selectivity could be well realized by utilizing the equivalent bis-*N,N'*-protected amino aldehyde (phenylalaninal), however the process involved additional steps.⁴⁶ The homologation methodology has been described as practical, simple, highly stereoselective, and chemically effective.⁴⁷

