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Silyl-Modified Analogues of 2-Tritylpyrrolidine: Synthesis and Applications in Asymmetric Organocatalysis

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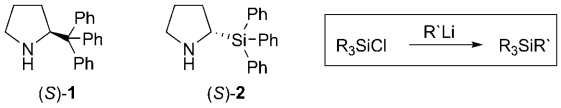
The design of efficient catalysts with new structural motifs[1] is one of the major challenges in the growing field of asymmetric organocatalysis.[2] Inspired by the dramatic effect of subtle steric and electronic modifications on catalyst activity,[2f] we set out to investigate the performance of silicon-based, enantiomerically pure pyrrolidines in organocatalytic reactions.[3] A remarkable feature of silicon is its tolerance of sterically demanding substituents, thus allowing straightforward access to quaternary silicon centers by nucleophilic substitution reactions of trialkylchlorosilanes (Scheme 1).[3,4] Hence, a diverse array of novel catalyst scaffolds should be accessible, which are hitherto unknown for carbon-based pyrrolidine catalysts. Recently, Maruoka et al. reported the asymmetric α-benzyloxylation of aldehydes using (*S*)-2-tritylpyrrolidine [(*S*)-**1**] as organocatalyst.[5] The synthesis of (*S*)-**1** involves a nucleophilic addition to a nitrone followed by hydrogenolysis and resolution of (±)-**1**.



Scheme 1. Silicon analogue (*S*)-**2** of the organocatalyst (*S*)-**1** and general route to functionalized organosilanes.

These results prompted us to render the corresponding silicon analogue (*S*)-**2** and related derivatives available for a direct comparison of their catalytic performance in enamine catalysis (Scheme 1).[6]

In an accompanying quantum-chemical study, we aimed to rationalize silicon effects on the new catalytic systems by studying electronic as well as steric differences between the carbon and silicon analogues **1** and **2**. For this purpose DFT calculations were performed at the B3LYP/6-31+G(d) level. Based on the energy-optimized structures **A1** and **B1** of a meaningful conformer for both catalysts, we studied the NBO charge (Figure 1) and calculated the electrostatic potential (Figure 2).

The comparison of the decisive bond length between pyrrolidine C-2 and silicon or carbon, respectively, revealed a significant elongation of this bond changing from carbon (**A**) to silicon (**B**), which is clearly visible in the space-filling models **A2** and **B2** (Figure 2) and may have an effect on the stereochemical outcome in catalytic asymmetric reactions.[7] Due to the overcrowded substitution sphere, the respective C–C distance (1.589 Å) is slightly longer than endocyclic C–C bonds, while the C–Si length (1.915 Å) lies in the normal range for carbon–silicon bonds in aminoalkyl silanes.[8] Furthermore, the NBO analysis of **B1** indicates a high positive charge of 1.818 at the silicon center and a definite negative charge at the carbon atoms (−0.516 to −0.542) directly attached to silicon (Figure 1). By contrast, the carbon analogue **A1** shows a well-balanced negative charge distribution across the carbon-atom backbone. Consequently, the electronic structure causes a more negatively charged electrostatic potential around the phenyl-substituted silyl moiety when compared to 2-tritylpyrrolidine, shown at the fast surface models **A3** and **B3** (Figure 2). In view of polar transition states in enamine and iminium catalysis, these electronic features possibly contribute to a deeper insight into the activity of novel catalytic systems.[9]

As part of our studies on aminoalkyl silanes[8] and with respect to the lack of applications in amine catalysis, we next disclosed a convenient asymmetric route to enantiopure 2-

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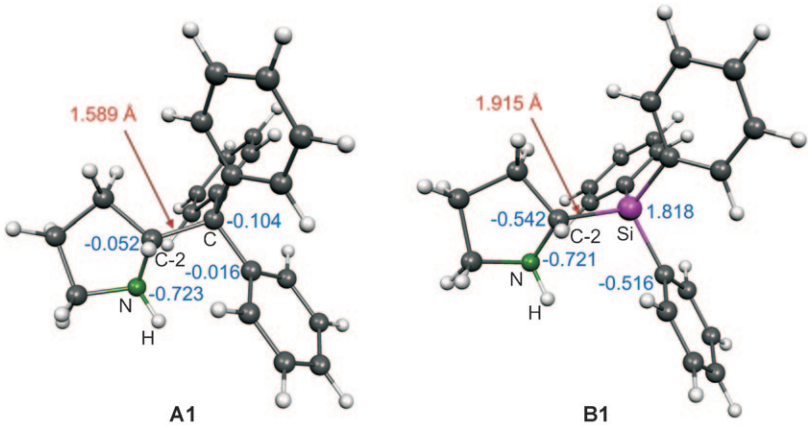


Figure 1. Molekel plot of pyrrolidines **1** (**A1**) and **2** (**B1**) including selected NBO charges and bond lengths; B3LYP/6-31+G(d).

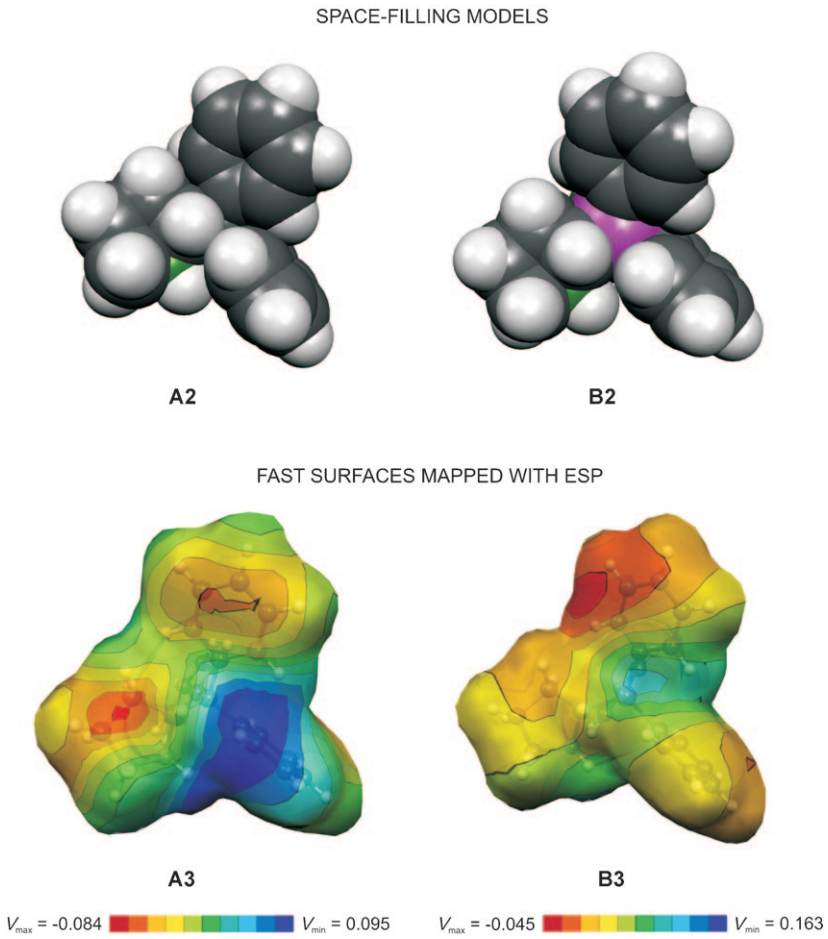
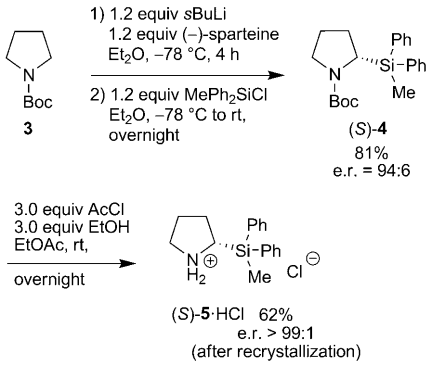


Figure 2. Space-filling models **A2** and **B2** and fast surfaces with mapped electrostatic potential (**A3**, **B3**) for the pyrrolidines **1** (left) and **2** (right).

silyl-substituted pyrrolidines as a conceptionally new class of potent organocatalysts. The generation of the stereogenic center adjacent to the nitrogen atom was achieved by asymmetric deprotonation of *N*-boc-pyrrolidine **3** with *s*BuLi in the presence of (−)-sparteine,[10] a method introduced by Beak and co-workers.[11] Subsequent reaction with methyldiphenylchlorosilane gave the desired silyl-substituted *N*-boc-pyrrolidine (*S*)-**4** in 81% yield with an e.r. of 94:6.[12] The deprotection of enantiomerically enriched (*S*)-**4** was carried out effectively according to a literature procedure[13] using acetyl chloride in ethanol to provide the respective hydrochloric salt (*S*)-**5**·HCl (Scheme 2). After recrystallization from 2-propanol, (*S*)-**5**·HCl was obtained as a single enantiomer in 62% yield. The enantiomeric ratio was determined by HPLC analysis on the basis of the boc-protected compound **4**.

X-ray crystallographic analysis of the HCl-salt (*S*)-**5**·HCl allowed the determination of its absolute configuration. The asymmetric unit contains two molecules of (*S*)-**5**, which are involved in hydrogen bond interactions (Figure 3).

An attempt to synthesize the triphenylsilyl-substituted pyrrolidine (*S*)-**7** (Scheme 3) in a similar manner by conversion of the enantiomerically enriched, lithiated *N*-boc-pyrrolidine with chlorotriphenylsilane was unsuccessful. Continuative exploratory studies were based on the consideration that the silane component has to be reactive enough at low temperatures to guarantee a high configurative stability of the chiral alkyllithium reagent[15] used in the course of the substitution reaction. In a following step the third phenyl group should be introduced again by nucleophilic attack at the silicon center. Initially, we focused on dialkoxysilanes as electrophiles of choice[16] for the generation of adequate alkoxy-functionalized *N*-boc-pyrrolidines, which are useful intermediates for further transformation reactions. Indeed, for the first time we examined synthetic access to triphenylsilyl-*N*-boc-pyrrolidine [(*S*)-**7**] via the



Scheme 2. Asymmetric synthesis of enantiomerically pure (*S*)-2-(methyldiphenylsilyl)pyrrolidine·HCl [(*S*)-**5**·HCl].

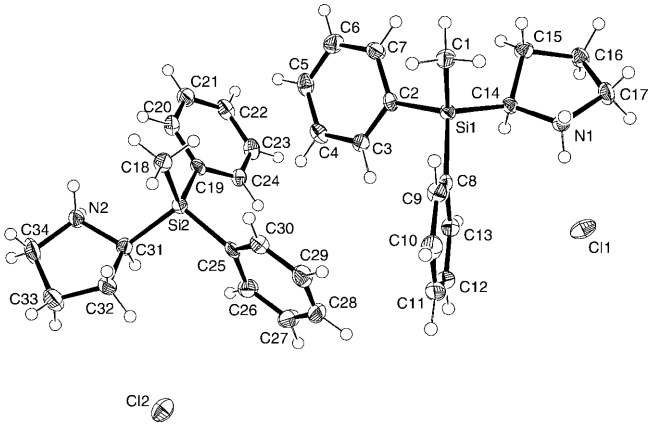
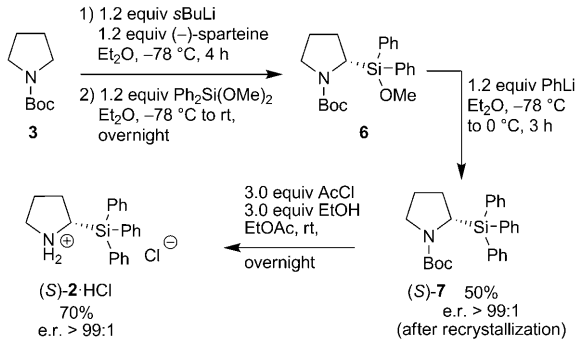


Figure 3. ORTEP plot of the molecular structure of (*S*)-2-(methyldiphenylsilyl)pyrrolidine·HCl [(*S*)-**5**·HCl].[14] Displacement ellipsoids drawn at the 50% probability level.



Scheme 3. Asymmetric synthetic route to enantiomerically pure (*S*)-2-(triphenylsilyl)pyrrolidine·HCl [(*S*)-**2**·HCl].

enantiomerically enriched methoxysilylpyrrolidine **6** and therefore to an appropriate precursor for the promising silicon analogue of the already known carbon catalyst **1**. As we found out, (*S*)-**7** was accessible in enantiomerically pure form by recrystallization from acetone. The enantiomeric ratio of (*S*)-**7** was determined by HPLC analysis. These findings led us to a simple asymmetric one-pot synthesis of (*S*)-**7** in overall 50% yield without the need for isolation and enantiomeric enrichment of the methoxysilylpyrrolidine **6** before further conversion to (*S*)-**7** (Scheme 3).

The absolute configuration of (*S*)-**7** was determined by X-ray crystallographic analysis (Figure 4).

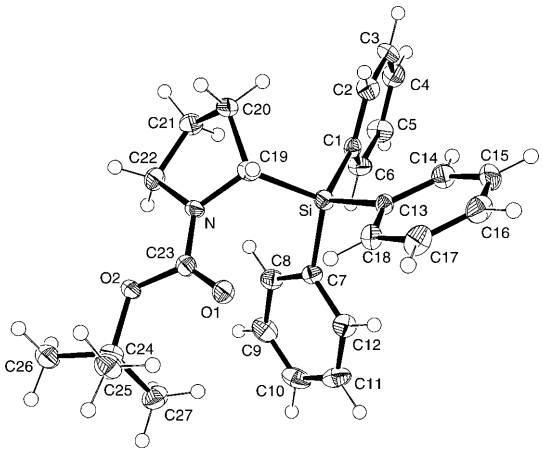


Figure 4. ORTEP plot of the molecular structure of (*S*)-2-(triphenylsilyl)-*N*-boc-pyrrolidine [(*S*)-**7**].[14] Displacement ellipsoids drawn at the 50% probability level.

Deprotection of (*S*)-**7** gave the enantiopure hydrochloride (*S*)-**2**·HCl in 70% yield (Scheme 3), which could be crystallized from chloroform affording single crystals suitable for X-ray structure determination analysis (Figure 5). For comparison, Figure 5 shows the molecular structure of the hydrochloric salt of (*S*)-2-tritylpyrrolidine [(*S*)-**1**·HCl]. The measured C1–C20 and C19–Si bond lengths of 1.573(2) Å and 1.904(3) Å, respectively, are slightly shortened compared with the corresponding distances in the calculated structures of the free amines **A1** and **B1**.[17] However, these results support the validity of our computational conclusions (Figure 5).

To benchmark the performance of (*S*)-**1** and (*S*)-**2**, both catalysts were tested in organocatalytic alkylations of enamines. As the first test reaction, we investigated the α-alkylation[18,19] of *n*-octanal (**9**) with bis[4-(dimethylamino)phenyl]-methanol (**10**),[20] recently developed by Cozzi and co-workers.[18c] Interestingly, in their studies only MacMillan's imidazolidinone catalysts[21] showed significant activity, whereas pyrrolidine-based catalysts[22] failed to catalyze the reaction with useful enantiomeric excess. In light of their observations, it is even more remarkable that both the trityl- and triphenylsilyl-substituted pyrrolidines (*S*)-**1** and (*S*)-**2** catalyze the S_N1-type reaction of **9** and **10** to the α-alkylated aldehydes (*R*)-**11** and (*S*)-**11**, respectively, albeit with moderate enantiomeric ratios and yields (Scheme 4). Attempts to optimize the reaction conditions are ongoing in our laboratories.

We also tested (*S*)-**1** and (*S*)-**2** in the conjugate addition[23] of propanal (**12**) to nitrostyrene (**13**).[1c,24,25] With (*S*)-2-trityl-

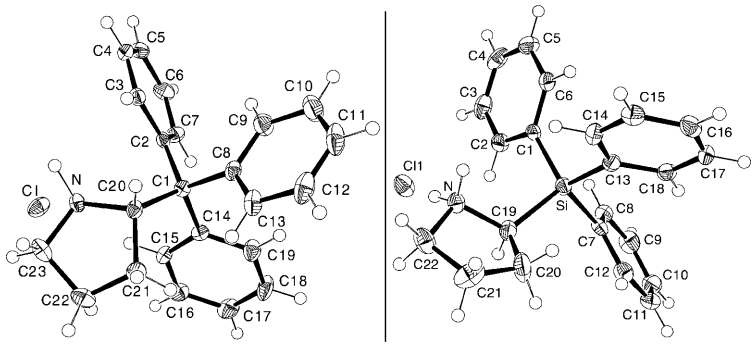
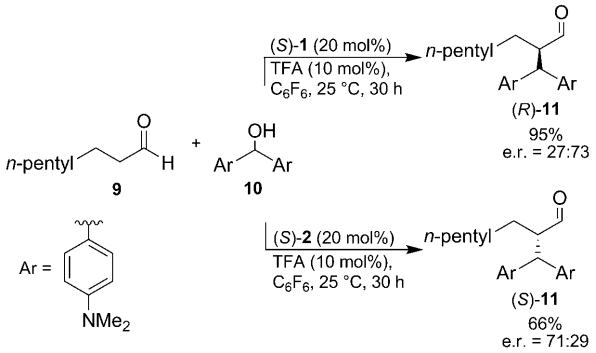


Figure 5. ORTEP plot of the molecular structures of (*S*)-tritylpyrrolidine [(*S*)-**1**·HCl] (left) and (*S*)-2-(triphenylsilyl)pyrrolidine·HCl [(*S*)-**2**·HCl] (right).[14] Displacement ellipsoids drawn at the 50% probability level.

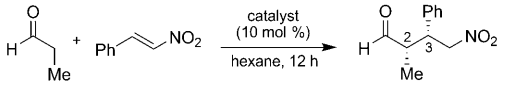


Scheme 4. Organocatalytic asymmetric α-alkylation of *n*-octanal (**9**) with bis[4-(dimethylamino)phenyl]methanol (**10**).

pyrrolidine [(*S*)-**1**] as the catalyst, the reaction was extremely sluggish and did not lead to full conversion after 72 h (Table 1, entry 1). The Michael adduct **14** was obtained in good yield but only moderate diastereoselectivity. Switching to the silicon catalyst (*S*)-**2** (Table 1, entry 2), the reaction was remarkably faster, affording nitroaldehyde **14** within 12 h with good diastereoselectivity (91:9) and an excellent enantiomeric ratio (97:3). Lowering the temperature to −20 °C raised the diastereomeric ratio to 95:5 without changing the enantioselectivity (Table 1, entry 3). However, the reaction rate was lowered. Most importantly, exchanging one phenyl group with a methyl group [(*S*)-**2** vs. (*S*)-**5**] had a negative impact on the enantioselectivity (Table 1, entries 4 and 5). These preliminary results suggest that a bulky substituent at C-2 on the pyrrolidine is essential for high enantioselectivity. Moreover, the longer Si–C distance between the pyrrolidine C-2 and the triphenylsilyl group might be the critical factor for retaining the catalyst's reactivity, as the comparable sterically demanding trityl substitutent clearly lowers the reactivity of the pyrrolidine catalyst.

In summary, we have reported the asymmetric synthesis of a new and promising class of chiral silicon-based pyrrolidine catalysts. Differing from the synthetic route to (*S*)-2-(methyldiphenylsilyl)pyrrolidine (*S*)-**5** using a chlorosilane as electrophile, the synthesis of the enantiomerically pure triphenylsilyl-substituted pyrrolidine (*S*)-**2** as the silicon analogue of tritylpyrrolidine [(*S*)-**1**)] has been employed according to a one-pot reaction via an in situ generated methoxysilane. In two model reactions, the enantioselective α-alkylation and the Michael reaction, (*S*)-**2** showed promising catalytic activity. Quantum-chemical studies as well as structural analysis provided insight into steric and electronic differences between the respective carbon- and silicon-substituted pyrrolidines. Future investigations will be concerned with the development of a wide variety of silyl-modified pyrrolidines with additional groups at the silicon center designated for bifunctional catalysis.

Table 1. Michael addition of propionaldehyde (**12**) and *trans*-β-nitrostyrene (**13**).[a]



Entry	Catalyst	Yield [%]	T [°C]	d.r.[b] (*syn*/*anti*)	e.r.[c]
1	(*S*)-**1**	52[d]	4	78:22	2:98
2	(*S*)-**2**	98	4	91:9	97:3
3[e]	(*S*)-**2**	97	−20	**95:5**	**97:3**
4	(*S*)-**5**	87	4	93:7	91:9
5	(*S*)-**5**	90	25	84:16	94:6

[a] Conditions: aldehyde **12** (2 mmol), nitroolefin **13** (0.2 mmol), catalyst (*S*)-**1**, (*S*)-**2**, (*S*)-**5** (0.02 mmol), solvent (1 mL), 12 h. [b] Determined by chiral HPLC. [c] Enantiomeric ratio (2*S*,3*R*)-**14**:(2*R*,3*S*)-**14** (*syn*-diastereomers) given. [d] Reaction was stopped after 72 h (incomplete conversion). [e] Reaction time: 48 h.

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Keywords: alkylation · asymmetric synthesis · organocatalysis · silicon · silylated pyrrolidines

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