Mechanistic insight into copper-catalysed allylic substitutions with bis(triorganosilyl) zincs. Enantiospecific preparation of α-chiral silanes†

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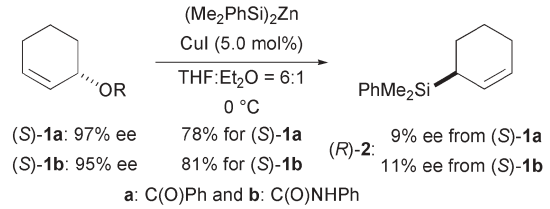
Isotopic desymmetrisation, as well as (stereo)chemical correlation, has illuminated significant aspects of the σ–π–σ mechanism of copper-catalysed allylic substitution reactions: an enantiospecific and regioselective access to α-chiral silanes is presented.

Allylic silanes offer a versatile synthetic chemistry.[1] Among the established methods for their direct preparation, the substitution of allylic substrates with $(Me_2PhSi)_2CuLi{\cdot}LiCN$ is particularly effective, if the regio- and diastereoselectivity are controllable elements.[2] Extensive investigations, mainly by Fleming *et al.*,[3] but also by Kitching *et al.*[4] and Clive *et al.*,[5] revealed the subtle influence of solvent mixtures and the $Me_2PhSiLi$–CuX ratio (X = CN or I) on the isomeric distribution. Lipshutz *et al.* later showed that the allylic substitution of vinylic epoxides is feasible using zincate $(Me_2PhSi)Me_2ZnLi$ in the presence of catalytic amounts of cuprate $Me_2CuLi{\cdot}LiCN$.[6] As we reported recently, the reagent–catalyst combination $(Me_2PhSi)_2Zn$ and CuI (5.0 mol%)[7] enables the facile copper-catalysed allylic substitution of selected allylic esters and carbamates with perfect regio- and/or diastereoselectivity.[8] Conversely, the enantiospecific preparation by these procedures of synthetically valuable α-chiral allylic silanes,[9] that is allylic silanes with silicon attached to a stereogenic carbon, is considerably more complex.[3c,d] The mechanism of these copper-mediated and, in particular, copper-catalysed allylic silylation reactions is still vague.[10]

In the light of the ready availability of chiral, non-racemic allylic alcohols and cognate esters, as well as carbamates, we targeted the direct access to α-chiral allylic silanes by our copper-catalysed allylic substitution route with bis(triorganosilyl) zinc, $(Me_2PhSi)_2Zn$. In this communication, we present a systematic investigation of its stereochemical course by a combination of isotopic desymmetrisation[11] and chemical correlation. A mechanism, not always likely to proceed through conventional σ–π–σ allylic isomerisation,[12] evolves from this study. Enantiospecific allylic displacement of the leaving group by an *anti*-S_N reaction pathway was accomplished.

Our investigation started with the copper-catalysed allylic substitution of enantioenriched cyclic (*S*)-**1a** and (*S*)-**1b** (Scheme 1), which were each prepared by palladium-catalysed deracemisation of the corresponding allylic carbonate[13] and subsequent regular acylation. We intentionally chose these substrates as *anti*-substitution is well documented[8] and therefore the lack of regiocontrol would directly correlate with racemisation. Indeed, standard reaction conditions‡ afforded allylic silane (*R*)-**2** as an almost racemic mixture (**1**→**2**, Scheme 1).

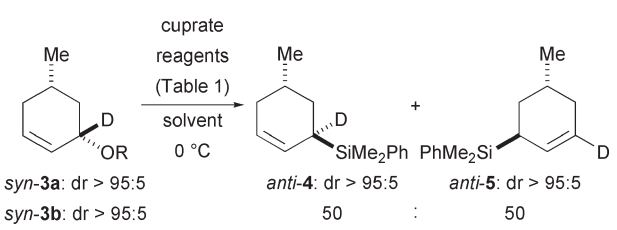


Scheme 1 Allylic substitution at a "symmetric" cyclic substrate.

In order to further substantiate this finding, we prepared ^{2}H-labelled *syn*-**3a** and *syn*-**3b** (regiochemical probe) substituted with a methyl group (stereochemical probe) (Scheme 2). As expected, substitution of both benzoate *syn*-**3a** and carbamate *syn*-**3b** produced a mixture of regioisomers *anti*-**4** and *anti*-**5** with an unchanged (inverted) diastereomeric ratio[8] (Table 1, entries 1 and 2). Accordingly, the copper-mediated allylic substitution reaction using $Me_2PhSiCu{\cdot}LiCN$ (Table 1, entries 3 and 4), the supposed catalytically-active species generated from $(Me_2PhSi)_2Zn$ and CuI (5.0 mol%),[7b] and $(Me_2PhSi)_2CuLi{\cdot}LiCN$ (Table 1, entries 5 and 6) gave identical results.

These experiments indicate that the copper-catalysed transfer of nucleophilic silicon from $(Me_2PhSi)_2Zn$ onto *cyclic* allylic substrates might involve symmetric (achiral) π allyl copper(III) intermediates (*vide infra*).

We then addressed the allylic substitution of *acyclic* substrates, in which the intermediacy of symmetric π allyl copper(III) complexes is also possible. Since 1,3-diphenylallyl esters failed to undergo substitution,[14] we decided to utilise alkyl-substituted benzoate **6a** and carbamate **6b** (Scheme 3 and Scheme 4). This time, the investigation commenced with the allylic substitution



Scheme 2 Mechanistic insight by ^{2}H-labelling (part 1).

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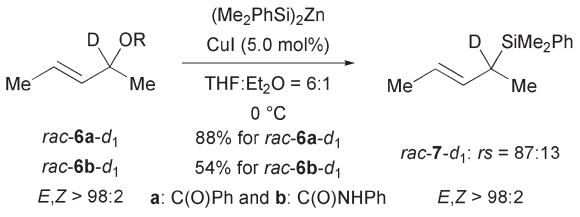
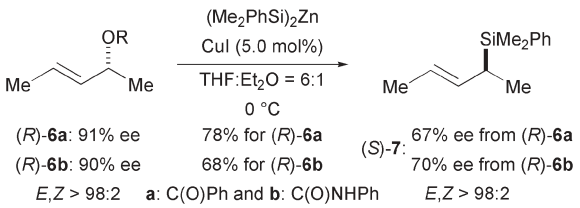
Table 1 Comparative survey of cuprate reagents

Entry	Compound	R	Cuprate reagent	Yield (%)[a]	*rs* (**4** : **5**) (%)[b]
1	**3a**	C(O)Ph	$(Me_2PhSi)_2Zn$–CuI (5.0 mol%)	77	50 : 50
2	**3b**	C(O)NHPh	$(Me_2PhSi)_2Zn$–CuI (5.0 mol%)	70	50 : 50
3	**3a**	C(O)Ph	$Me_2PhSiCu\cdot LiCN$	62	50 : 50
4	**3b**	C(O)NHPh	$Me_2PhSiCu\cdot LiCN$	72	50 : 50
5	**3a**	C(O)Ph	$(Me_2PhSi)_2CuLi\cdot LiCN$	73	50 : 50
6	**3b**	C(O)NHPh	$(Me_2PhSi)_2CuLi\cdot LiCN$	78	50 : 50

[a] Yield of analytically pure product after purification by flash chromatography. [b] The ratio of regioisomers was determined from the ^{1}H NMR spectra by integration of the baseline-separated resonance signals prior to purification.



Scheme 3 Mechanistic insight by ^{2}H-labelling (part 2).

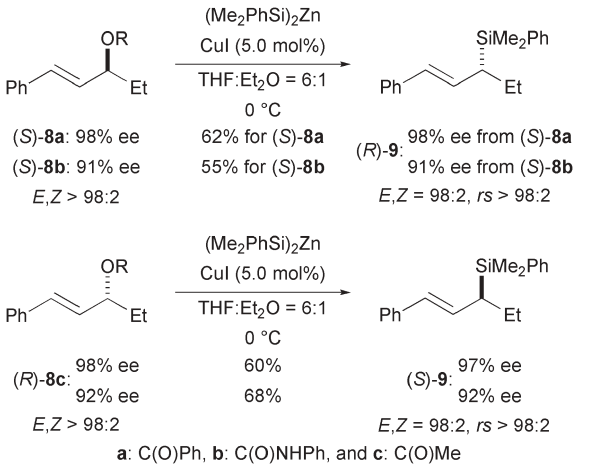


Scheme 4 Allylic substitution at a "symmetric" acyclic substrate.

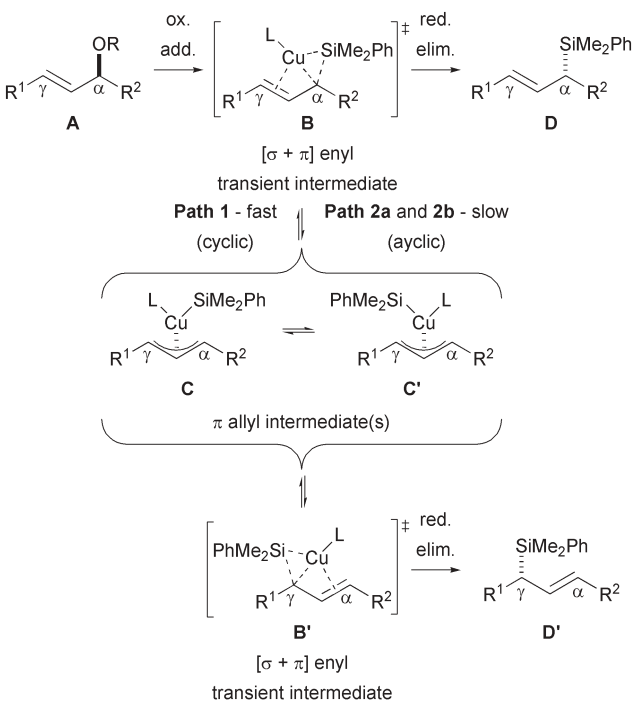
reaction of ^{2}H-labelled racemic *rac*-**6**-d_1. In sharp contrast to the cyclic system (Scheme 2), allylic transfer of the silicon nucleophile proceeded with moderate regioselectively in the case of the acyclic system (*rac*-**6**-d_1→*rac*-**7**-d_1, Scheme 3).[15] This unexpected observation was corroborated in the analogous substitution reactions of enantioenriched substrates (*R*)-**6**, which were again accessed by palladium-catalysed deracemisation.[13] Importantly, enantioenriched α-chiral allylic silane (*S*)-**7** was obtained with only a minor loss of stereochemical information (**6**→**7**, Scheme 4).

This remarkable conservation of the absolute configuration (*anti*-S_N mechanism), occasionally termed a memory effect, was also found in rhodium-[16] and palladium-catalysed[17] allylic alkylation reactions, yet it was interpreted by entirely different explanations. Similar to the rhodium catalysis reported by Evans *et al.*,[16] the copper-catalysed allylic substitution of acyclic substrates might favour non-symmetric (chiral) σ allyl or [σ + π] enyl[18] rather than π allyl copper(III) intermediates (*vide infra*).

In the enantiospecific substitution of allylic substrates with different substituents, the issues of regio- and enantioselectivity are separated. For this, we prepared (*S*)-**8a**, (*S*)-**8b** and (*R*)-**8c** by enzymatic kinetic resolution of the parent alcohol.[19] To our delight, allylic substitution provided α-chiral allylic silanes (*R*)-**9** and (*S*)-**9** with excellent regio- and enantioselectivity, independent of the leaving group (**8**→**9**, Scheme 5).[20] This inversion (formal *anti*-S_N mechanism) at the silicon-bearing stereogenic carbon was unambiguously secured by chemical correlation in two synthetic operations:[21] racemisation-free hydrogenation of the double bond in (*S*)-**9** followed by oxidative degradation of the carbon–silicon bond under retention of configuration (Fleming oxidation[22]).



Scheme 5 Allylic substitution at a "non-symmetric" acyclic substrate.



Scheme 6 Unified mechanistic rationale (ox. add. = oxidative addition, red. elim. = reductive elimination, L = solvent or counter-ion).

From these experimental findings, we deduce the unified mechanistic picture outlined in Scheme 6. We propose that allylic substrate **A** oxidatively adds to catalytically-active monosilylcopper

$Me_2PhSiCu{\cdot}ZnX_2$ (X = Me_2PhSi, Cl and I),[7b] thereby forming the [σ + π] enyl copper(III) transient intermediate **B**;[18] the related σ allyl copper(III) complex is not shown. This oxidative addition proceeds in an *anti*-S_N fashion, that is, inversion and no α/γ transposition (**A→B**). Then, reductive elimination (**B→D**) and conventional σ–π–σ isomerisation[12] (**B→C/C′→B′**) are possible reaction pathways; again, the σ allyl copper(III) complex, corresponding to **B′**, is not shown. Depending on the individual structural features and the substitution pattern of the allyl fragment, two scenarios might explain our observations (Scheme 6):[23]

• Path 1 (*anti*-S_N/*anti*-S_N' and α-adduct/γ-adduct): If [σ + π] enyl complex **B** is *cyclic*, and R^1 and R^2 are not capable of establishing π-conjugation, isomerisation (**B→C/C′**) will be faster relative to the rate of reductive elimination (**B→D**). Achiral π allyl complexes **C** and **C′** will be in equilibrium with **B** and **B′**, which will eventually suffer reductive elimination (**B→D** and **B′→D′**). With $R^1 = R^2 = -(CH_2)_3-$, racemisation is observed (**1→2**, Scheme 1).

• Path 2a (*anti*-S_N and α-adduct): If [σ + π] enyl complex **B** is *acyclic*, and R^1 and R^2 are not capable of establishing π-conjugation, reductive elimination (**B→D**) will be slightly faster relative to the rate of isomerisation (**B→C/C′**). With $R^1 = R^2$ = Me, partial erosion of the stereochemical information, and hence overall inversion of configuration, is observed (**6→7**, Scheme 4). Identical behaviour is seen for a related acyclic substrate ($R^1 = R^2$ = Et).

• Path 2b (*anti*-S_N and α-adduct): If [σ + π] enyl complex **B** is *acyclic*, and either R^1 or R^2 are capable of establishing π-conjugation, direct reductive elimination (**B→D**) is again likely to be faster than isomerisation (**B→C/C′**). Even if σ–π–σ isomerisation occurs, intermediate π allyl complex **C** is likely to predominantly isomerise to the more stable [σ + π] enyl complex **B**, favouring conjugation. This assumption is supported by a recent theoretical study by Nakamura *et al.*[18] Reductive elimination will then occur with retention of configuration (**B→D**). With $R^1 \neq R^2$, R^1 = Ph and R^2 = Et, overall inversion of configuration is observed (**8→9**, Scheme 5).

In conclusion, we have developed an enantiospecific synthesis of α-chiral allylic silanes by copper-catalysed allylic silylation of readily available enantioenriched allylic substrates. Isotopic labelling and assignment of absolute configurations by chemical correlation have disclosed useful insights, which have clarified the mechanistic trends for several substrates.[23]

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Notes and references

‡ *General experimental procedure:* A suspension of CuI (5.0 mol%) and THF (1.0 mL) was pre-cooled to −78 °C and treated with bis(dimethylphenylsilyl) zinc[8] (1.0 equiv.) *via* a syringe. The auburn-coloured reaction mixture was allowed to warm to 0 °C and maintained at this temperature for 0.5 h. Addition of the allylic substrate (1.0 equiv.) in THF (1.0 mL) was followed by stirring for 1 h at 0 °C. Upon completion of the reaction, the reaction mixture was poured into saturated aqueous NH_4Cl (5.0 mL) and the flask rinsed with *tert*-butyl methyl ether (10 mL). The aqueous phase was separated and extracted with *tert*-butyl methyl ether (3 × 10 mL). The combined organic phases were washed with brine (10 mL). After drying (Na_2SO_4), the solvents were evaporated under reduced pressure and the crude product purified by flash chromatography on silica gel using cyclohexane as the solvent. All new compounds gave satisfactory characterisation data (ESI†).

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20 (*a*) An isomeric mixture of 1-phenyl-2-pentene was detected as a major by-product, indicating the formation of *exo*,*exo* and *exo*,*endo* π allyl copper(III) intermediates; (*b*) It should be noted that treatment of (*R*)-**8c** (92% ee) with $(Me_2PhSi)_2CuLi{\cdot}LiCN$ also afforded (*S*)-**9** (92% ee) with excellent regiocontrol[3d].
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23 At present, we cannot entirely rule out direct nucleophilic substitution pathways, as well as a sequence consisting of *anti*-S_N' (oxidative addtion) and *syn*-S_N' (reductive elimination). However, the latter, being complementary to Paths 2a and 2b, seems unlikely because of the involvement of a *syn*-S_N' reductive elimination from an intermediate [σ + π] enyl species[18].