

Silicon–(Thio)urea Lewis Acid Catalysis

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S Supporting Information

ABSTRACT: We present a new class of catalysts based on the combination of *N,N'*-diaryl(thio)ureas and weak silicon Lewis acids (e.g., SiCl₄). Such silicon–(thio)urea catalysts effectively catalyze the stereospecific rearrangement of epoxides to quaternary carbaldehydes.

Both (thio)urea¹ and silicon-based catalysts have been successful individually for a large variety of reactions. Herein we show that the use of a catalyst that combines an *N,N'*-diaryl(thio)urea with a weak SiCl₂R₂ Lewis acid is a powerful new approach. There are three strategies to activate silicon for catalysis: incorporation into a strained cycle,² connection to a strongly electron-withdrawing group,³ and activation with Lewis bases.⁴ Here we combine the first and second approach by *in situ* formation of a strained silacycle^{2h} from readily available precursors: (thio)urea derivatives, halosilanes, and tertiary amines (Scheme 1).

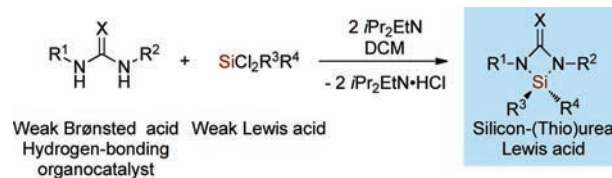
We chose as our test reaction the rearrangement⁵ of trisubstituted epoxides to aldehydes, which is demanding in terms of selectivity for the alkyl versus hydrogen shift, availability of catalytic variants, and stereospecificity (Scheme 2). For instance, Pd,⁶ Bi,⁷ Ir,⁸ In,⁹ V,¹⁰ Er,¹¹ Fe,¹² and Cu¹³ complexes promote the hydrogen shift, while B,¹⁴ Al,¹⁵ and Cr¹⁶ favor alkyl migration. The rearrangement of alkyl groups *cis* to an aryl moiety is particularly challenging; indeed, such alkyl migrations occur stereospecifically only for Cr complexes.¹⁶ The selectivities are highly sensitive to the substitution pattern of the epoxide. Quaternary carbaldehydes are versatile building blocks in organic synthesis and are attractive targets for catalysis.

1-Phenyl-1,2-cyclohexene oxide (**1a**) was selected to determine the optimal conditions for the rearrangement. Various chlorosilanes **X** were chosen to react with thiourea **T1** to give the corresponding catalysts **T1·X**. The rearrangement proceeded well in polar aprotic solvents such as dichloromethane (DCM), chloroform, and acetonitrile. In tetrahydrofuran (THF), toluene, and EtOAc, no product formed. No combination of reagents other than that given in Scheme 3 led to the rearrangement product [for details, see the Supporting Information (SI)].

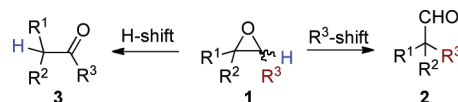
The yield of the rearrangement may depend on the electron-withdrawing ability of the (thio)urea derivative or the propensity for formation of the catalyst (**TX·A**–**UX·A**) by SiCl₄ (**A**) in combination with various *N,N'*-diaryl(thio)ureas (**TX**–**UX**) (Scheme 4).

Catalyst **T1·A** proved to be the most reactive and was applied in the rearrangement of various trisubstituted epoxides

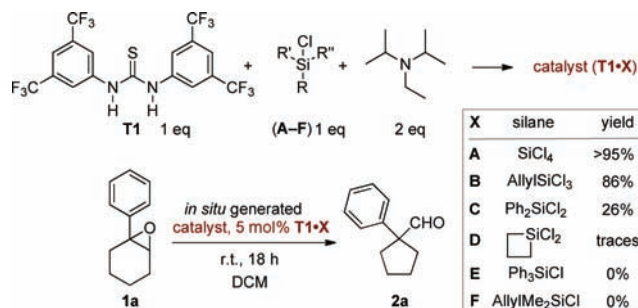
Scheme 1. In Situ Preparation of the Silicon–(Thio)urea Catalyst (X = O, S)



Scheme 2. Rearrangement of Epoxides to Aldehydes or Ketones Catalyzed by Lewis Acids



Scheme 3. Screening of Silane Precursors^a

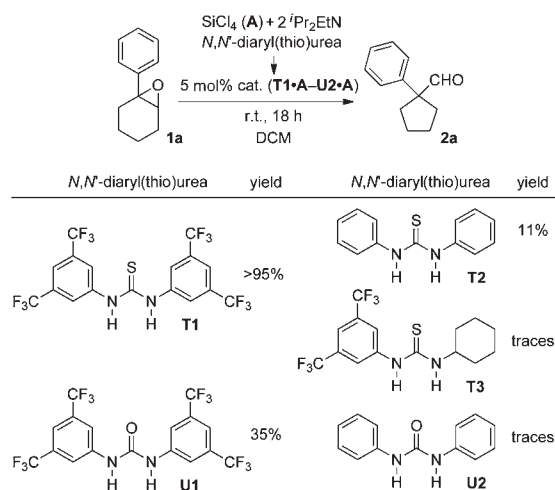


^a NMR yields are given.

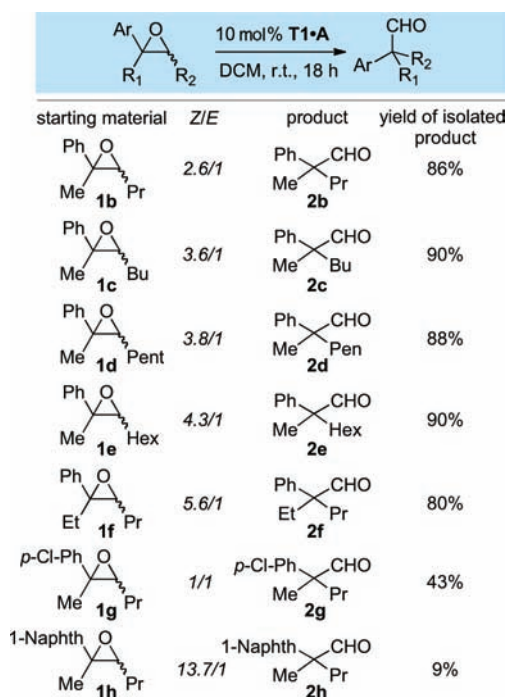
(Scheme 5). The precursor alkenes were prepared by a Wittig reaction that produced mixtures of *E* and *Z* isomers; *m*-chloroperoxybenzoic acid (*m*-CPBA) oxidation furnished the corresponding epoxides. The product distributions and conversions as well as the *E/Z* ratios of the unreacted epoxide starting materials for the rearrangement are summarized in Scheme 5 and the SI. Typically, the alkyl shift *trans* to the aryl moiety was considerably faster than that for the *cis* configuration, reaching completion within 1 h (vs 18 h for *cis*).

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Scheme 4. Screening of *N,N'*-Diaryl(thio)urea Precursors^a^a NMR yields are given.

Scheme 5. Rearrangement of Epoxides to Quaternary Aldehydes Using Silicon–Thiourea Catalyst T1·A



We then turned our attention to the viability of our structural proposal¹⁷ for the best catalyst T1·A (see Scheme 1) by utilizing a combination of NMR and IR spectroscopy, mass spectrometry (see the SI), and density functional theory (DFT) computations (Figures 1 and 2). The changes in the ¹H and ¹³C NMR chemical shifts upon addition of 1 equiv of *N,N*-diisopropylethylamine (DIPEA) to T1 (Figure 1A, B and D, E) suggest monodeprotonation of T1. Although the p*K*_a value of T1 is not known, it is likely to be just below or around that of protonated DIPEA (p*K*_a = 11.4); diphenylurea has a p*K*_a of 13.4,¹⁸ so it is reasonable to assume that the thiourea congener with the four added CF₃ groups is considerably more acidic. Hence, there should be a

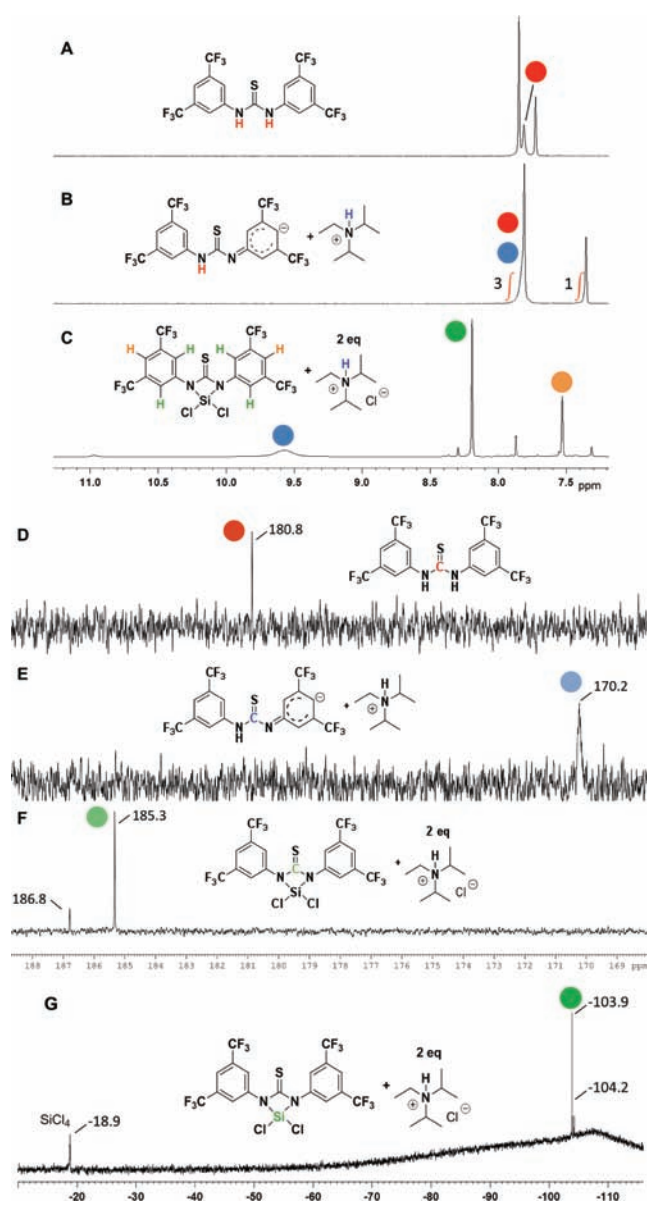


Figure 1. (A–F) ¹H and ¹³C NMR spectra, respectively, of (A, D) T1 alone; (B, E) after addition of 1 equiv of DIPEA (the NH signals are under the broadened signal at 7.8 ppm); and (C, F) after addition of 2 equiv of DIPEA and 1 equiv SiCl₄ to give T1·A. (G) ²⁹Si NMR spectrum of T1·A.

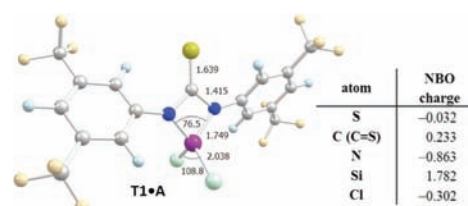
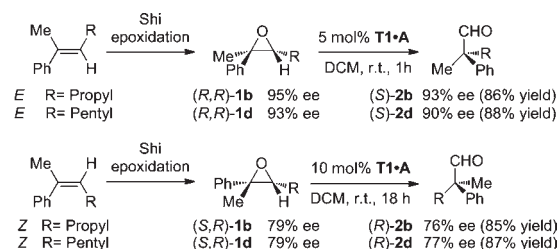
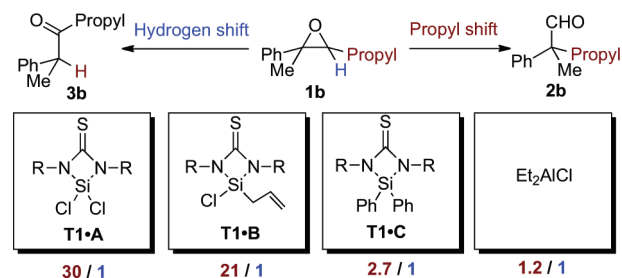


Figure 2. B3LYP/6-31+G(d,p)-optimized structure of T1·A. NBO charges (in e) and selected bond lengths (in Å) and angles (in deg) are shown.

protonation/deprotonation equilibrium between T1 and the base, as also evidenced by the disappearance (in part under the CH signal at 7.8 ppm) of the N–H resonances. The C=S carbon

Scheme 6. Stereospecificity of the Rearrangement and Absolute Configurations of the Products^a^a Isolated yields are given.

Scheme 7. Chemoselectivity: Alkyl versus Hydrogen Shift



signal appeared upfield (by 10.6 ppm), in agreement with stronger shielding of the delocalized anion. The IR spectra of the same solutions (Figure S3 in the SI) support this analysis: the single N–H signal for **T1** at 3375.2 cm^{-1} split into two and lost intensity significantly. Upon addition of 1 equiv of SiCl_4 (along with another 1 equiv of DIPEA) to this mixture, **T1**·**A** formed (Figure 1C, F), and the C=S carbon signal moved downfield by 15.1 ppm. The N–H signal no longer exchanged and appeared at 9.6 ppm. Similar changes were observed in the ^{29}Si spectra (Figure 1G; also see the SI). We also identified a ^4J coupling of the thiourea ortho protons with Si, indicating that they must be in close proximity (Figure S17). The IR difference spectra (Figure S23) of a 1:2 mixture of **T1** and DIPEA with and without **A** also showed the disappearance of the **T1** N–H absorption (3400 cm^{-1}) and the appearance of the ammonium salt N–H bands at 2661 cm^{-1} .

Additionally, we identified small signals in the ^1H and ^{13}C NMR spectra (Figure 1C, F) indicative of a small concentration of another species, probably a dimer of **T1**·**A**. Our high-resolution (nanospray negative-ion mode) mass spectrometric experiments (Figures S18–S22) underline this observation. While it is unlikely that a spirocycle with Si in the center is involved,¹⁷ we were unable to draw definitive conclusions about the exact nature of this minor component.

B3LYP/6-31+G(d,p) computations (Figure 2; also see the SI) identified **T1**·**A** as a minimum with a planar four-membered central ring. The natural bond orbital (NBO) charges indicated that this structure may be regarded as an internal salt of a resonance-stabilized thiourea dianion with a Si dication. The large positive charge on Si in the complex suggests high tunability of the catalyst through substitution.

Next, the stereospecificity of the rearrangement was studied utilizing the *E* and *Z* isomers of **1b** and **1d** (Scheme 6). When 5 mol% **T1**·**A** was used, the enantioenriched (*E*)-epoxides

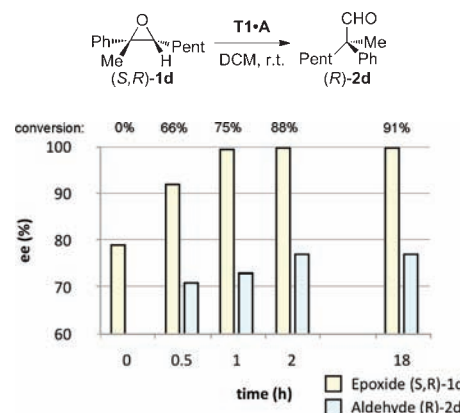


Figure 3. Change in ee over time in the rearrangement of (*S,R*)-**1d** to (*R*)-**2d** catalyzed by **T1**·**A**.

Scheme 8. Simplified Mechanistic Proposal for the Epoxide Rearrangements Catalyzed by **T1**·**X** [Ar = 3,5-Bis(trifluoromethyl)benzene]

rearranged in good yields to the corresponding aldehydes **2b** and **2d**, respectively, within 1 h with only marginal losses of enantiopurity. The absolute configurations of the products were determined by comparison with published data.¹⁹

The enantioenriched *Z* derivatives (*S,R*)-**1b** and (*S,R*)-**1d** (from Shi epoxidation)²⁰ underwent partial hydrogen shifts, leading to ketones as byproducts: 3% ketone **3b** (74% ee) and 5% ketone **3d** (76% ee) formed. We screened the chemoselectivities (Scheme 7) with **T1**·**X** and found that **T1**·**A** was the most selective, affording 85% aldehyde **2b** (76% ee) and only 3% ketone **3b** (74% ee). For comparison, the rearrangement of (*S,R*)-**1b** catalyzed by 25 mol % Et_2AlCl ²¹ in toluene gave 47% aldehyde (*R*)-**2b** stereospecifically, with the same stereochemistry as with **T1**·**X**. This implies that these catalyst systems are mechanistically similar.

Surprisingly, the enantiopurity of the rearranging (*S,R*)-**1b** and (*S,R*)-**1d** increased over time with all **T1**·**X** (as shown for **T1**·**A** in Figure 3). The product ee also increased until it reached that of the starting material. The increase in the enantiomeric purity of the starting material was not due to autocatalysis by the product, as demonstrated by a negative control experiment utilizing racemic **1b** with 5 mol% **T1**·**A** [(*R*)-**2b** (10%, 76% ee)]. We preliminarily rationalize these findings in terms of a mechanism similar to a kinetic resolution of nonracemic starting materials.²² The increase in ee during the reaction may be due to diastereomeric transition structures formed in the simplest case

through complexation of $T1 \cdot X$ with the starting material. This would lead to diastereomeric matched and mismatched combinations in the transition states (Scheme 8). A full mechanistic investigation is in progress.

We have shown that Lewis acid catalysis can be combined with (thio)urea catalysis, as exemplified by the novel catalyst $T1 \cdot A$ that enables the stereospecific rearrangement of trisubstituted epoxides to quaternary aromatic carbaldehydes. A natural extension of this work is the use of chiral thio(urea) derivatives and the application to enantioselective reactions.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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