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α-Silicon effect assisted Curtin–Hammett allylation using allylcopper reagents derived from 1,3-dienylsilanes†

Shang Gao and Ming Chen *

Cu-catalyzed stereoselective synthesis of (*E*)-δ-silyl-*anti*-homoallylic alcohols from 1,3-dienylsilane was developed. Mechanistic studies revealed that the borocupration of dienylsilane proceeded through a 1,2-addition pathway to give an allylcopper intermediate with Cu distal to the silyl group. However, the subsequent aldehyde allylation proceeded *via* Curtin–Hammett control to give (*E*)-δ-silyl-*anti*-homoallylic alcohols with high diastereoselectivities. This method was applied to the synthesis of the C_{1-9} fragment of a polyketide natural product, mycinolide IV.

Introduction

Stereoselective transformation of carbon–carbon multiple bonds catalyzed by transition-metal complexes is a powerful approach to generate molecular complexity from structurally simple π-bonds.[1] In particular, reactions employing 1,3-conjugated dienes are attractive because of multiple potential reaction pathways that can be involved in these processes. By proper selection of the catalyst/ligand combination, distinct products can be generated with high selectivities from these reactions.[2] Such processes are valuable because they can often form several chemical bonds, generate several stereocenters, and provide highly useful intermediates for chemical synthesis. Over the past several decades, significant advances in stereoselective transformation of 1,3-conjugated dienes,[3–7] enynes and allenes as well have been achieved,[8] and many highly innovative strategies have been developed.

Recently, transition-metal catalyzed reactions of 1,3-conjugated dienes with carbonyl compounds have emerged as an important method to synthesize alcohol products.[9–11] Synthetically valuable homoallylic alcohols in particular[12] can be produced from 1,3-conjugated dienes with high stereoselectivities.[10] The Krische group demonstrated that allyl-Ru intermediates, which can be catalytically generated from 1,3-butadiene, reacted with aldehydes to furnish homoallylic alcohols with high enantiopurities.[10] Ni-catalyzed borylative 1,3-diene-aldehyde coupling, developed by the Morken group, proceeds through a different mechanism to produce homoallylic alcohols with high diastereoselectivities.[11] By contrast, Cu-catalyzed reactions using 1,3-conjugated dienes and carbonyl compounds received much less attention.[13] Liao and co-workers reported a three-component coupling of 1,3-butadiene, B_2pin_2 and imines to generate *syn*-homoallylic amines.[13a] The Yu group recently showed a Cu-catalyzed reductive hydroxymethylation of 1,3-dienes with CO_2 and silane.[13b] And Cu-catalyzed enantioselective reductive coupling of ketones with 2-azadienes and dienes was disclosed by Malcolmson and Buchwald.[13c,d]

While 1,3-butadiene and aryl-substituted 1,3-butadiene were employed in these studies, we were intrigued whether 1,3-dienylsilanes can be used to produce silyl substituted homoallylic alcohols. With our continuing interest in carbonyl allylation chemistry,[14] we herein report a Cu-catalyzed stereoselective synthesis of (*E*)-δ-silyl-*anti*-homoallylic alcohols from B_2pin_2, aldehydes and 1,3-dienylsilanes. A notable feature of this method is that the homoallylic alcohol products obtained from the reactions contain a stereochemically defined 1,3-diol unit, and an *E*-vinyl silane group that is amenable to a variety of subsequent transformations. Mechanistic studies revealed that the reaction proceeded through 1,2-borocupration of the terminal alkene unit to generate an allylcopper intermediate, with Cu residing distal to the silyl group. Subsequent aldehyde allylation occurred under Curtin–Hammett control to give homoallylic alcohol products with high selectivities.

Results and discussion

Inspired by recent studies on Cu–B addition to carbon–carbon multiple bonds[15] and allylcopper chemistry,[16–18] we envisioned a Cu-catalyzed reaction of dienylsilane, B_2pin_2 and an aldehyde to synthesize δ-silyl-homoallylic alcohols. As shown in Scheme 1, we anticipated that *in situ* generated, monodentate ligand-bound Cu–Bpin species would undergo 1,4-borocupration of dienylsilane **1a** to form an allylcopper intermediate (*Z*)-**2** first. It is conceivable that the kinetic product (*Z*)-**2** could undergo

Department of Chemistry and Biochemistry, Auburn University, Auburn, AL 36849, USA. E-mail: mzc0102@auburn.edu

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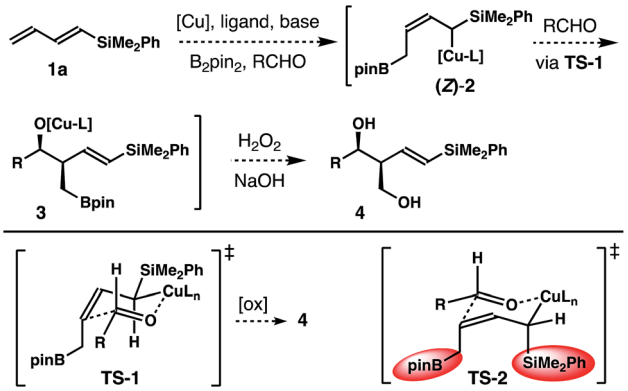
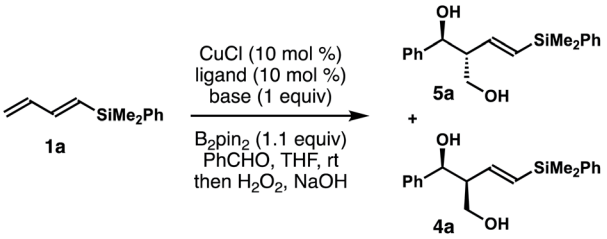


Scheme 1 Proposed approach to (*E*)-*syn*-δ-silyl homoallylic alcohols.

reversible 1,3-metalloshifts to give an (*E*)-isomer that is thermodynamically more stable. However, we surmised that such 1,3-metalloshifts might be slow owing to the electronic stabilization provided by the neighbouring –SiMe$_2$Ph group (silicon α-anion effect).[19] Subsequent nucleophilic addition of the allyl-Cu intermediate (*Z*)-**2** to aldehyde substrates[17,18] should proceed through the well-established Zimmerman–Traxler transition state[20] (**TS-1**, Scheme 1) to produce (*E*)-δ-silyl-*syn*-homoallylic alcohol products **4** upon oxidative workup. The competing transition state for the allyl addition step, **TS-2**, which would lead to the formation of a (*Z*)-olefin isomer, suffers from a severe A^{1,3} allylic strain (shown in red in **TS-2**)[21] and therefore is disfavoured. Consequently, the formation of *syn*-homoallylic alcohols **4** was anticipated from this reaction sequence.

To implement the proposed strategy, we initiated our studies to identify suitable conditions for the stereoselective reaction of dienylsilane **1a**, B$_2$pin$_2$ and benzaldehyde (Table 1). The initial experiments were conducted in the presence of 10 mol% CuCl and a ligand, 1.0 equiv. of dienylsilane **1a**, 1.0 equiv. of a base, 1.1 equiv. of B$_2$pin$_2$ and 1.2 equiv. of benzaldehyde in THF at ambient temperature. Surprisingly, when a monodentate NHC ligand IPr·HCl was utilized with NaO*t*-Bu as the base, the reaction did not produce any detectable amount of the product (entry 1, Table 1). The reaction with IMes·HCl as the ligand and NaO*t*-Bu as the base, however, generated a 6 : 1 mixture of **5a** and **4a** in 21% yield (entry 2). In contrast to the anticipated *syn* relative configuration, the major product **5a** is an *anti*-isomer as determined by coupling constant analysis of the corresponding acetonide derivative (please see the ESI† for details). The reaction with SICy·HCl as the ligand precursor gave inferior results (entry 3). Next, reactions with a bidentate phosphor ligand were conducted. The reaction with dppbz as the ligand produced a 3 : 1 mixture of **5a** and **4a** in 32% yield (entry 4). The diastereoselectivity was improved to 10 : 1 when Xantphos was utilized (entry 5). A brief evaluation of the base such as LiO*t*-Bu or KO*t*-Bu showed either a lower yield or selectivity (entries 6 and 7). While modification of the base was not fruitful, the yield of reaction was improved to 77% at the expense of diastereoselectivity with toluene as the solvent (entry 8). The reaction did not occur in the absence of any base or ligand (entries 9 and 10). Gratifyingly, we discovered that when Cu(OMe)$_2$ was

Table 1 Evaluation of the reaction conditions[a]



Entry	Ligand	Base	*Anti* : *syn*[b]	Yield (**4a** + **5a**)[c] (%)
1	IPr·HCl	NaO*t*-Bu	N.D.	N.R.
2	IMes·HCl	NaO*t*-Bu	6 : 1	21
3	SICy·HCl	NaO*t*-Bu	2 : 1	19
4	dppbz	NaO*t*-Bu	3 : 1	32
5	Xantphos	NaO*t*-Bu	10 : 1	40
6	Xantphos	LiO*t*-Bu	10 : 1	26
7	Xantphos	KO*t*-Bu	7 : 1	61
8[d]	Xantphos	NaO*t*-Bu	6 : 1	77
9	No ligand	NaO*t*-Bu	N.D.	N.R.
10	Xantphos	No base	N.D.	N.R.
11[e]	Xantphos	No base	14 : 1	87
12[e]	No ligand	No base	N.D.	N.R.

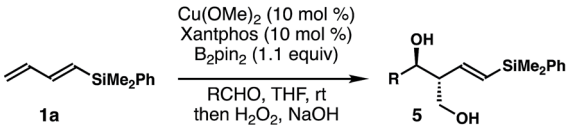
[a] Reaction conditions: dienylsilane **1a** (0.1 mmol, 1 equiv.), CuCl (10 mol%), ligand (10 mol%), base (0.1 mmol, 1 equiv.), B$_2$pin$_2$ (0.11 mmol, 1.1 equiv.), benzaldehyde (0.12 mmol, 1.2 equiv.), and THF (0.3 mL); rt, 12 h. [b] The *anti*/*syn* and *E*/*Z* ratios were determined by ^{1}H NMR analysis of the crude reaction products. [c] Yields of isolated products are listed. [d] The reaction was conducted in toluene. [e] Cu(OMe)$_2$ (10 mol%) was used as the catalyst.

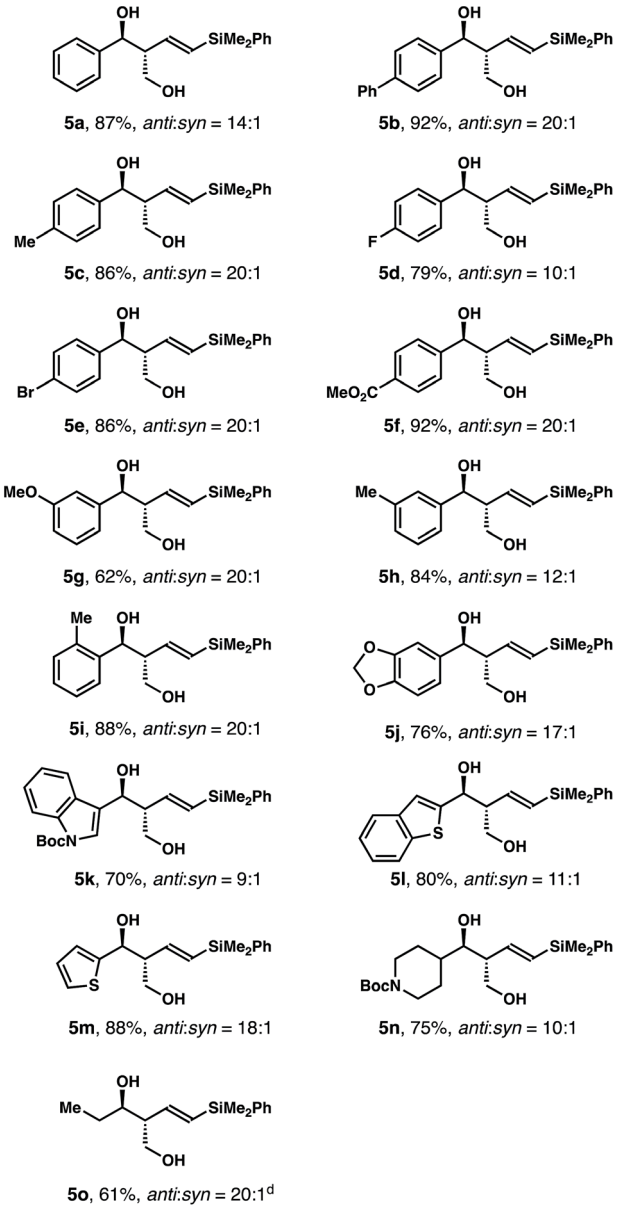
employed as the catalyst *in lieu* of CuCl, the reaction provided a 14 : 1 mixture of **5a** and **4a** in 87% yield without the addition of any base (entry 11).[22] Again, the presence of the xantphos ligand is crucial; the reaction in the absence of xantphos failed to provide any product with Cu(OMe)$_2$ as the catalyst, which suggests that the ligand-bound Cu-complex is the active catalyst for this reaction (entry 12).

The scope of the aldehyde that participated in the reactions with dienylsilane **1a** is summarized in Table 2. In general, the reaction worked well with a variety of aldehydes. For example, aromatic aldehydes with substitution at the *para*-position regardless of the electronic properties reacted to give products **5a–f** in 79–92% yields with 10–20 : 1 *anti*/*syn* ratios. Reactions with aromatic aldehydes substituted at the *meta*- or *ortho*-position proceeded to provide alcohols **5g–j** in 62–88% yields with 12–20 : 1 diastereoselectivities. Reactions with heteroaromatic aldehydes proceeded smoothly to deliver diols **5k–m** in 70–88% yields with 9–18 : 1 diastereoselectivities. Finally, aliphatic aldehydes participated in the reaction as well to give products **5n–o** in 61–75% yields with 10–20 : 1 *anti*/*syn* ratios. The olefin geometry of alcohols **5** was assigned as *E* based on ^{1}H NMR analysis of the coupling constant of olefinic protons.

To probe whether the size of the silyl group of 1,3-diene has any impact on the stereochemical outcomes of the reaction, dienylsilanes **1b–d** substituted with a different sized silyl group were synthesized, and reactions with these dienylsilanes under

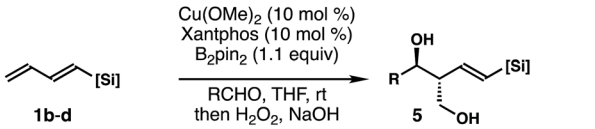
Table 2 Scope of aldehyde for reactions with dienylsilane **1a**[a,b,c]

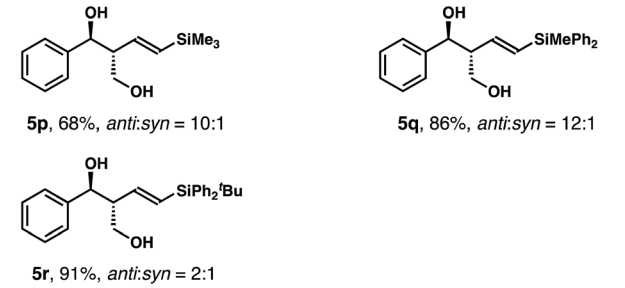




[a] Reaction conditions: diene **1a** (0.1 mmol, 1 equiv.), $Cu(OMe)_2$ (10 mol%), Xantphos (10 mol%), B_2pin_2 (0.11 mmol, 1.1 equiv.), aldehyde (0.12 mmol, 1.2 equiv.), and THF (0.3 mL); rt, 12–48 h. [b] Diastereoselectivities were determined by ^1H NMR analysis of the crude reaction products. [c] Yields of isolated products are listed. [d] Reactions were conducted at 0 °C.

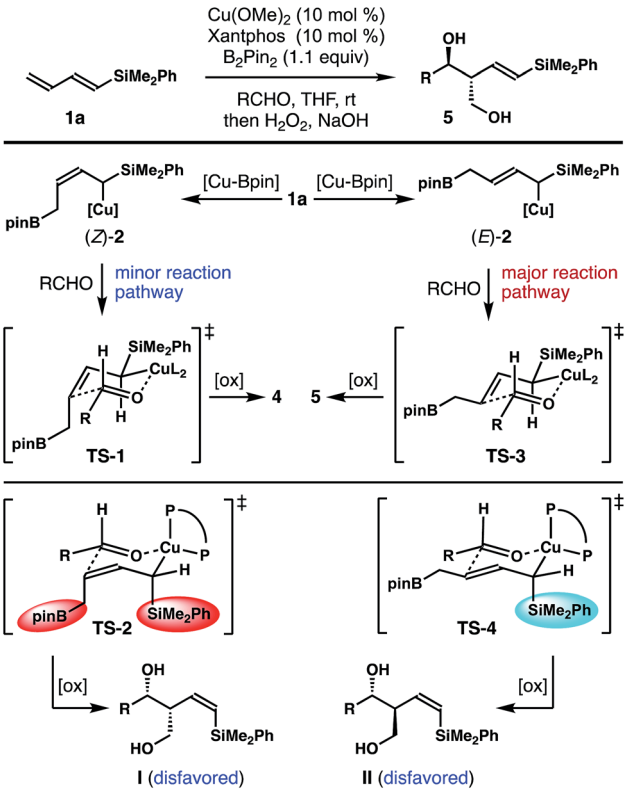
Table 3 Reactions with dienylsilanes **1b–d**



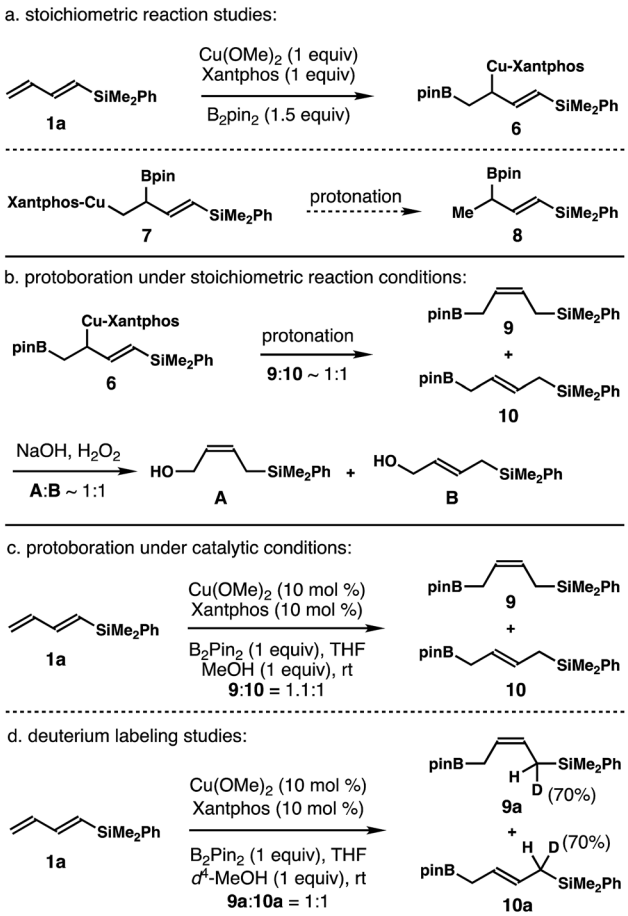


the developed conditions were conducted. As shown in Table 3, the reaction of less sterically demanding trimethylsilyl substituted 1,3-diene **1b** with benzaldehyde under standard conditions afforded the diol product **5p** in 68% yield with 10 : 1 *anti*/*syn* selectivity. Diphenylmethylsilyl substituted 1,3-diene **1c** also reacted to generate product **5q** in 86% yield with 12 : 1 *anti*/*syn* selectivity. The reaction of benzaldehyde with a much more sterically demanding $-SiPh_2{}^tBu$ substituted 1,3-diene **1d** under standard conditions provided diol **5r** as a 2 : 1 mixture of *anti* and *syn* isomers in 91% combined yield, with the *anti* adduct as the major product. In all cases, the formation of any isomer with *Z*-olefin geometry was not observed. Overall, the results indicate that the size of the silyl group of 1,3-diene does affect the *anti*/*syn* selectivity of the reaction, particularly in the case of the bulky $SiPh_2{}^tBu$ group substituted 1,3-diene **1d**.

It has been well-established that the addition of allyl copper species to aldehyde proceeded by way of a 6-membered, chair-like transition state.[16,20] Therefore, the *anti* relative stereochemistry of homoallylic alcohols **5** suggests that the dominant reaction pathway of aldehyde addition is through the allylcopper intermediate (*E*)-**2** (Scheme 2). The reaction of aldehyde with isomer (*Z*)-**2** is only a minor pathway. As shown in Scheme 2, the minor reaction pathway involves the addition of (*Z*)-**2** to an aldehyde *via* **TS-1** to give the *syn*-isomer **4** because the competing transition state **TS-2** suffers from a severe $A^{1,3}$ allylic strain (shown in red in **TS-2**).[21] Therefore, the formation of the (*Z*)-homoallylic alcohol product **I** was disfavoured, and only the *syn*-adduct **4** was formed in this minor reaction pathway. On the other hand, the addition of (*E*)-**2** to the aldehyde proceeded through a transition state **TS-3** to deliver alcohol **5** as the product in the major reaction pathway. It is worth noting that, although the competing transition state **TS-4** lacks $A^{1,3}$ allylic strains, the reaction of (*E*)-**2** with an aldehyde did not proceed through **TS-4** with pseudo axial placement of the $-SiMe_2Ph$ group in the transition state (shown in light blue in **TS-4**) to provide product **II** with *Z*-olefin geometry (alcohol **II** was not detected from the reaction). Instead, $-SiMe_2Ph$ was oriented in the pseudo equatorial position in **TS-3** to give product **5** with *E*-olefin geometry. Based on the studies of stereoelectronic effects in allylboration chemistry conducted by Hoffmann,[23] σ–π* delocalization between the σ-orbital of the C–Si single bond and the π*-orbital of the olefin unit in **TS-3** is presumably responsible for the observed *E*-alkene stereoselectivity in product **5**. In



Scheme 2 Transition state analysis.



Scheme 3 Mechanistic studies.

addition to the stereoelectronic effect, the large –$SiMe_2Ph$ group occupying a pseudo equatorial position in the transition state **TS-3** could also make **TS-3** more favourable than **TS-4**.

Although the data indicate that the dominant reaction pathway of aldehyde addition is through the allylcopper intermediate (*E*)-**2** (Scheme 2), it is not clear whether allylcopper (*E*)-**2** was generated as the major product from the addition of Xantphos-ligated Cu–Bpin species to dienylsilane **1a**. To gain mechanistic insight into this process, stoichiometric reaction studies with dienylsilane **1a** were conducted. As shown in the top panel of Scheme 3, 1 equiv. of $Cu(OMe)_2$, Xantphos (1 equiv.), dienylsilane **1a** (1 equiv.), and B_2pin_2 (1.5 equiv.) were stirred at ambient temperature, and the reaction progress was monitored by ^{1}H-NMR spectroscopy until dienylsilane **1a** was completely consumed. Surprisingly, we only observed one set of two olefinic proton signals (dd, $J = 18.7$ Hz and d, $J = 18.7$ Hz), which corresponds to a characteristic vinylsilane group with a methine group adjacent to one vinyl proton. Proton signals corresponding to either (*E*)-**2** or (*Z*)-**2** were not detected. The data indicate that the allylcopper species generated from the initial Cu–Bpin addition to diene **1a** should be a 1,2-borocupration adduct, **6** or **7** (Scheme 3a).

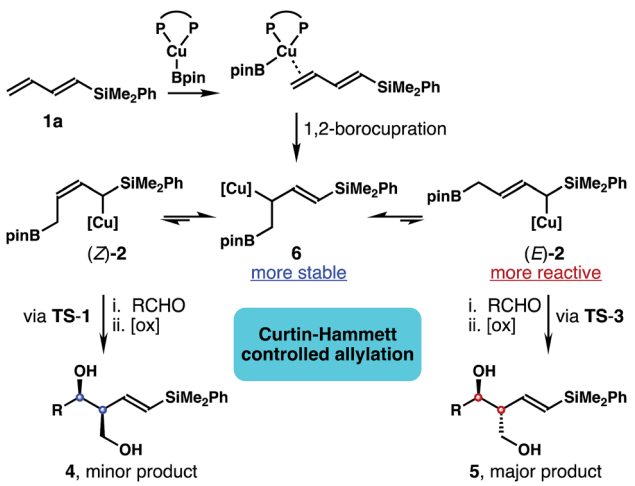
To determine which 1,2-addition product, **6** or **7**, was generated from the reaction, protonation of the intermediate obtained from stoichiometric borocupration of diene **1a** was performed. As shown in Scheme 3a, protonation of the intermediate formed *via* the stoichiometric reaction did not produce any detectable amount of the boronate intermediate **8**, which would be the product from protonation of intermediate **7**. Instead, a 1 : 1 mixture of (*Z*)- and (*E*)-allylboronates **9** and **10** was generated through a S_E2' pathway from allylcopper species **6** (Scheme 3b). A direct S_E2 protonation product from **6** was not observed. Oxidation studies further corroborated the identity of **9** and **10** as a 1 : 1 mixture of (*Z*)- and (*E*)-allylic alcohols, **A** and **B**, was formed upon oxidation (Scheme 3b). Protoboration studies of dienylsilane **1a** under the developed catalytic conditions were also conducted. As shown in Scheme 3c, the reaction of dienylsilane **1a** with 1 equiv. of B_2pin_2 and 1 equiv. of MeOH in the presence of 10 mol% $Cu(OMe)_2$ and 10 mol% Xantphos ligand provided a 1.1 : 1 mixture of (*Z*)- and (*E*)-allylboronates **9** and **10**. Again, the formation of allylboronate **8** was not detected. Finally, deuterium-labeling studies of dienylsilane **1a** were conducted with d^4-MeOH under the developed catalytic conditions. As shown in Scheme 3d, the reaction of **1a** in the presence of 1 equiv. of d^4-MeOH provided a 1 : 1 inseparable mixture of (*Z*)- and (*E*)-allylboronates **9a** and **10a** with 70% deuterium incorporation at the positions α to the –$SiMe_2Ph$ group. These data further support the S_E2' protonation pathway of allylcopper intermediate **6** to give allylboronates **9** and **10**.

These data clearly demonstrate that the most stable allylcopper intermediate generated from the initial borocupration is the 1,2-adduct **6** with copper residing distal to the –$SiMe_2Ph$

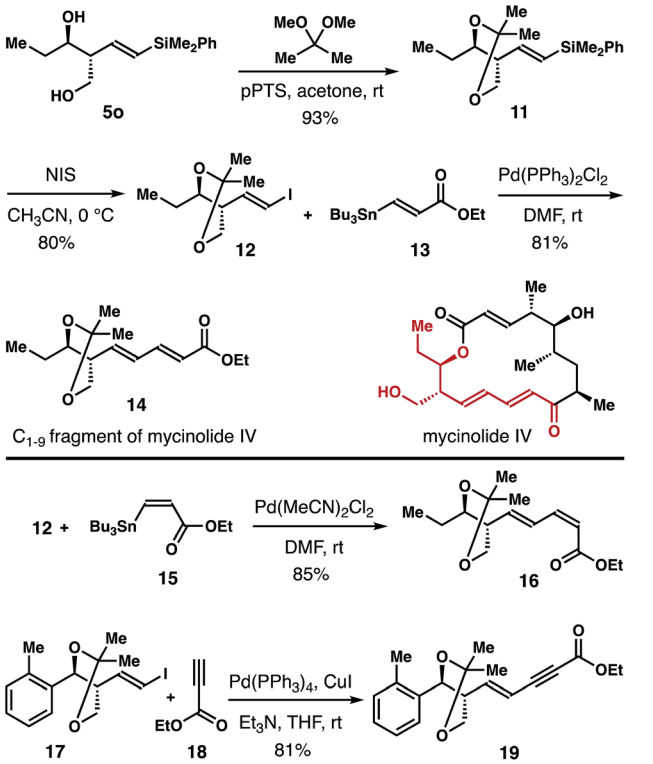
group, not the speculated allylcopper (*E*)-**2** or (*Z*)-**2** as shown in Scheme 2. Presumably the steric interaction between the Cu–Xantphos group and the –$SiMe_2Ph$ group (as in either (*E*)-**2** or (*Z*)-**2** shown in Scheme 2) is too severe to overcome by the stereoelectronic stabilization from the –$SiMe_2Ph$ group. By contrast, the results in Tables 1 and 2 indicate that the major reactive intermediate in the reactions is allylcopper (*E*)-**2**, and we were not able to detect any allylation product derived from allylcopper **6**.[25] Therefore, we conclude that (1) the activation energy for the addition of allylcopper species (*E*)-**2** to aldehyde is much lower than that of allylcopper species **6**; (2) a fast equilibrium exists among allylcopper intermediates (*E*)-**2**, (*Z*)-**2** and **6** through facile 1,3-metallo shifts; (3) the rate of equilibration among (*E*)-**2**, (*Z*)-**2** and **6** is much faster than that of allylation with aldehydes.

Based on the data obtained from these studies, we propose the following reaction pathway. As illustrated in Scheme 4, the *in situ* generated Xantphos–Cu–Bpin species coordinates to the terminal alkene unit of dienylsilane **1a** to form a Cu–olefin complex. Subsequent borylcupration[24] of diene **1a** occurred in a 1,2-addition pathway to give intermediate **6** as the most stable allylcopper species. Although **6** was generated as the predominant allylcopper species from the initial 1,2-borylcupration, the addition to the aldehyde did not occur *via* allylcopper **6**. Instead, intermediate **6** equilibrates with (*E*)-**2** and (*Z*)-**2** *via* rapid and reversible 1,3-metalloshifts,[25] and subsequent nucleophilic addition to the aldehyde proceeded *via* the more reactive allylcopper (*E*)-**2**.[26] Therefore, intermediate **6** is funnelled to allylcopper (*E*)-**2** under Curtin–Hammett control[27] to generate the *anti*-adduct **5** from the allylation. Presumably the stereoelectronic benefit from the σ–π* delocalization of the α-silyl group makes **TS-3** the lowest energy transition state for the allylation.

The homoallylic alcohol product **5** obtained from the reaction is highly valuable because it contains a stereochemically defined 1,3-diol unit, and a vinyl silane group that is amenable to a variety of subsequent transformations.[28] Synthetic applications of this method are shown in Scheme 5.



Scheme 4 Proposed reaction pathway.



Scheme 5 Synthesis of the C_{1-9} fragment of mycinolide IV and derivatization of reaction products.

Diol **5o** was converted into acetonide **11** in 93% yield. Then acetonide **11** was transformed into vinyl iodide **12** in 80% yield with NIS as the iodination reagent. Pd-catalyzed Stille-coupling of vinyl iodide **12** with (*E*)-vinyl stannane **13** [29] gave product **14** in 81% yield, which corresponds to the C_{1-9} fragment of the polyketide natural product mycinolide IV. In addition, Pd-catalyzed cross-coupling of **12** and (*Z*)-vinyl stannane **15** [30] delivered diene **16** in 85% yield. Sonogashira coupling of **17** with ethyl propiolate (**18**) furnished enyne **19** in 81% yield.[31]

Conclusions

In summary, we developed Cu-catalyzed diastereoselective synthesis of (*E*)-δ-silyl-*anti*-homoallylic alcohols from 1,3-dienylsilanes.[32] Mechanistic studies revealed that the borocupration proceeded through a 1,2-addition pathway to give the allylcopper intermediate **6** as the most stable allylcopper species. However, the allylcopper intermediate **6** was funnelled to more reactive allylcopper species (*E*)-**2** *via* reversible 1,3-metallo shifts under Curtin–Hammett control in the subsequent aldehyde allylation step to give (*E*)-δ-silyl-*anti*-homoallylic alcohols with high diastereoselectivity. The α-silicon effect is proposed to be the underlying driving force for the observed selectivity. This method was applied to the synthesis of the C_{1-9} fragment of a polyketide natural product mycinolide IV. Other synthetic applications of this method will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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