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The highly enantioselective transformation of silylketenes into α-silylthioesters catalysed by cinchona alkaloids

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Abstract—The reaction of silylketenes with thiophenol, mediated by cinchona alkaloid catalysts, proceeds to give α-silylthioester products in good chemical yield and with enantiomeric excess values in the range 79–93%. The absolute configuration of one of the thioester products was determined by X-ray diffraction.

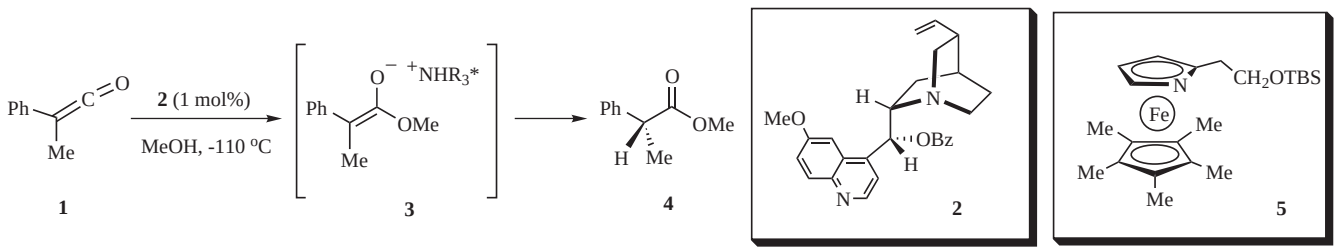
Forty years ago the research group of Pracejus reported a remarkable transformation in which simple ketenes, such as phenyl methyl ketene **1**, react with alcohols in the presence of sub-stoichiometric quantities of cinchona alkaloid catalysts, such as quinine derivative **2**, to give ester products **4** in up to 76% ee, Scheme 1.[1]

Despite the obvious potential of this reaction for the asymmetric synthesis of carboxylic acid derivatives rather little directly related research has been carried out subsequently.[2] Quite recently this process was re-examined by Fu and co-workers, employing the synthetic azaferrocene derivative **5** as catalyst in place of the alkaloid, and selectivities of up to 80% ee were obtained.[3]

In this communication we describe our independent studies in this area, which have uncovered a novel variant of this reaction which enables the highly enantioselective (typically 80–90% ee) transformation of silylketenes into chiral thioester products.

On recognising the potential of the Pracejus asymmetric transformation we were immediately attracted to the possibility of applying the reaction to silylketenes.[4] These compounds are readily prepared, are reasonably stable and might lead to interesting chiral silylesters when transformed according to Scheme 1. Following established protocols, alkylation of the parent α-silylacids **6** (R = Me, Ph), gave a range of derivatives **7**, which could then be converted into the required silylketenes **8** (Table 1).[5]

These preparations were not optimised and it is thought that the yields of many ketenes could be improved. In our hands the alkylations of trimethylsilylacetic acid **6** (R = Me) were more facile than those of the more



1 3 4 2 5

Scheme 1.

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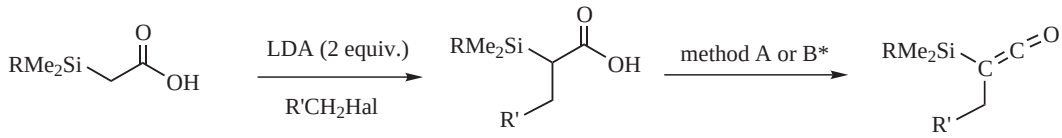
Table 1. Preparation of silylketenes



6 **7** **8**

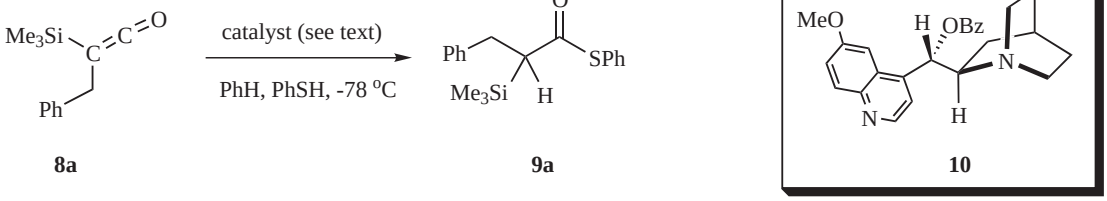
Entry	R	R′	**7** (%)	**8** (%)
1	Me	Ph	**7a** 93	**8a** 45 (A)
2	Me	2-Naphthyl	**7b** 88	**8b** 48 (A) 65 (B)
3	Me	^{n}Pr	**7c** 72	**8c** 29 (A)
4	Me	$PhCH_2$	**7d** 90	**8d** 27 (A)
5	Ph	Ph	**7e** 71	**8e** 67 (B)
6	Ph	$(CH_2)_2CH{=}CH_2$	**7f** 41	**8f** 72 (B)

Method A: (i) $(COCl)_2$, DMF, CH_2Cl_2 (ii) Br_2 (iii) Zn, THF. Method B: $(COCl)_2$, Et_3N.

hindered dimethylphenylsilyl derivative **6** (R = Ph). For the conversion of acids **7** into the corresponding ketenes we employed either dehalogenation (method A) or dehydrochlorination (method B).[6]

Initial attempts to apply the Pracejus reaction to a typical silylketene **8a** were very disappointing, with very little reaction being observed in the presence of methanol and alkaloid catalyst at the low temperature usually employed. After some experimentation we turned instead to PhSH as a more nucleophilic partner for the ketene and found that smooth addition occurred to give α-silylthioester **9a** (Scheme 2).[7]

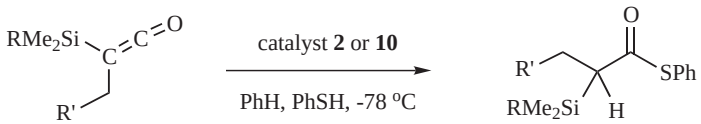
To our delight, the use of 2.5–10% of quinine derivative **2** gave (−)-**9a** in yields of ca. 95% and ee values of



8a **9a** **10**

Scheme 2.

Table 2. Asymmetric synthesis of α-silylthioesters



8 **9**

Entry	Ketene	Catalyst	Product (%)	ee[a]
1	**8a**	**2**	(−)-**9a** (97)	91
2	**8a**	**10**	(+)-**9a** (99)	91
3	**8b**	**2**	(−)-**9b** (99)	93
4	**8b**	**10**	(+)-**9b** (99)	94
5	**8c**	**2**	(−)-**9c** (99)	89
6	**8d**	**2**	(−)-**9d** (86)	89
7	**8e**	**2**	(+)-**9e** (94)	82
8	**8e**	**10**	(−)-**9e** (84)	79
9	**8f**	**2**	(+)-**9f** (86)	84[b]
10	**8f**	**10**	(−)-**9f** (84)	82[b]

[a] Determined by HPLC, see: Ref. 10.
[b] Approximate values due to incomplete enantiomer separation.

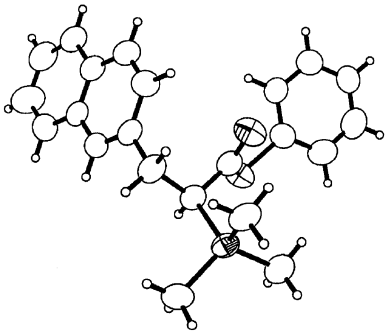


Figure 1. X-Ray structure of (+)-**9b**.

90–93%. The catalyst loading could be reduced to 1%, but the reaction then took longer to proceed to completion and there was a drop in the selectivity to around 80% ee. Commercially available $(DHQ)_2PHAL$ gave similar results to **2**,[8] and the use of the pseudoenantiomeric quinidine-derived catalyst **10** resulted in the formation of (+)-**9a** in similarly high yield and similar ee of 84%. Lowering the reaction temperature to ca. −105°C or running the reaction at −45°C resulted in lower ee values, with some by-product formation being observed at the higher temperature.

Following this initial exploration we applied the optimal conditions to the ketenes prepared earlier and obtained the results shown in Table 2.[9]

The reactions are very clean, and give high yields of thioester products in good enantiomeric excess. In the case of the trimethylsilyl derivatives the quinine catalyst **2** gave (−)-products and the quinidine catalyst (+)-products, with the reverse being apparent for the dimethylsilyl compounds. In the case of (+)-**9b** we were able to crystallise the product and obtain an enantiomerically pure sample suitable for X-ray analysis (Fig. 1).[11]

The structure clearly shows the (*S*)-configuration for this product and, given the trends in the sign of $[\alpha]_D$ values and HPLC properties, we believe that the other members of the trimethylsilyl series of products are also of the same configuration.

The results can be rationalised on the basis of the mechanism originally proposed by Pracejus, i.e. analogous to that shown in Scheme 1, which involves initial addition of thiol to the ketene to generate a thioester enolate that undergoes stereoselective proton transfer from the chiral ammonium counterion to the enolate carbon centre. Alternatively, it is possible that the initial attack on the ketene **11** is by the cinchona alkaloid to generate an ammonium enolate **12** that protonates selectively and then undergoes attack by thiolate to give the product **14** and regenerate the alkaloid catalyst.

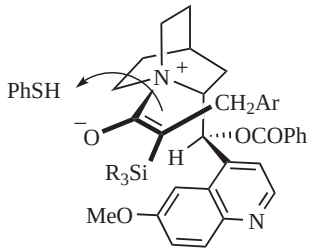


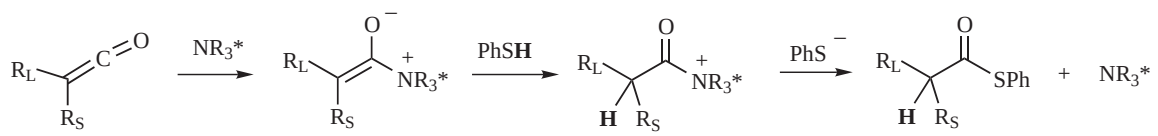
Figure 2. Model for the asymmetric protonation of intermediate **12** (vinyl group of quinuclidine system omitted for clarity).

Whichever mechanism operates, it is assumed that one isomer of the intermediate enolate is formed by attack on the ketene *anti* to the largest group, R_L in ketene **11**, which we assume is the bulky silicon group in our examples. In the case of the Pracejus mechanism it is especially difficult to account for the observed selectivity because of the unknown spatial relationship of the ion-pair prior to proton transfer. In the case of the mechanism outlined in Scheme 3 the stereochemical outcome of the quinidine catalysed reaction leading to (*S*)-**9b** can be reasonably accounted for based on the model of Wynberg for the related ketene-chloral cycloaddition (Fig. 2).[12]

In order to establish some preliminary idea of the utility of the novel chiral silicon-containing products we next carried out the range of transformations illustrated in Scheme 4.

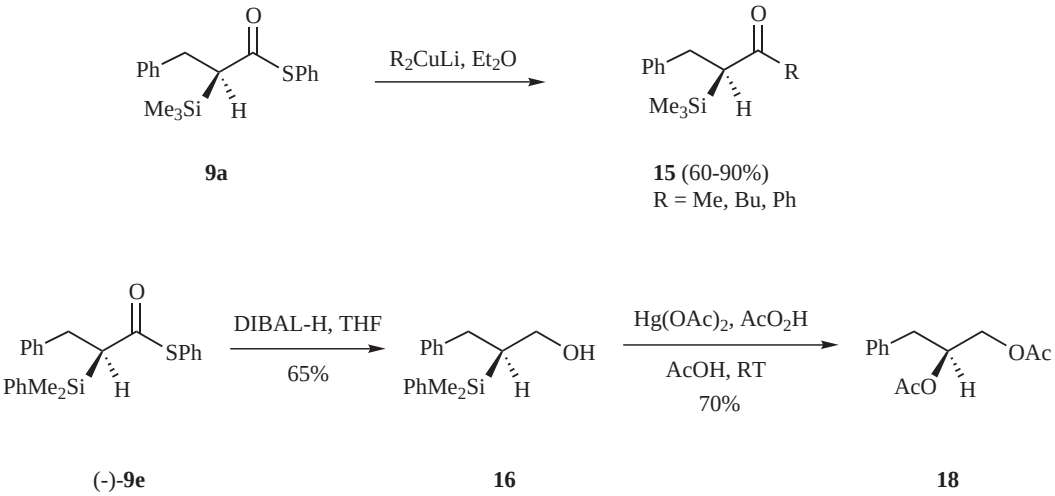
Reaction of the trimethylsilylthioester **9a** with organocuprate reagents generated from the corresponding organolithium and $CuBr–SMe_2$ gave the expected ketones **15** in good to excellent yield.[13] This type of ketone has been demonstrated by Enders and co-workers to be extremely useful in stereocontrolled aldol reactions.[14] Reduction of dimethylphenylsilyl derivative (−)-**9e**, thought to have the (*S*)-configuration shown,[15] with DIBAL gave alcohol **16** which, when treated under the conditions described by Fleming, was smoothly transformed into the diester **18**.[16]

These transformations would be expected to occur with little or no loss of stereochemical integrity, although at present we have not proved the levels of enrichment of the products.



11 **12** **13** **14**

Scheme 3.



Scheme 4.

In conclusion, we have demonstrated a novel, and highly enantioselective transformation of silylketenes that has potential for the synthesis of both silicon containing compounds, such as allylsilanes, and silicon-free products such as diols (cf. **18**). Further work is underway to establish the scope of the new process with other types of ketene.[17]

Acknowledgements

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6. We initially favoured a method (method A) employed for the synthesis of phenyltrimethylsilylketene, which involves α-bromination of an intermediate acid chloride and then dehalogenation with activated zinc, see: Brady, W. T.; Cheng, T. C. *J. Organomet. Chem.* **1977**, *137*, 287. This approach is useful for ensuring that volatile or relatively unstable derivatives are free of amine, but gives somewhat modest yields. However, we then discovered that the more stable dimethylphenylsilyl series were very easily prepared in much better yield by simple dehydrohalogenation of the intermediate acid chlorides.
7. For related work, see: Fehr, C.; Stempf, I.; Galindo, J. *Angew Chem., Int. Ed. Engl.* **1993**, *32*, 1044.
8. $(DHQ)_2PHAL$ = dihydroquinine 1,4-phthalazinediyl diether, available from the Aldrich Chemical Company.
9. General experimental procedure:
Thiophenol (1 equiv.) was added dropwise to a solution of the ketene (1 equiv.) and alkaloid catalyst (0.1 equiv.) in toluene at −78°C. After 1 h the solvent was evaporated and the residue dissolved in a small amount of pentane and filtered to remove insoluble alkaloid catalyst. The crude thioester products obtained this way were estimated to be >95% pure by ^1H and ^{13}C NMR analysis and were normally used without purification. The dimethylphenylsilyl series of thioester products are stable enough to be further purified by flash column chromatography without serious losses if necessary.
10. Determination of ee values was carried out using a Chirapak OD column using small amounts of ^{i}PrOH (typically 0.25%) in hexane as eluant.
11. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: CCDC 155471. The absolute configuration shown follows from refinement of a Flack parameter [value 0.0(2)], see: Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
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15. We were able to convert alcohol **16** into an allylsilane, prepared previously by Enders,[18] by Swern oxidation followed by methylenation, although in very low (ca. 10%) yield. The $[\alpha]_D$ (−22.5, $c = 0.32$, $CHCl_3$) for the small amount (8 mg) of allylsilane prepared was in accord with the stereochemistry shown for **16**. Confirmation of this result must await further work.

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