Abstract: A two-step sequence for the enantio- and diastereoselective synthesis of exclusively alkyl-substituted acyclic allylic systems with a stereocenter in the allylic position is reported. The asymmetric induction and the site selectivity are controlled in an enantio- and regioconvergent nickel-catalyzed C(sp³)–C(sp³) cross-coupling of regioisomeric mixtures of racemic α-γ-silylated allylic halides and primary alkylzinc reagents. The silyl group steers the allylic displacement towards the formation of the vinylsilane regioisomer, and the resulting C(sp³)–Si bond serves as a linchpin for the installation of various C(sp³) substituents in a subsequent step.

Enantioselective nickel catalysis involving radical intermediates is already a key technology for forging C(sp³)–C(sp³) bonds from racemic alkyl electrophiles in an enantioconvergent fashion.[1] A broad range of zinc-based nucleophiles and various electrophilic coupling partners can be used for that purpose, thereby enabling an impressive number of otherwise challenging bond formations.[2] This field has largely been shaped by Fu, and it was also his laboratory to recently disclose the synthesis of α-chiral silanes from racemic α-bromo-substituted alkylsilanes (Scheme 1, top left).[3] With our interest in silicon chemistry, we had developed a similar method employing α-silylated alkyl iodides and reported our protocol at exactly the same time (Scheme 1, top right).[4] The next step for us was to investigate the related C(sp³)–C(sp³) cross-coupling of the corresponding racemic silylated allylic systems (Scheme 1, bottom).[5]

Son and Fu had accomplished a Negishi-type reaction for a diverse set of allylic chlorides in the presence of NiBr₂·glyme and Pybox ligand L₃ (R = CH₂Bn; see gray box in Scheme 1).[2c] The regioselectivity was consistently high for 2° and 3° alkyl as well as electron-withdrawing groups as one and a methyl substituent as the other in the α and γ positions of the allyl unit (not shown) but was modest with two 1° alkyl groups (Scheme 2, top). With the high regiocontrol for tert-butyl/methyl and the known steering effect of silyl groups in transition-metal-catalyzed allylic displacements,[6,7] we anticipated that an enantioconvergent cross-coupling of regioisomeric mixtures of silylated allylic halides would regioselectively yield vinylsilanes with a stereogenic carbon
atom in the allylic position (Scheme 1, bottom). The silyl group attached to a C(sp³) carbon atom could then be a placeholder for another 1° alkyl group, thereby providing a two-step regioselective access to exclusively alkyl-substituted acyclic allylic systems with excellent diastereo- and high enantiocontrol (Scheme 2, bottom).

For the optimization of the reaction conditions, we chose silylated allylic bromide rac-1a as a mixture of regioisomers (\(\alpha,\gamma = 53:47\)) and 2.0 equiv of primary alkylzinc bromide 2a as model substrates (Table 1). Upon variation of the reaction parameters, we found that NiBr₂-diglyme as precat-

Table 1: Selected examples of the optimization.[a]

| Entry | Deviation from the standard conditions | Yield [%][b] | e.r.[c] |
|-------|---------------------------------------|-------------|--------|
| 1     | None                                  | 88 (80)     | 92:8   |
| 2     | 0°C instead of RT                      | 75          | 92:8   |
| 3     | −10°C instead of RT                    | 37          | 93:7   |
| 4     | Alkyl chloride instead of rac-1a       | 64          | 89:11  |
| 5     | Alkyl acetate instead of rac-1a        | 4           | 92:8   |
| 6     | 1.5 equiv of 2a                        | 74          | 92:8   |
| 7     | 1.2 equiv of 2a                        | 69          | 92:8   |
| 8     | 5.0 mol % of NiBr₂-diglyme and 7.5 mol % of L4 | 77 | 91:9 |

[a] All reactions were performed on a 0.10 mmol scale. [b] Determined by GLC analysis with tetracosane as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Isolated yield after purification by flash chromatography on silica gel.

allyl bromide (not shown). Functional groups include another acetal (as in 2b), an ether as well as a silyl ether (as in 2c and 2j), a phenyl group (as in 2d), a nitrile (as in 2e), an ester (as in 2f) and an alkenyl group (as in 2i). Unfunctionali-

Scheme 3. Scope I: Variation of the primary alkylzinc bromide.
our delight, β-methyl-substituted rac-12c was stable during purification by conventional flash chromatography on silica gel. Moreover, the cross-coupling of regioisomerically pure rac-12c and alkylzinc reagent 2a afforded product 8ca under the standard setup in good yield and with high enantioselectivity (68% and e.r. 98:2; not shown). We did a brief reassessment of the reaction conditions and could further increase the yield to 80% and the enantiomeric ratio to 99:1 when using NiI₂ instead of NiBr₂-diglyme (see Table S2 in the Supporting Information for details). With the modified conditions in hand, we used 2a–g in the reaction of rac-12c as the coupling partner (Scheme 5, top). As expected, the functional-group tolerance was excellent (cf. Scheme 4), and isolated yields were good throughout. The enantiomeric ratios were very high, reaching 99:1 for 8cd. A longer alkyl chain instead of a methyl group at the allyl fragment as in rac-12d was also compatible with the setup, furnishing 8da in 90% yield and with an enantiomeric ratio of 97:3 (Scheme 5, bottom).

The value of the present method lies in its regioconver-gence. Such regioselectivity had not been achieved with allylic substrates decorated with two 1° alkyl substituents yet. The controlling element is the silyl group which is at the same time a handle for the installation of another 1° alkyl group. Tsubouchi and co-workers developed a copper-promoted protocol for the cross-coupling of BnMe₂Si-substituted vinylsilanes and alkyl electrophiles. To demonstrate the potential synthetic utility of our chiral vinylsilanes, we had included the BnMe₂Si-substituted allylic bromides rac-7a and rac-7b into our scope. The resulting products 11aa and 11ba were applied to the C(sp³)–C(sp³) cross-coupling with two different C(sp³)–X coupling partners 13a and 13b (Scheme 6). These reactions proceeded in good yields to produce 14aaa–bab as single regioisomers and diastereomers without any erosion of the enantiomeric excess. The expected absolute configuration of product 14aab is in accordance with the literature. In summary, we developed an enantioconvergent nickel-catalyzed C(sp³)–C(sp³) cross-coupling of vinylsilanes with an allylic stereocenter and C(sp³) electrophiles.
carbon electrophiles such as allyl and alkyl halides. By this two-step sequence, 1,3-dialkyl-substituted acyclic allylic systems with a stereocenter in the allylic position become available in enantio- and diastereoselective manner.

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**Conflict of interest**

The authors declare no conflict of interest.

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