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Transition-Metal-Free Synthesis of Enantioenriched Tertiary and Quaternary α-Chiral Allylsilanes

Rubén Pérez Sevillano,[a] Franck Ferreira,*[a] and Olivier Jackowski*[a]

Access to enantioenriched tertiary and quaternary α-chiral allysilanes without any transition-metal catalyst is reported. This was achieved by enantioselective allylic displacement of γ-silylated allylic bromides through Lewis base activation of Grignard reagents by a bidentate chiral NHC ligand. The process afforded both high γ-regio- and enantioselectivity and is compatible with a wide range of silyl groups on the substrates.

Introduction

Allysilanes, in particular α-chiral allylsilanes, constitute an important class of silicon compounds widely used in the synthesis of natural and non-natural complex molecules.[1] Over the past decades, many enantioselective catalytic methods have been reported for their preparation including transition-metal-catalyzed hydrosilylation and silaboration of 1,3-dienes[2,3] and allenes,[4,5] cross-coupling of α-silylated alkyl Grignard reagents with vinyl bromides,[6] or hydride γ-addition to γ-silylated allylic carbonates.[7] Enantioselective regioselective copper-catalyzed α- or γ-silylation of allylic electrophiles[8] as well as γ-alkylation or arylation of γ-silylated allylic electrophiles represent two valuable alternatives and have attracted much interest from chemists in recent years.[9] Although, high regio- and enantioselectivity are generally observed, the phenyldimethylsilyl motif is quasi-exclusively used, which restrains the use of the α-chiral allylsilanes obtained as pronucleophiles in subsequent reactions such as the Hosomi-Sakurai carbonyl allylation. To address this issue, we envisioned to develop a new enantioselective access to these synthetically interesting building blocks under conditions compatible with the widest possible range of silyl motifs. Inspired by recent works, we then thought that α-chiral allylsilanes could be easily obtained by metal-free asymmetric allylic alkylation of γ-silylated allylic electrophiles using organometallic reagents activated by chiral Lewis bases. In pioneering work, Hoveyda et al. showed that chiral NHC ligands were able to accomplish this activation.[10] In particular, chiral sulfonate-containing NHC ligand **1** was found to allow γ-addition of dialkylzinc reagents and Me_3Al to allylic phosphates with moderate-to-excellent enantioselectivity (Figure 1).[11] The alkylation scope could further be extended using NHC ligands developed by Woodward (Figure 1, ligand **2**),[12] Okamoto (Figure 1, ligand **3**)[13] and Fuchter (Figure 1, ligands **4a** and **4b**)[14] that enabled activation of various and easily prepared Grignard reagents, offering moderate regio- and/or enantioselectivity. The key of these reactions was the ability of Grignard reagents to deprotonate the imidazolium salt without requiring metal carbenes. More recently, Alexakis et al.[15] designed bidentate chiral NHC ligands **5a** and **5b** which afforded the best results. The flexible benzylic group along with the three carbon atoms between the core nitrogen atom and the coordinating hydroxyl group were shown to be crucial to attain high enantioselectivity.

We present herein an efficient transition-metal-free method to accomplish regio- and enantioselective allylic alkylation of γ-silylated primary allylic bromides with Grignard reagents (scheme 1). This method tolerates various silyl moieties on the

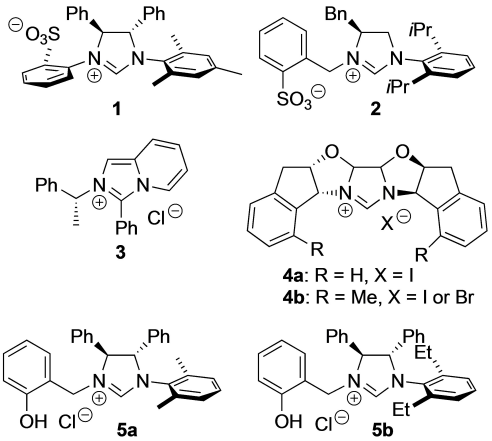
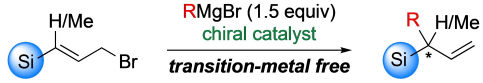


Figure 1. Chiral NHC ligands used for transition-metal-free asymmetric allylic allylation with Grignard reagents.



Scheme 1. This work: transition-metal-free synthesis of enantioenriched tertiary and quaternary α-chiral allylsilanes.

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substrates and, to the best of our knowledge, represents the first example reporting the use of Grignard reagents to prepare enantioenriched tertiary and quaternary α-chiral allylsilanes.

Results and Discussion

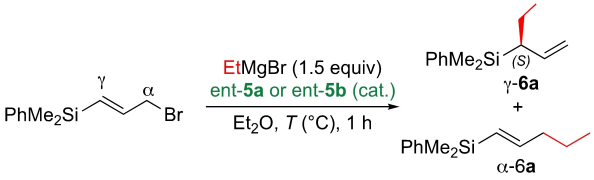
We first focused our attention on bidentate chiral NHC ligands **5a** and **5b** which have been shown to be advantageously used in asymmetric allylic alkylation. A preliminary investigation was then undertaken under the reaction conditions developed by Alexakis et al. employing a slight excess of EtMgBr and (*E*)-3-(dimethylphenylsilyl)allyl bromide in the presence of ligand ent-**5a**.

To our delight, using 2 mol% of ligand ent-**5a** without any metal catalyst led to 95% conversion within 1 h at −15 °C (Table 1, entry 1), giving products γ-**6a** and α-**6** with encouraging regioselectivity (γ/α = 79:21) and promising enantiomeric ratio (er = 88:12) for γ-**6a**. As expected from literature,[15b] ligand ent-**5b** offered slightly better results (Table 1, entry 2), affording complete conversion with improved regio- and enantioselectivity (γ/α = 86/14 and er = 90/10). Roughly equivalent results were obtained when carrying out the reaction in the presence of 2 mol% of copper(I) thiophene-2-carboxylate (Table 1, entry 3). In sharp contrast, α-**6a** was formed as the major product (γ/α = 31:69) when the copper-catalyzed reaction was performed without ligand (Table 1, entry 4), while incomplete conversion was observed and only α-**6a** was detected (γ/α < 1:99) in the absence of both catalyst and ligand (Table 1, entry 5).

These results showed that the use of bidentate NHC ligand ent-**5b** was essential to attain both high regio- and enantioselectivity. They also strongly suggested that γ-**6a** was kinetically favored in the presence of ent-**5b**. Decreasing temperature to −40 °C did not affect enantioselectivity but was detrimental for kinetics (Table 1, entry 6). Surprisingly, carrying out the reaction at rt (Table 1, entry 7) offered significantly better regioselectivity (γ/α = 91/9) with unhanged enantioselectivity (er = 88:12 er). Moreover, as little as 0.5 mol% catalyst loading could be used at rt with quite similar results (Table 1, entry 8). Finally, slow addition of EtMgBr over a 20-min period (Table 1, entry 9) prevented the formation of α-**6a**, via direct S_N2 addition of EtMgBr, enabling complete conversion into γ-**6a** with perfect regioselectivity (γ/α > 98/2) and excellent enantiomeric ratio (er = 93:7). Other solvents and leaving groups were tested under these reaction conditions but all offered lower regio- and/or enantioselectivity (see Supporting Information for details). The sense of the stereoinduction, which was initially deduced from previous work on asymmetric allylic allylation with ligand **5b**,[15a] could be confirmed, and the (*S*)-configuration unambiguously assigned to the stereogenic carbon atom of γ-**6a** by comparison of its specific rotation with the value reported in literature.[9a]

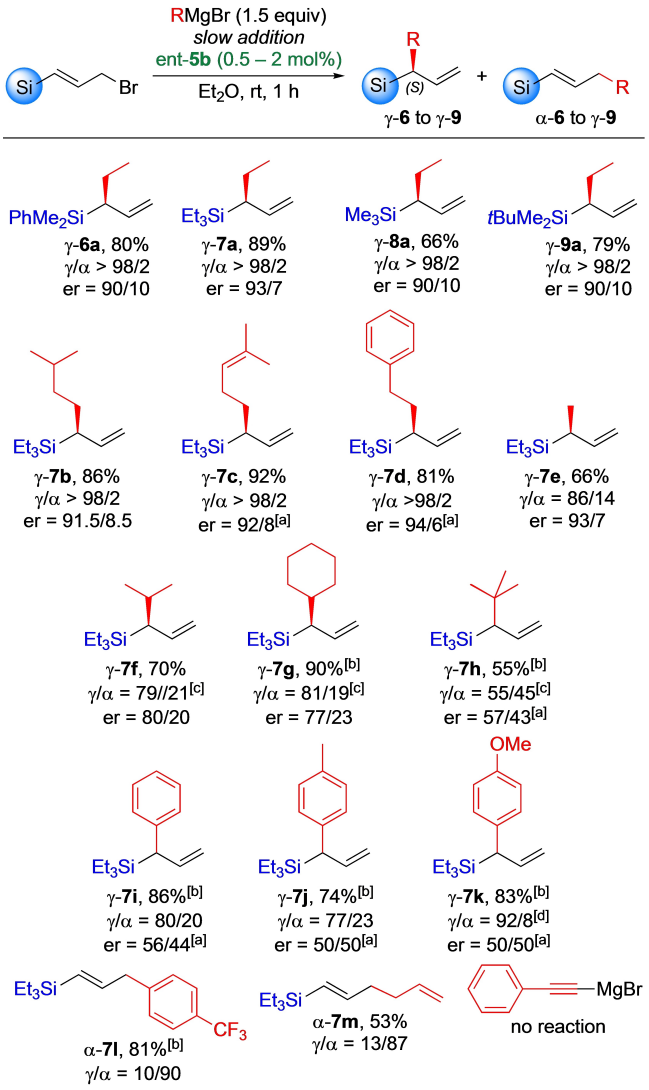
The optimal conditions in hands, the scope of the reaction was examined (Scheme 2). The reaction could be first extended to trialkysilyl patterns, including sterically demanding *t*BuMe$_2$Si, giving tertiary α-chiral allylsilanes γ-**6a** to γ-**9a** in good-to-excellent isolated yields (66–92%) with perfect regioselectivity (γ/α > 98/2) and high enantiomeric purity (er ≥ 90/10).[16] A wide array of alkyl Grignard reagents was also evaluated. The reaction with primary reagents yielded products γ-**7b–d** with similar remarkable results (81–92% yield, γ/α ≥ 98/2 and er ≥ 91.5/8.5). Gratifying, even MeMgBr, which was previously shown to lead to moderate enantioselectivity in asymmetric allylic alkylation, gave product γ-**7e** in good yield (66%) with high enantiomeric ratio (er = 93/7), albeit with significant deterioration of regioselectivity (γ/α = 87/13). The (*S*)-configuration of all these products was assigned by analogy with γ-**6a**. Conversely, the reaction was found very sensitive to the steric hindrance of

Table 1. Optimization of conditions for the synthesis of enantioenriched tertiary α-chiral allylsilanes.[a]



Entry	Ligand [mol%]	Catalyst [mol%]	*T* [°C]	Conv [%][b]	γ/α ratio[b]	er[c]
1	ent-**5a** (2 mol%)	none	−15	95	79/21	88/12
2	ent-**5b** (2 mol%)	none	−15	> 99	86/14	90/10
3	ent-**5b** (2 mol%)	CuTC[d] (2 mol%))	−15	> 99	83/17	88/12
4	none	CuTC[d] (30 mol%)	−15	> 99	31/69	50/50
5	none	none	−15	50	< 1/99	–
6	ent-**5b** (2 mol%)	none	−40	37	87/13	88/12
7	ent-**5b** (2 mol%)	none	rt	> 99	91/9	88/12
8	ent-**5b** (0.5 mol%))	none	rt	> 99	91/9	90/10
9[e]	ent-**5b** (0.5 mol%)	none	rt	> 99	> 98/2	93/7

[a] ried out under N_2 atmosphere. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Determined by chiral GC analysis. [d] CuTC = copper(I) thiophene-2-carboxylate. [e] Addition of EtMgBr over a 20-min period.



Scheme 2. Transition-metal-free enantioselective synthesis of tertiary α-chiral allylsilanes. Isolated yields of inseparable γ- and α- regioisomers. Unless otherwise stated, γ/α ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures and er were determined by GC or chiral HPLC analysis. [a] er determined by chiral HPLC analysis of the alcohol obtained by hydroboration and subsequent oxidation of the carbon-carbon double bond. [b] 2 mol% of ent-**5b** used. [c] Detection of dimerized side-products (see Supporting Information). [d] After purification.

the Grignard reagent, *i*PrMgBr, CyMgBr and *t*BuMgBr all affording compounds γ-**7f–h** with dramatic decrease in both regio- and enantioselectivity, even when using 2 mol% of ligand. In addition, the formation of these compounds was accompagnied with about 10–30% of dimerized side-products (see Supporting Information for more details). The results were also disappointing with aryl, allyl and alkynyl Grignard reagents. On one hand, the former required up to 2 mol% catalyst loading to achieve complete conversion within 1 h, leading to products γ-**7i–k** with almost no chiral induction and product α-**7l** as major regioisomer. On the other hand, allylmagnesium bromide afforded exclusively α-product α-**7m** and no reaction occurred at all with phenylethynylmagnesium bromide.

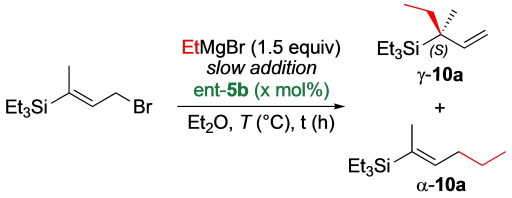
Chiral ligand **5b** was also advantageously used to promote asymmetric allylic alkylation of hampered γ,γ-disubstituted allylic bromides.[15a,b,d] We thus study its ability to allow the formation of quaternary α-chiral allylsilanes from 3-silylated (*E*)-1-bromobut-2-enes. Optimization of the conditions was undertaken with ent-**5b** and 3-triethylsilyl-substituted substrate and EtMgBr (Table 2). Under the previous optimized conditions (Table 2, entry 1), the reaction led to incomplete conversion into γ-**10a**, presumably with the (*S*)-configuration, with moderate regioselectivity (γ/α = 70/30) and good, albeit notably eroded, enantioselectivity (er = 87/13). Increasing ligand loading up to 2 mol% (Table 2, entries 2 and 3) improved regioselectivity (γ/α up to 98/2) while enantioselectivity remained unchanged. Performing the reaction at −15 °C significantly increased enantioselectivity (er = 97.5/2.5), although conversion was incomplete within 1 h (Table 2, entry 4). Finally, carrying out the reaction with 2 mol% of ligand ent-**5b** for 5 h at -15 °C (Table 2, entry 5) enabled complete conversion with perfect regioselectivity (γ/α > 98/2) and remarkable enantiomeric ratio (er = 98/2).

These conditions could then be applied with success to other primary alkyl Grignard reagents (Scheme 3). In all cases, products γ-**10b–e** were formed as exclusive products in good-to-high isolated yields (81–92%) with better enantiomeric ratios (er ≥ 95.5/4.5) than those obtained for the synthesis of tertiary analogs. Besides, in order to prove the robustness of this method, the scale-up for the preparation of γ-**10b** was carried out affording similar selectivities (γ/α > 98/2 and er = 98 : 2) with a notable increase to 90% yield (see Supporting Information). In sharp contrast, congested alkyl Grignard reagents failed again to afford quaternary α-chiral allylsilanes satisfactorily; no regioselectivity was observed in the formation of γ-**10f** with *i*PrMgBr (γ/α = 50/50), while α-**10g** was exclusively formed with *t*BuMgBr (γ/α < 2/98). Moreover, in both cases, an unidentified side-product was detected to some extent (about 30–40% yield). Results were also not satisfactory with PhMgBr which only led to product γ-**10h**, but with incomplete conversion, even after a 72-h reaction, and poor regioselectivity (γ/α = 57/43). Pleasantly, the reaction with primary alkyl Grignard reagents could be extended to 3-phenyldimethylsilyl-substituted substrates that yielded products γ-**11a–e** with very similar remarkable results. The (*S*)-configuration of the stereogenic carbon atom of product γ-**11a** was confirmed by comparison of its specific rotation with that reported in literature[9a] and was assigned to all other products γ-**10** and γ-**11** by analogy.

The reaction was also found enantiodivergent since (*E*) and (*Z*) substrates afforded γ-products with opposite configurations (Scheme 4). Although regioselectivity was perfect, a dramatically eroded enantioselectivity was observed with the (*Z*) substrate.

The excellent enantioselectivity obtained from (*E*) allylic bromides could be rationalized by considering two competitive chair-like transition states **TS1** and **TS2** in which the bulky silyl group occupies a pseudo-equatorial position (Figure 2). Due to the smaller apparent size of the bromine atom compared to that of the alkyl group R (A-values of 1.6 kJ·mol^{-1} and > 7.1 kJ·mol^{-1}, respectively), steric interaction with the backbone

Table 2. Optimization of conditions for the preparation of enantioenriched quaternary α-chiral allylsilanes.[a]



Entry	X [mol %]	*T* [°C]	t [h]	Conv [%][b]	γ/α ratio[b]	er[c]
1	0.5	rt	1	56	70/30	87/13
2	1	rt	1	95	95/5	88/12
3	2	rt	1	>99	98/2	87.5/12.5
4	2	−15	1	50	>98/2	97.5/2.5
5	2	−15	5	>99	>98/2	98/2

[a] Reactions carried out under N_2 atmosphere. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Determined by chiral GC analysis.

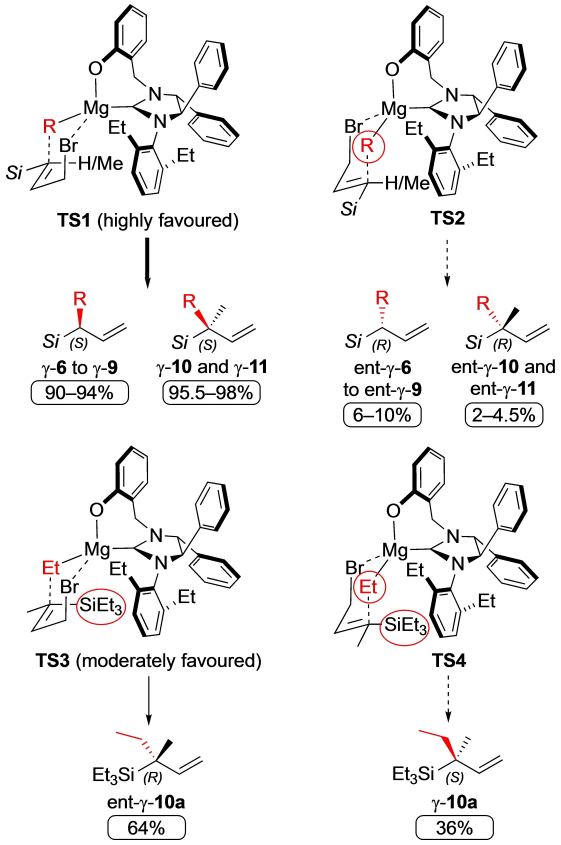


Figure 2. Proposed transition states.

phenyl ring was assumed to be less in **TS1** than in **TS2**, leading to high facial enantiodifferentiation and yielding predominantly (*S*)-products. In the case of γ,γ-disubstituted substrates, the additional steric interaction caused by the methyl substituent could explain the better enantioselectivity observed for the formation of quaternary products γ-**10** and γ-**11** than for that of tertiary products γ-**6a** to γ-**9a**, by increasing the energy difference between **TS1** and **TS2**. Conversely, the formation of product ent-γ-**10a** with very low enantioselectivity (er = 64/36) from the corresponding (*Z*) allylic bromide was postulated to result from two constrained chair-like transition states **TS3** and **TS4** in which the silyl group occupies a pseudo-axial position.

Conclusions

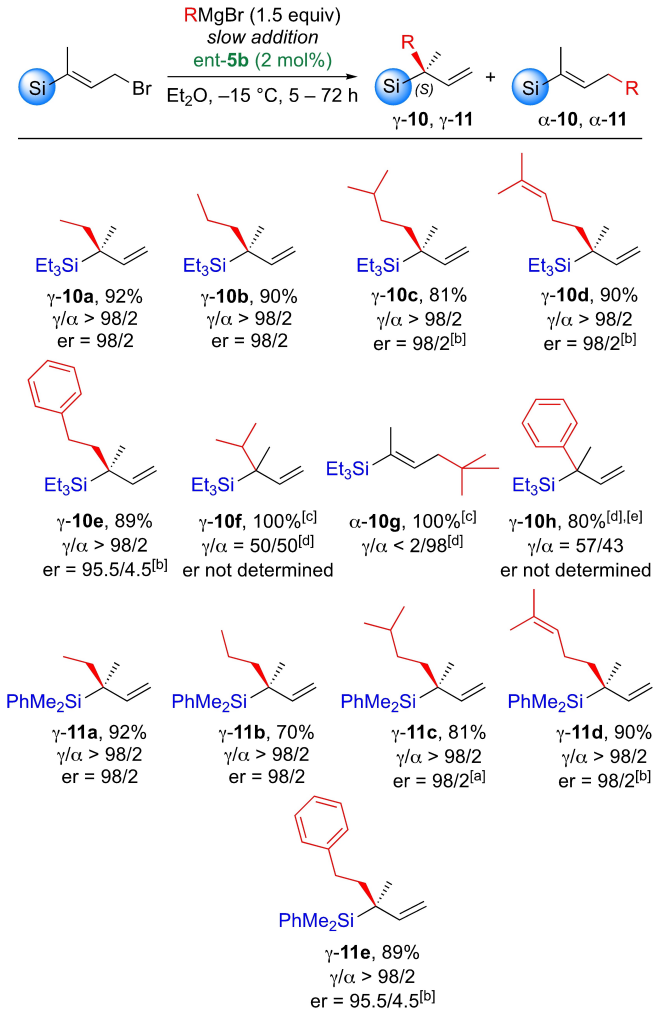
In summary, we have developed an enantioselective allylic substitution reaction of γ-silylated primary (*E*) allylic bromides in the absence of transition metal. The reaction uses primary alkyl Grignard reagents and an Alexakis-type bidentate NHC ligand as chiral inducer. It provides enantioenriched tertiary and quaternary α-chiral allylsilanes with high regioselectivity (γ/α > 98:2 in most cases) and enantioselectivity (er ranges from 90/10 to > 98:2) and represents a valuable competitive alternative to established copper-catalyzed procedures using diorganozinc reagents.

Experimental Section

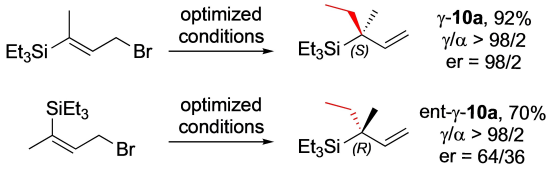
Under argon atmosphere, in a flame-dried Schlenk equipped with a stir bar, to a solution of γ-silylated allylic bromide (0.3 mmol) and ent-**5b** (0.5–2 mol%) in 1.4 mL of anhydrous Et_2O was added dropwise over 20 min the Grignard reagent (1.5 equiv. in Et_2O) at rt or −15 °C. After complete conversion by TLC, the solution was diluted with 1 mL of THF and quenched by addition of K_2CO_3 (23.5 mg, 0.17 mmol) and benzylamine (0.02 mL, 0.19 mmol). After 15 min of stirring, 2 mL of Et_2O and 5 mL of H_2O were added. The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel to offer a mixture of γ- and α-regioisomers.

Supporting Information

The authors have cited additional references within the Supporting Information.[17–27]



Scheme 3. Transition-metal-free enantioselective synthesis of quaternary α-chiral allylsilanes. γ- and α- regioisomers. Isolated yields of inseparable γ- and α- regioisomers. Unless otherwise stated. Unless otherwise stated, γ/α ratios were determined by ^{1}H NMR analysis of crude mixture and er were determined by GC or chiral HPLC analysis. [a] er determined by chiral HPLC analysis of the acryloyl ester after cross-metathesis. [b] er determined by chiral HPLC analysis of the alcohol obtained by hydroboration and subsequent oxidation of the carbon-carbon double bond. [c] Conversion by ^{1}H NMR. [d] Side-product detected. [e] 72 h reaction time.



Scheme 4. Enantiodivergence. The reactions were carried out with 2 mol% of ent-**5b** by slow addition of EtMgBr (1.5 equiv.) in Et_2O at −15 °C.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: allylsilanes · allylic substitution · enantioselectivity · Grignard reagents · *N*-heterocyclic carbenes

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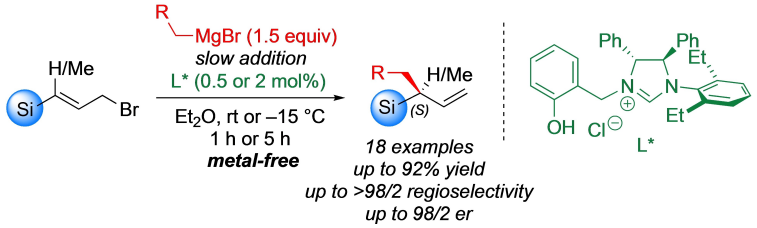

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Transition-Metal-Free Synthesis of Enantioenriched Tertiary and Quaternary α-Chiral Allylsilanes

Enantioenriched tertiary and quaternary α-chiral allylsilanes have been obtained by metal-free asymmetric allylic alkylation of γ-substituted primary allylic bromides with primary alkyl Grignard reagents activated by a chiral Alexakis-type NHC ligand.