Asymmetric Syntheses of (*Z*)- or (*E*)-β,γ-Unsaturated Ketones via Silane-Controlled Enantiodivergent Catalysis

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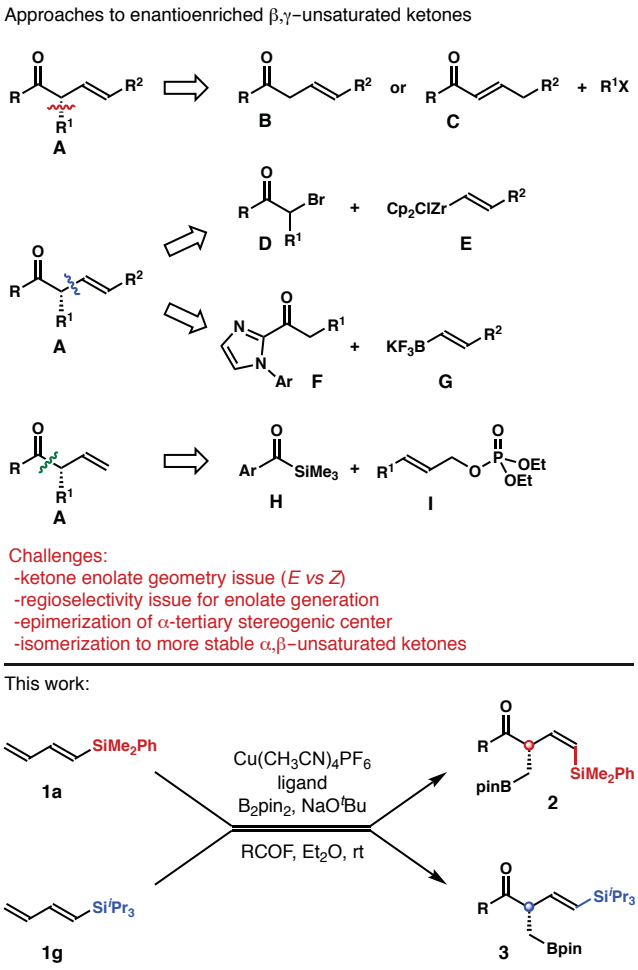
ABSTRACT: A Cu-catalyzed highly stereoselective and enantiodivergent syntheses of (*Z*)- or (*E*)-β,γ-unsaturated ketones from 1,3-butadienyl silanes is developed. The nature of silyl group of the dienes has a significant impact on the stereo- and enantioselectivity of the reactions. Under the developed catalytic systems, the reactions of acyl fluorides with phenyldiemthylsilyl-substituted 1,3-diene gave (*Z*)-β,γ-unsaturated ketones bearing an α-tertiary stereogenic center with excellent enantioselectivities and high *Z*-selectivities, where the reactions with triisopropylsilyl-substituted 1,3-butadiene formed (*E*)-β,γ-unsaturated ketones with high optical purities and excellent *E*-selectivities. The products generated from the reactions contain three functional groups with orthogonal chemical reactivities, which can undergo a variety of transformations to afford synthetically valuable intermediates.

INTRODUCTION

Enantioenriched small molecules with multiple functional groups are valuable intermediates in synthetic organic chemistry.[1] In this context, chiral nonracemic, acyclic β,γ-unsaturated ketones with an α-tertiary stereocenter (e.g., **A** in Scheme 1) are of great importance. Such entities are common scaffolds in bioactive natural products,[2,3] and more importantly, the functional groups embedded in these molecules provide useful handles for further derivatization.[4] However, several challenges exist for asymmetric syntheses of chiral nonracemic acyclic β,γ-unsaturated ketones **A**.[5] For classic base-mediated enolate alkylation chemistry, the Enders' SAMP/RAMP chiral auxiliary-assisted ketone α-alkylation for instance, the enolate geometry and the π-facial selectivity of the alkylation will dictate stereochemical outcomes of the C–C bond formation event.[6] In the cases of ketones **B** and **C**, regioselective formation of stereodefined enolates is challenging when R is an alkyl group with hydrogen atom(s) α to the carbonyl group.[7] Moreover, the α-tertiary stereocenter in **A** is prone to epimerization via enolization under basic conditions typically required for the enolate generation. Modern Pd-catalyzed cross-coupling chemistry has seen much success in ketone α-vinylation that forms a quaternary stereocenter at the α-position.[8] However, an analogous process to generate enantioenriched acyclic ketones with an α-tertiary stereocenter has yet to be accomplished, likely owing to the similar epimerization issue. Moreover, in contrast to the carbonyl compounds bearing an α-quaternary stereocenter, the alkene group in ketones **A** could undergo isomerization to form thermodynamically more stable α,β-unsaturated ketones and abolish the stereogenic center at the α-position in **A**.

Not surprisingly, the development of novel methods that can overcome these challenges and permit the access to enantioenriched acyclic β,γ-unsaturated ketones has attracted significant attention from the organic synthesis community. In the past ten years, several approaches have been disclosed for asymmetric syntheses of such ketones.[9,10] As shown in Scheme 1, Fu and coworkers developed an elegant Ni-catalyzed enantioconvergent cross-coupling of racemic α-bromoketone **D** with *E*-alkenylzirconium reagent **E** to generate β,γ-unsaturated ketone **A** with high enantioselectivity.[9a,b] By taking advantage of the single electron transfer processes in electrochemistry, the Meggers group showed that enantioenriched ketone **A** can be synthesized via nucleophilic α-alkenylation of 2-acyl imid-

Scheme 1. Methods for Enantioselective Syntheses of β,γ-Unsaturated Ketones with an α-Tertiary Stereocenter

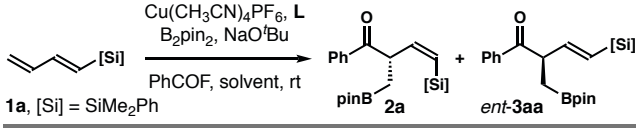


azole **F** with potassium alkenyl trifluoroborate **G**.[9c] More recently, Sawamura and coworkers reported a copper-catalyzed asymmetric acylation of allylic phosphate **I** with acylsilane **H** to generate β,γ-unsaturated ketone **A** under photochemical conditions.[9d] In spite of these important achievements, methods that could allow for rapid construction of such enantioenriched ketones with the flexibility of controlling the alkene geometry would be valuable.

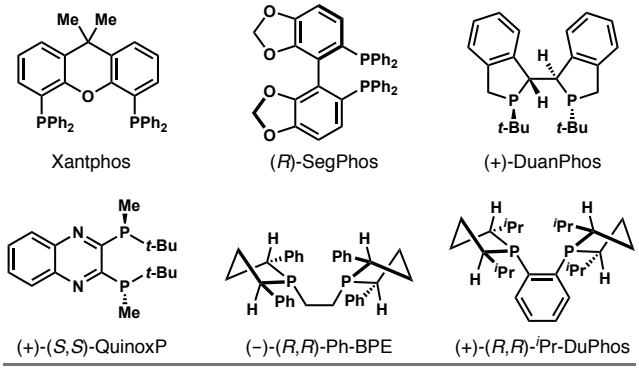
As our continuing research interest in asymmetric catalysis, we report herein Cu-catalyzed enantiodivergent syntheses of acyclic (*E*)- or (*Z*)-β,γ-unsaturated ketones with an α-tertiary stereocenter from 1,3-butadienyl silanes and acyl fluorides (Scheme 1).[11] We discovered that, with an appropriate silyl group in place, either *Z*- or *E*-isomers can be synthesized with high stereo- and enantioselectivities via distinct α-silyl-allylic copper intermediates. Intriguingly, the absolute configuration of the α-tertiary stereocenter in the *Z*-isomers is opposite to the one in the *E*-isomers using the same (*R*,*R*)-Ph-BPE ligand. The products generated from the reactions contain three functional groups, a ketone, a vinyl silane and an alkyl boronate, which have orthogonal chemical reactivities. Chemoselective transformations of these functional groups provide a variety of valuable intermediates for organic synthesis.

RESULTS AND DISCUSSION

Table 1. Evaluation of Reaction Conditions [a]



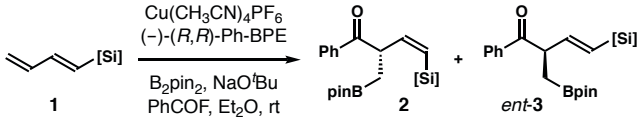
entry	Ligand (**L**)	solvent	*Z*:*E* [b]	yield (%)[c]	ee (**2a**) (%)[d]
1	no ligand	Et_2O	ND	NR	ND
2	Xantphos	Et_2O	1:>20	76	ND
3	(*R*)-SegPhos	Et_2O	1:4	74	36
4	(+)-DuanPhos	Et_2O	1:4	83	14
5	(*S*,*S*)-QuinoxP	Et_2O	1:2	69	65
6	(*R*,*R*)-Ph-BPE	Et_2O	7:1	90	99
7	(*R*,*R*)-Ph-BPE	THF	6:1	29	98
8	(*R*,*R*)-Ph-BPE	toluene	7:1	88	96
9	(*R*,*R*)-Ph-BPE	MTBE	7:1	90	97
10	(*R*,*R*)-Ph-BPE	dioxane	7:1	57	95
11	(*R*,*R*)-Ph-BPE	cyclohexane	7:1	90	92
12	(*R*,*R*)-^{i}Pr-DuPhos	Et_2O	>20:1	81	99



(a) Reaction conditions: diene **1a** (0.1 mmol, 1.0 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), ligand (12 mol %), B_2pin_2 (1.5 equiv), NaO^tBu (1.5 equiv), PhCOF (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *Z*/*E*-selectivities were determined by ^1H NMR analysis of the crude reaction products. (c) Yields of isolated products are listed (**2a** and *ent*-**3aa** combined). (d) Enantioselectivities were determined by HPLC analysis using a chiral stationary phase.

Reaction Development: We began our studies by identifying a suitable catalytic system to synthesize β,γ-unsaturated ketone using diene **1a** and benzoyl fluoride as the model substrates.[12] As shown in Table 1, initial experiments were conducted with $Cu(CH_3CN)_4PF_6$ as the precatalyst and NaO^tBu as the base. The reaction did not occur without the ligand (entry 1). In the presence of 10 mol % of $Cu(CH_3CN)_4PF_6$, 12 mol % of Xantphos, 1.5 equiv of B_2pin_2 and NaO^tBu, the reaction of diene **1a** with PhCOF proceeded in Et_2O at ambient temperature to give racemic product **3aa** in 76% yield with excellent *E*-selectivity (entry 2). When Xantphos was replaced by a chiral, nonracemic bidentate phosphine ligand (*R*)-SegPhos, ketones *ent*-**3aa** and **2a** were obtained in 74% combined yield and 4:1 *E*-selectivity with 36% ee for ketone **2a** (entry 3). The reaction with (+)-DuanPhos as the ligand gave *ent*-**3aa** and **2a** in a similar yield and *E*-selectivity (83% combined, 4:1) with poor enantioselectivity for **2a** (14% ee, entry 4). In the presence of ligand (*S*,*S*)-QuinoxP, the reaction generated *ent*-**3aa** and **2a** in 69% combined yield with 2:1 *E*-selectivity, although in this case respectable enantiomeric excess (65% ee) was observed for ketone **2a** (entry 5). The reaction conducted with (*R*,*R*)-Ph-BPE as the ligand, intriguingly, afforded a 7:1 mixture of ketones **2a** and *ent*-**3aa**, favoring *Z*-isomer **2a**. More importantly, excellent enantiomeric excess was observed for **2a** (99% ee, entry 6). Encouraged by the results, we further explored the reaction parameters aiming to improve the *Z*-selectivity of the reaction. Examining the experiments with several solvents revealed that the *Z*-selectivity is not sensitive to the reaction media (6-7:1), while there is some degree of variation in enantioselectivities (92-98% ee for **2a**, entries 7-11). In the case with THF as the solvent, a significant amount of *t*-butyl benzoate was obtained from the reaction of PhCOF with NaO^tBu, and **2a** was isolated only in 29% yield (entry 7). Varying the copper precatalyst and the base did not improve the *Z*-selectivity of the reaction either (data not shown). Gratifyingly, when (*R*,*R*)-^{i}Pr-Duphos was utilized as the ligand, product **2a** was obtained in 81% yield with >20:1 *Z*-selectivity and 99% ee (entry 12). The catalyst loadings can be decreased to 5 mol % or 2.5 mol %; and ketone **2a** with an epimerizable α-tertiary stereocenter was isolated in similar levels of yields, *Z*-selectivities and enantioselectivities under these conditions.

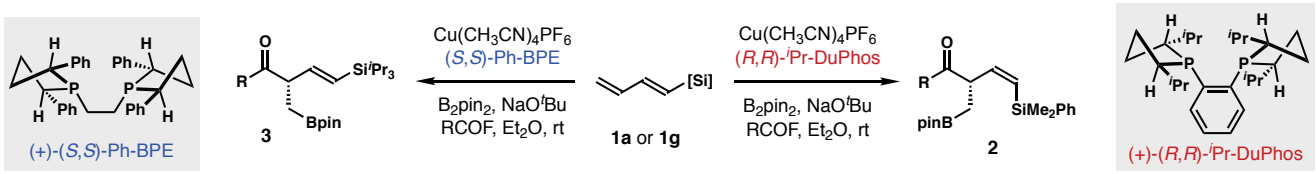
Table 2. Evaluation of the Impact of Silyl Group of Diene 1 on the Selectivities of the Reaction [a]

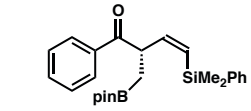


entry	[Si]	*Z*/*E* [b]	yield (%)[c]	ee (**2**) (%)[d]	ee (*ent*-**3**) (%)[d]
1	$SiMe_2Ph$ (**1a**)	7:1	90	99	ND
2	$SiMe_3$ (**1b**)	6:1	73	90	ND
3	$SiMePh_2$ (**1c**)	3:1	89	95	68
4	$SiEt_3$ (**1d**)	1:1	75	94	71
5	$SiMe_2{}^tBu$ (**1e**)	1:2	83	98	86
6	$SiPh_2{}^tBu$ (**1f**)	1: >20	82	ND	90
7	Si^iPr_3 (**1g**)	1: >20	93	ND	96

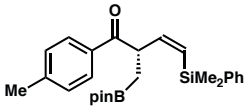
(a) Reaction conditions: diene **1** (0.1 mmol, 1.0 equiv), $Cu(CH_3CN)_4PF_6$ (2.5 mol %), ligand (3 mol %), B_2pin_2 (1.5 equiv), NaO^tBu (1.5 equiv), PhCOF (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *Z*/*E*-selectivities were determined by ^1H NMR analysis of the crude reaction products. (c) Yields of isolated products are listed (**2** and *ent*-**3** combined). (d) Enantioselectivities were determined by HPLC analysis using a chiral stationary phase.

Scheme 2. Scope of Acyl Fluorides in Reactions with Dienes 1 [a-d]

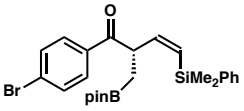




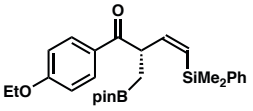
2a, 81%, *Z*:*E* > 20:1, 99% ee



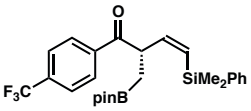
2b, 85%, *Z*:*E* > 20:1, 99% ee



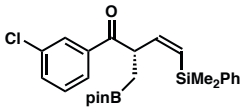
2c, 82%, *Z*:*E* > 20:1, 99% ee



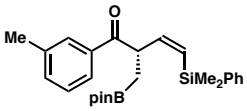
2d, 90%, *Z*:*E* > 20:1, 99% ee[e]



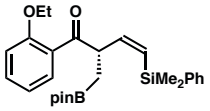
2e, 57%, *Z*:*E* = 5:1, 99% ee



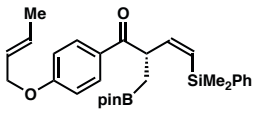
2f, 84%, *Z*:*E* > 20:1, 99% ee



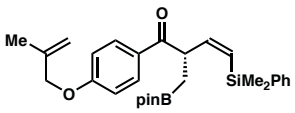
2g, 81%, *Z*:*E* > 20:1, 99% ee



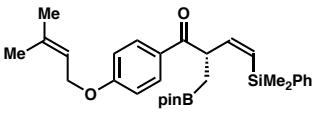
2h, 82%, *Z*:*E* = 9:1, 99% ee[e]



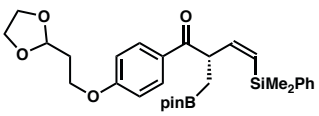
2i, 90%, *Z*:*E* > 20:1, 98% ee[e]



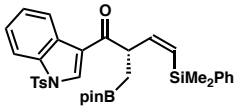
2j, 84%, *Z*:*E* > 20:1, 99% ee[e]



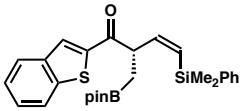
2k, 61%, *Z*:*E* > 20:1, 99% ee[e]



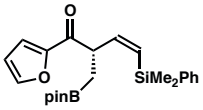
2l, 84%, *Z*:*E* > 20:1, 99% ee[e]



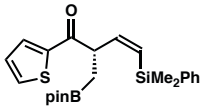
2m, 70%, *Z*:*E* = 9:1, 99% ee



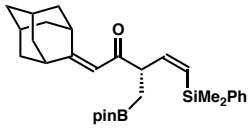
2n, 74%, *Z*:*E* = 9:1, 98% ee



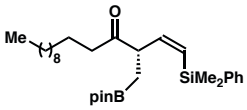
2o, 83%, *Z*:*E* > 20:1, 99% ee



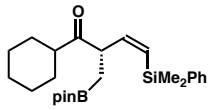
2p, 84%, *Z*:*E* > 20:1, 98% ee



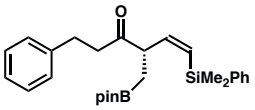
2q, 75%, *Z*:*E* > 20:1, 99% ee



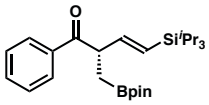
2r, 68%, *Z*:*E* > 20:1, 99% ee



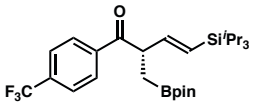
2s, 54%, *Z*:*E* > 20:1, 99% ee



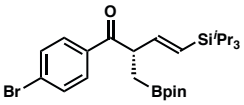
2t, 51%, *Z*:*E* > 20:1, 99% ee



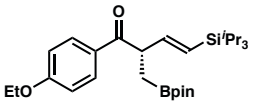
3a, 93%, *E*:*Z* > 20:1, 96% ee



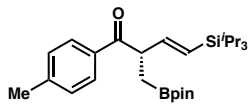
3b, 94%, *E*:*Z* > 20:1, 86% ee



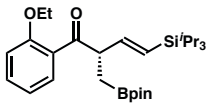
3c, 94%, *E*:*Z* > 20:1, 86% ee



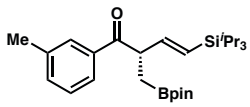
3d, 86%, *E*:*Z* > 20:1, 88% ee



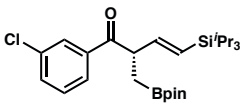
3e, 85%, *E*:*Z* > 20:1, 87% ee



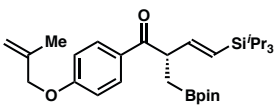
3f, 78%, *E*:*Z* > 20:1, 85% ee



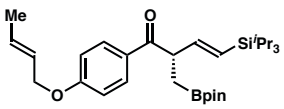
3g, 88%, *E*:*Z* > 20:1, 92% ee



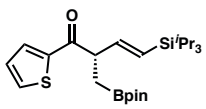
3h, 92%, *E*:*Z* > 20:1, 84% ee



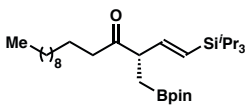
3i, 88%, *E*:*Z* > 20:1, 90% ee



3j, 90%, *E*:*Z* > 20:1, 88% ee



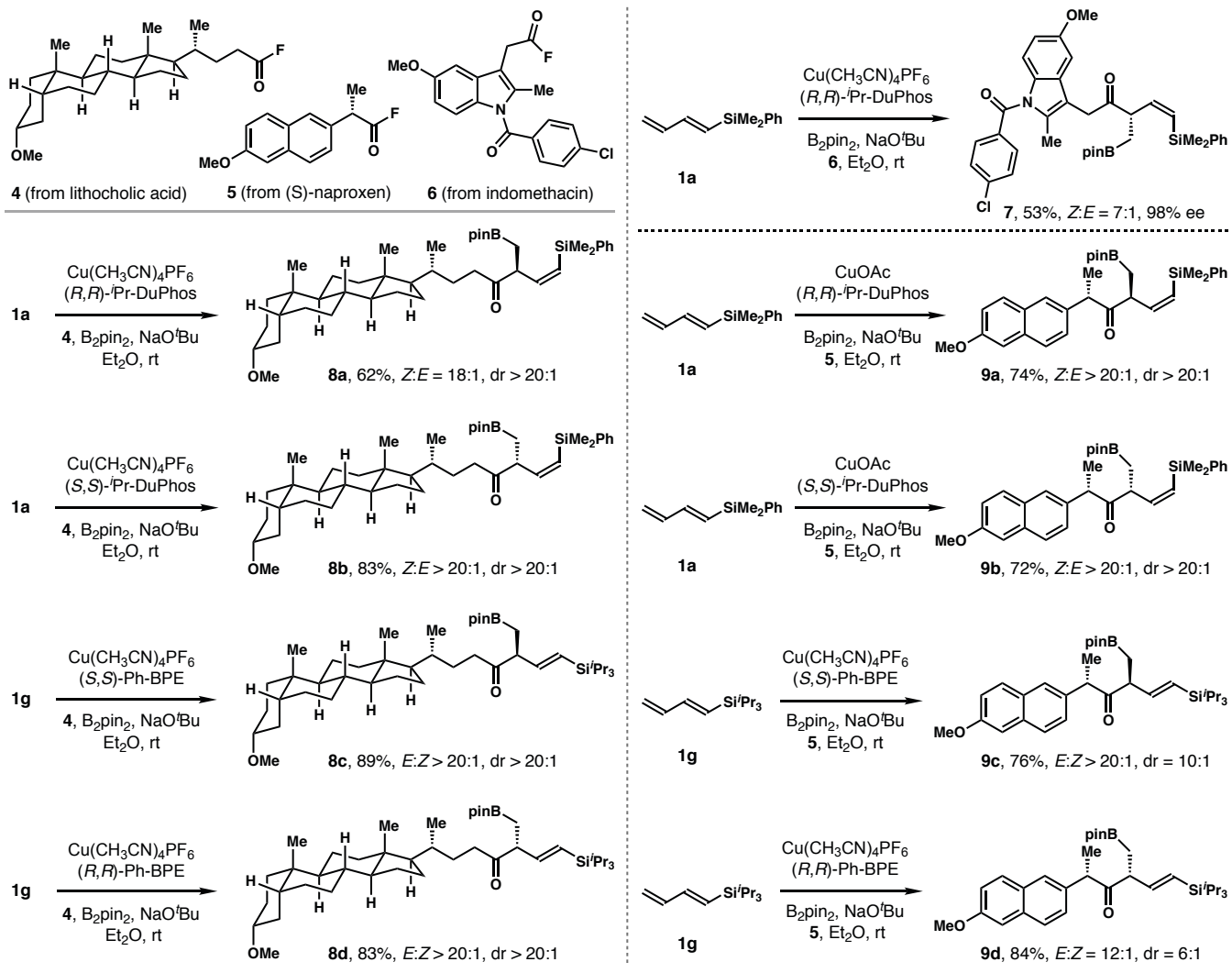
3k, 91%, *E*:*Z* > 20:1, 88% ee



3l, 67%, *E*:*Z* > 20:1, 90% ee

(a) Reaction conditions: dienylsilane **1** (0.1 mmol, 1.0 equiv), $Cu(CH_3CN)_4PF_6$ (5 mol %), ligand (6 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), acyl fluoride (1.5 equiv), Et_2O (1.5 mL), rt, 0.5-3 h. Reactions with 2.5 mol % catalyst and 3 mol % ligand loadings gave products with similar levels of yields, *E*/*Z*-selectivities and enantioselectivities. (b) The *E*/*Z*-selectivities were determined by ^{1}H NMR analysis of the crude reaction mixture. (c) Yields of isolated products are listed. (d) Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. (e) B_2pin_2 (1.05 equiv) was used.

Scheme 3. Reactions with Complex Molecule-Derived Acyl Fluorides [a-d]

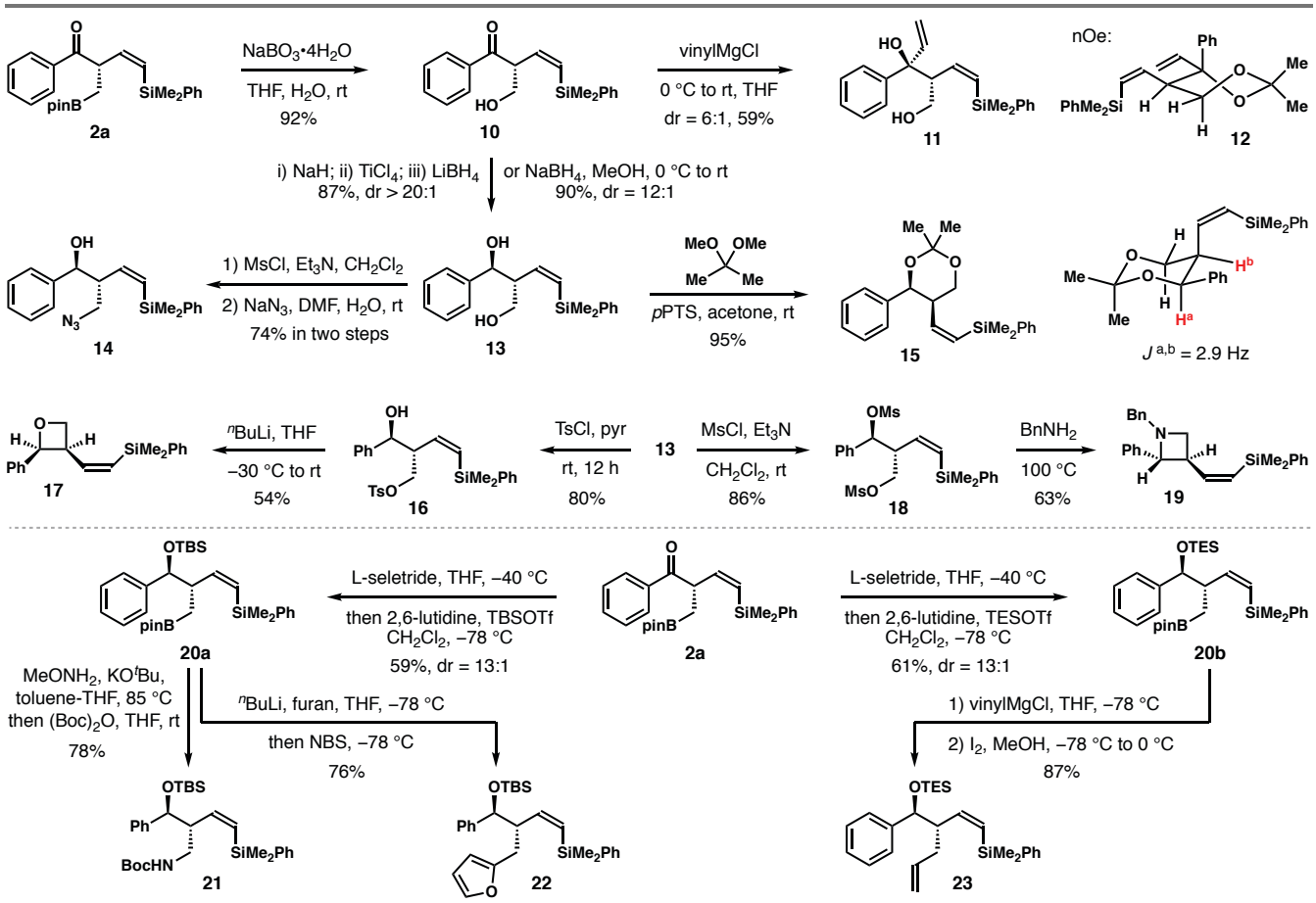


(a) Reaction conditions: dienylsilane **1** (0.10 mmol, 1.0 equiv), [Cu] catalyst (5 mol %), ligand (6 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), acyl fluoride (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *E*/*Z*-selectivities and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixture. (c) Yields of isolated products are listed. (d) Enantiomeric excess of **7** was determined by HPLC analysis using a chiral stationary phase.

To investigate whether the nature of silyl group has any impact on the *E*/*Z*-selectivity and enantioselectivity of the reaction, we synthesized a variety of 1,3-dienes **1b**-**g** with different silyl groups[13] and conducted the reactions under the standard conditions with (*R*,*R*)-Ph-BPE as the ligand. As shown in Table 2, the reaction with Me_3Si-substituted diene **1b** formed *Z*-isomer **2** as the major product (*Z*:*E* = 6:1) with 90% ee (entry 2). Poor *E*/*Z*-selectivities were observed for $MePh_2Si$-, Et_3Si-, or ^{t}BuMe$_2$Si-substituted diene **1c**, **1d** or **1e** (entries 3-5). While the optical purities of *Z*-products **2** are high in these reactions (94-98% ee), the enantiomeric excesses of the *E*-isomers *ent*-**3** are moderate (68-86% ee). Unexpectedly, when the reactions were conducted with Ph$_2$^{t}BuSi- or ^{i}Pr$_3$Si-substituted diene, **1f** or **1g**, excellent *E*-selectivities (>20:1) were observed, and formation of the *Z*-isomers was not detected (entries 6-7). In the case of ^{i}Pr$_3$Si-substituted diene **1g**, the enantioselectivity of the *E*-product was 96% ee (entry 7). Slightly lower enantioselectivity (90% ee) was observed for the reaction with diene **1f** (entry 6). It is worth mentioning that, under identical catalytic system with (*R*,*R*)-Ph-BPE as the ligand, the absolute configuration of the α-tertiary stereocenter in the *Z*-isomer **2** (entry 6, Table 1) is opposite to that in the *E*-isomer *ent*-**3** (entries 6-7, Table 2), although the *Z*-selectivity can be further improved by employing (*R*,*R*)-^{i}Pr-Duphos as the ligand (entry 12, Table 1).

Substrate Scope: Scheme 2 summarizes the scope of acyl fluorides that participated in the reactions with dienes **1** under the optimized conditions. For diene **1a**, (*R*,*R*)-^{i}Pr-Duphos was employed as the ligand, and in the case of diene **1g**, ligand (*S*,*S*)-Ph-BPE was utilized. In general, the reactions worked well with a broad range of acyl fluorides, including aromatic, heteroaromatic and aliphatic acyl fluorides to generate ketones **2** or **3** in good yields with high enantioselectivities. For instance, reactions of **1a** with *para*-substituted benzoyl fluorides gave products **2b**–**d** in 82-90% yields with 99% ee and excellent *Z*-selectivities (>20:1). In the case of **2e**, the *Z*-selectivity is moderate, although the enantiomeric excess remains high (99% ee). Reactions of benzoyl fluorides bearing a substituent at either the *meta*- or *ortho*-position proceeded smoothly to furnish ketones **2f**–**h** in 81-84% yields with 99% ee and 9-20:1

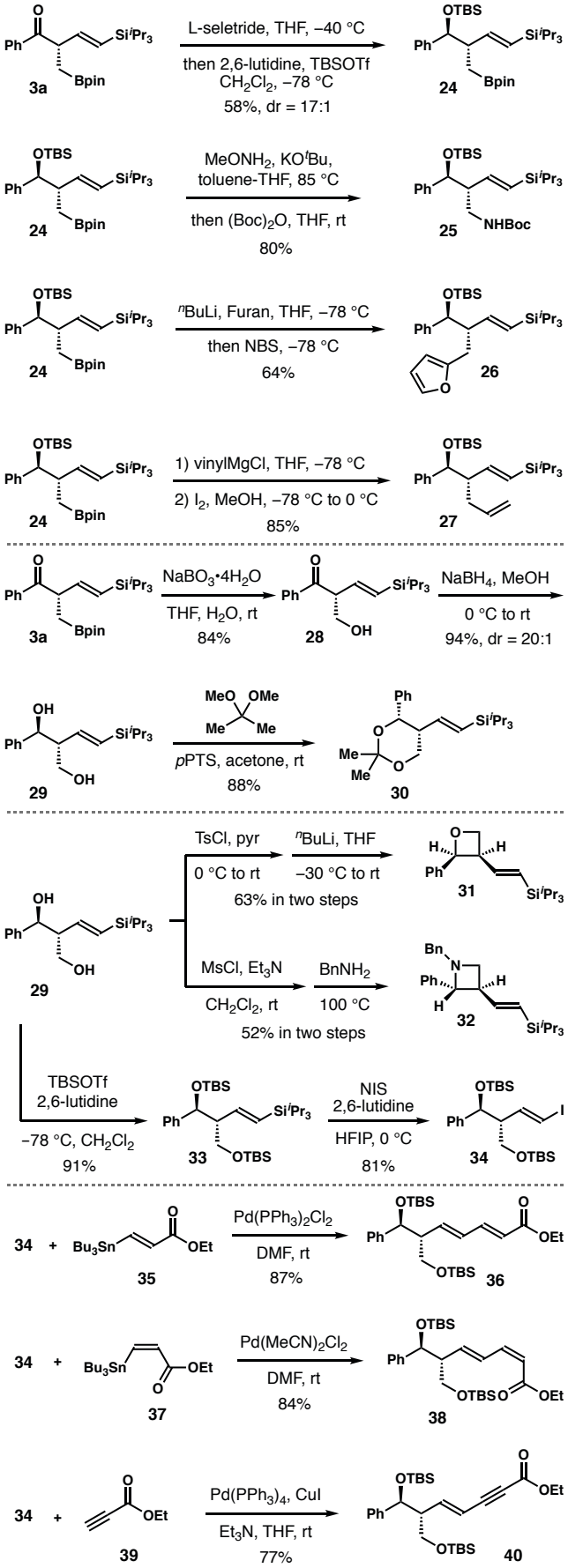
Scheme 4. Transformation of Reaction Products from Diene 1a



Z-selectivities. The reaction tolerates alkenes with various substitution patterns, affording ketones **2i–k** in 61-90% yields with 98-99% ee and >20:1 *Z*-selectivities. Benzoyl fluoride with a cyclic acetal is also a suitable substrate for the reaction, and ketone **2l** was isolated in 84% yields with 99% ee and >20:1 *Z*-selectivity. Acyl fluorides containing a heterocycle such as an indole, benzothiophene, furan, or thiophene reacted under the standard conditions to generate products **2m–p** in 70-84% yields with 98-99% ee and high *Z*-selectivities. The reaction with an α, β-unsaturated acyl fluoride gave ketone **2q** in 75% yield with 99% ee and >20:1 *Z*-selectivity. Importantly, a variety of aliphatic acyl fluorides participated in the reactions to deliver products **2r–t** with 99% ee and excellent *Z*-selectivities, albeit in moderate yields (51-68%). The absolute configuration of tertiary stereocenter was assigned by modified Mosher ester analysis of the diol derivatives and coupling constant analysis of the acetonides derived from the diols (c.f., compounds **13** and **15**, Scheme 4).[14] The scope of acyl fluorides that reacted with diene **1g** in the presence of ligand (*S*,*S*)-Ph-BPE was explored next. As shown in the bottom panel of Scheme 2, a range of acyl fluorides reacted with diene **1g** to give ketones **3a–l** in 67-94% yields with 84-96% ee. Although in general the enantioselectivity in this series is not as high as those from the reactions with diene **1a**, the stereoselectivity remains excellent (>20:1 *E*-selectivities in all cases).

Reactions with Complex Molecule-Derived Acyl Fluorides: To probe whether the reaction can be applied to more complex systems, we prepared several acyl fluorides **4-6** derived from lithocholic acid, (*S*)-naproxen and indomethacin.[15] As shown in Scheme 3, the reaction of acyl fluoride **6** with diene **1a** utilizing (*R*,*R*)-^{i}Pr-Duphos as the ligand gave ketone **7** in 53% yield with 98% ee and 7:1 *Z*-selectivity. The reactions between acyl fluoride **4** and diene **1a** with either (*R*,*R*)-^{i}Pr-Duphos or (*S*,*S*)-^{i}Pr-Duphos as the ligand gave ketones **8a–b** in 62-83% yields and excellent diastereoselectivities. A slightly lower *Z*-selectivity (18:1) was observed in the case of **8a**. Similar results were achieved in reactions with diene **1g**, furnishing ketones **8c–d** in 83-89% yields with excellent diastereoselectivities and *E*-selectivities. For (*S*)-naproxen-derived acyl fluoride **5** with an epimerizable tertiary stereocenter, reactions with diene **1a** were conducted with CuOAc as the precatalyst to achieve higher conversions. Ketone products **9a–b** were isolated in 72-74% yields with >20:1 *Z*-selectivities and diastereoselectivities. The reaction with diene **1g** employing (*S*,*S*)-Ph-BPE as the ligand gave ketone **9c** in 76% yield with 10:1 diastereoselectivity and >20:1 *E*-selectivity. A synthetically useful diastereoselectivity (6:1) and *E*-selectivity (12:1) were observed when the reaction was conducted with (*R*,*R*)-Ph-BPE as the ligand, affording **9d** as the major product (84% combined yield). These data indicate that reactions with complex molecule-derived acyl fluorides proceeded under the catalyst-control with good to excellent diastereoselectivities. Notably, the mild conditions tolerate racemizable acyl fluorides such as **5**, and the results from these diastereoselective reactions bode well for further synthetic applications of this method.

Scheme 5. Product Derivatization



Product Derivatization: Ketone products **2** generated from the reactions with diene **1a** contain three functional groups, ketone, alkyl boronate and *Z*-alkenyl silane, which can undergo a variety of chemoselective transformations to afford synthetically valuable building blocks. As shown in Scheme 4, oxidation of the alkyl boronate group of **2a** with $NaBO_3$ gave keto-alcohol **10** in 92% yield. Chelation-controlled vinyl Grignard addition to **10** afforded tertiary alcohol **11** in 59% yield with 6:1 diastereoselectivity.[16] The stereochemistry of **11** was assigned by nOe analyses of acetonide derivative **12**. Treatment of **10** sequentially with NaH, $TiCl_4$ and $LiBH_4$ provided diol **13** in 87% yield with >20:1 diastereoselectivity.[17] Alternatively, direct reduction of **10** with $NaBH_4$ gave diol **13** in 90% yield with 12:1 diastereoselectivity.[18] The primary hydroxyl group of diol **13** was selectively converted into an azide group, and product **14** was isolated in 74% yield by using the two-step reaction sequence. Diol **13** was transformed into acetonide **15** under the standard conditions. The coupling constant analyses established the *anti*-relative stereochemistry of **13**.[19] Tosylation of diol **13** occurred selectively at the primary hydroxyl group to give **16** in 80% yield. Treatment of tosylate **16** with BuLi formed oxetane **17** in 54% yield.[20] Mesylation of both hydroxyl groups of diol **13** gave product **18** in 86% yield. Exposure of bismesylate **18** to $BnNH_2$ at 100 °C gave azetidine **19** in 63% yield.[21] The Bpin group in ketones **2** also offers a handle for product derivatization. For instance, reduction of the carbonyl group of **2a** followed by protection of the resulting alcohol gave TBS-ether **20a** in 59% yield with a 13:1 dr. Amination of the Bpin group using the protocol developed by the Morken group furnished product **21** in 78% yield.[22] By adopting the method developed by the Aggarwal group,[23] the Bpin group was converted into a furyl group, and product **22** was isolated in 76% yield. Similarly, ketone **2a** was converted into TES-ether **20b** in 61% yield. Subsequent vinylation of the Bpin group afforded product **23** in 87% yield.[24]

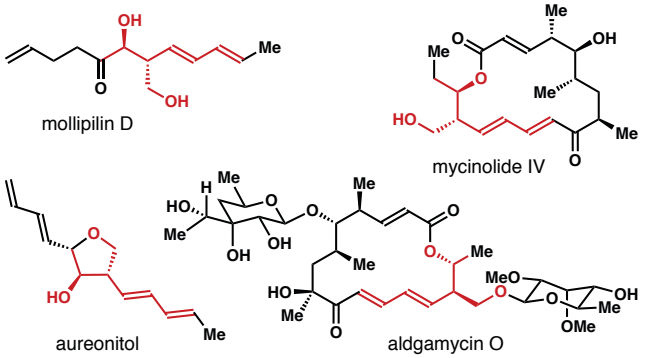
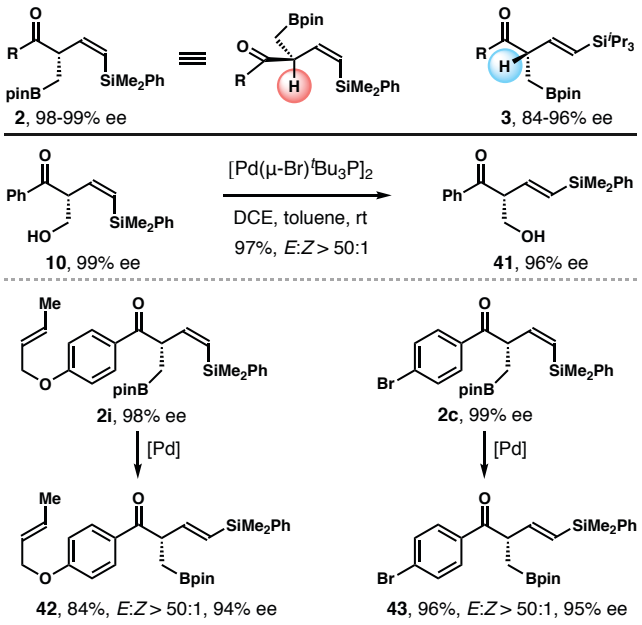


Figure 1. Selected natural products

Scheme 5 summarizes the transformations of ketone products **3** generated from diene **1g**. Ketone **3a** was transformed into a TBS-ether using the same reduction-protection reaction sequence, affording **24** in 58% yield and 17:1 dr. Amination, arylation or vinylation of the Bpin group of **24** delivered products **25**-**27** in 64-85% yields. The alkyl boronate group of **3a** also underwent oxidation with $NaBO_3$ to give keto-alcohol **28** in 84% yield. Reduction of the carbonyl group of **28** with $NaBH_4$ formed diol **29** in 94% yield with 20:1 diastereoselectivity. The *anti*-relative stereochemistry of **29** was confirmed by coupling constant analyses of acetonide derivative **30**. Tosylation of the primary alcohol of diol **29** and base-mediated

cyclization afforded oxetane **31** in 63% yield. Diol **29** was converted into azetidine **32** in 52% yield using a mesylation-cyclization reaction sequence. Additionally, the vinyl silane group of diol **29** can also participate in reactions to construct a C-C bond. Protection of diol **29** under the standard conditions gave silyl ether **33**. Treatment of **33** with NIS and 2,6-lutidine furnished vinyl iodide **34** in 81% yield.[25] Pd-catalyzed Stille coupling of **34** with *E*-vinylstannane **35** generated *E*,*E*-1,3-diene **36** in 87% yield.[26] Such a diene is a common structural motif in numerous natural products, for instance, mollipilin D, mycinolide IV and aldgamycin O (Figure 1).[27] Vinyl iodide **34** also reacted with *Z*-vinyl stannane **37** to afford *E*,*Z*-diene **38** in 84% yield. Sonogashira coupling of **34** with ethyl propiolate **39** occurred to deliver enyne **40** in 77% yield.[28] These derivatization studies (Schemes 4 and 5) highlight the synthetic utilities of ketones **2** and **3**, as these reactions provide a variety of highly valuable building blocks for organic synthesis.

Scheme 6. Alkene Isomerization Approach to Highly Enantioenriched α-Tertiary (*E*)-β,γ-Unsaturated Ketones



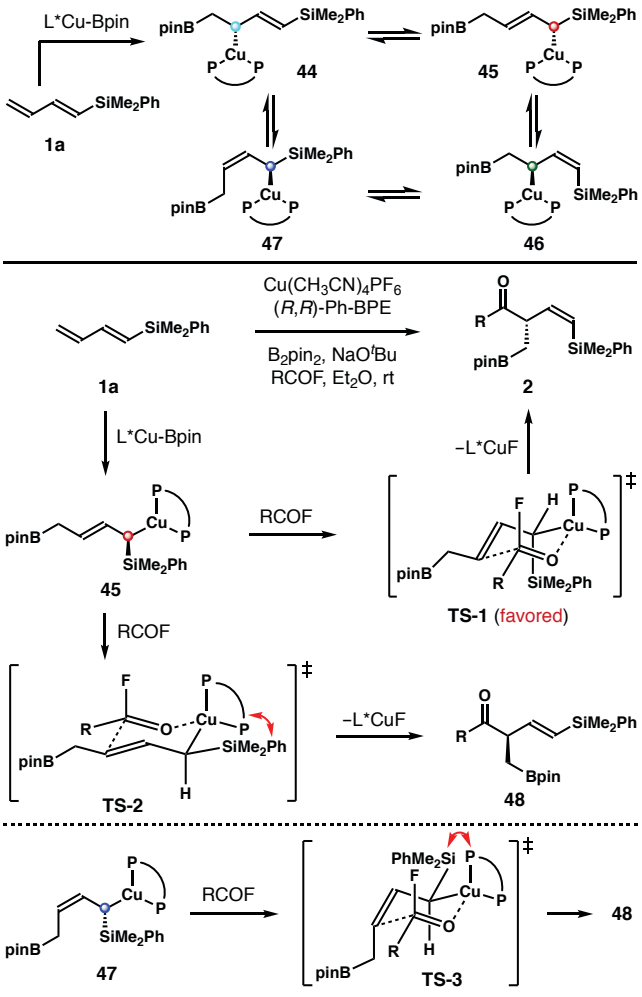
Alkene Isomerization Studies: As shown in Scheme 2, the enantiopurities of ketone **3** with an *E*-alkene group are not as high as ketone **2** with a *Z*-alkene. One factor might contribute to such a discrepancy is the potential racemization of ketone **3** under the reaction conditions, owing to the acidity of the allylic hydrogen in **3**. As shown in Scheme 6, for ketone **2** with a *Z*-alkene unit, the allylic hydrogen (highlighted in red in compound **2**, Scheme 6) should occupy an eclipse position with the $SiMe_2Ph$ group to minimize the $A^{1,3}$ allylic strain.[29] Such a spatial arrangement would only permit the C–H bond to be perpendicular to the carbonyl group, which is stereoelectronically required for the deprotonation event as shown by Evans in his pioneering studies.[30] Consequently, the pKa of the allylic hydrogen in **2** should be close to the pKa of an hydrogen at the α-position of a simple ketone. Therefore, deprotonation-enolization of **2** is likely prevented under the reaction conditions. By contrast, for ketone **3** with an *E*-alkene group, the lack of $A^{1,3}$ allylic strain would allow the allylic hydrogen (highlighted in blue in compound **3**, Scheme 6) to orient orthogonally to both π–systems of the carbonyl and the alkene groups, which enforces the overlap between the σ orbital of the scissile C–H bond and both π* orbitals of the carbonyl and *E*-alkene groups. Such a stereoelectronic alignment will substantially increase the acidity of the allylic hydrogen of **3**. Therefore, slow racemization could occur to erode the enantiopurity of **3** under basic reaction conditions (NaO^tBu).

To obtain ketone **3** with high optical purity, conditions that could prevent deprotonation-enolization would be desirable. While we were not able to perform the reaction under neutral conditions, we were intrigued whether it is possible to isomerize the *Z*-alkene of ketone **2** to an *E*-alkene using a transition metal complex. The conditions for alkene isomerization are typically neutral, which should prevent product racemization. To validate this hypothesis, we conducted alkene isomerization with ketone **10** first. Upon exposure of **10** (99% ee) to Pd-complex, $[Pd(\mu\text{-}Br)^tBu_3P]_2$, in DCE for 2 h, ketone **41** with an *E*-alkene was isolated in 97% yield and >50:1 *E*-selectivities, and remarkably, with 96% ee (Scheme 6).[31] We also performed isomerization studies with ketones **2c** (99% ee) and **2i** (98% ee), which contain an aryl bromide or an alkene group that may not be compatible with the Pd complex. To our satisfaction, products **42** and **43** were obtained in 84-96% yields and >50:1 *E*-selectivity with minimum loss of enantiomeric purities (94-95% ee). To test whether racemization could occur under basic conditions to erode the optical purities of ketones **2** and **3**, we subjected ketones **2c** (*Z*-alkene, 99% ee) and **43** (*E*-alkene, 95% ee) separately to the reaction conditions shown in Scheme 2. After two hours, the recovered ketone **43** suffered a substantial loss of enantiopurity (84% ee), while the ee of ketone **2c** remained the same (even after 12 h). This observation provides the support for our analyses of different acidity of allylic hydrogen of ketones **2** and **3**. Slow racemization of ketones **3** under basic reaction conditions is likely the origin of lower enantioselectivities of ketones **3**. This issue can be solved through alkene isomerization of ketones **2** to access highly enantioenriched ketones with an *E*-alkene unit.

Mechanistic Analyses: While the mechanism of Cu-catalyzed alkene addition with boron reagents has been well established, the stereochemical outcomes and enantiodivergence we observed are worthy of commenting.[32] One of the elementary steps in the Cu-catalyzed reaction with **1a** is the diene addition with ligand-bound copper complex, L*Cu-Bpin, generated from $Cu(CH_3CN)_4PF_6$, (*R*,*R*)-Ph-BPE, B_2pin_2 and NaO^tBu. It has been shown that a bidentate phosphine-ligated Cu-Bpin complex reacted with 1,3-dienes in a 1,2-addition manner.[33] Therefore, it is anticipated that the initially generated Cu-complex from diene addition should be **44** (Scheme 7) where the (*R*,*R*)-Ph-BPE-ligated Cu-Bpin complex adds to the terminal alkene group of diene **1a**. Owing to facile and reversible 1,3-metallo shifts of allylcopper species,[34] complex **44** should equilibrate with $^1\eta$–allylcopper species **45**, **46**, and **47**, or $^3\eta$–allylcopper species (structures not shown).[35] Reactions of allylcopper with aldehydes are known to proceed by way of a cyclic, Zimmerman-Traxler transition state.[34,36] It is therefore reasonable to assume that an analogous chairlike transition state is operable for the reactions of allylcopper with acyl fluorides. The structural features of product **2** indicate that α-silyl allylcopper **45** and/or **47** should be the reactive intermediates, as a ketone product with a vinyl silane unit will be generated through the allyl addition from these two copper species via a chairlike transition state.[37] As shown in Scheme 7, the addition of **45** to the *si* face of the acyl fluoride via transition state **TS-1**

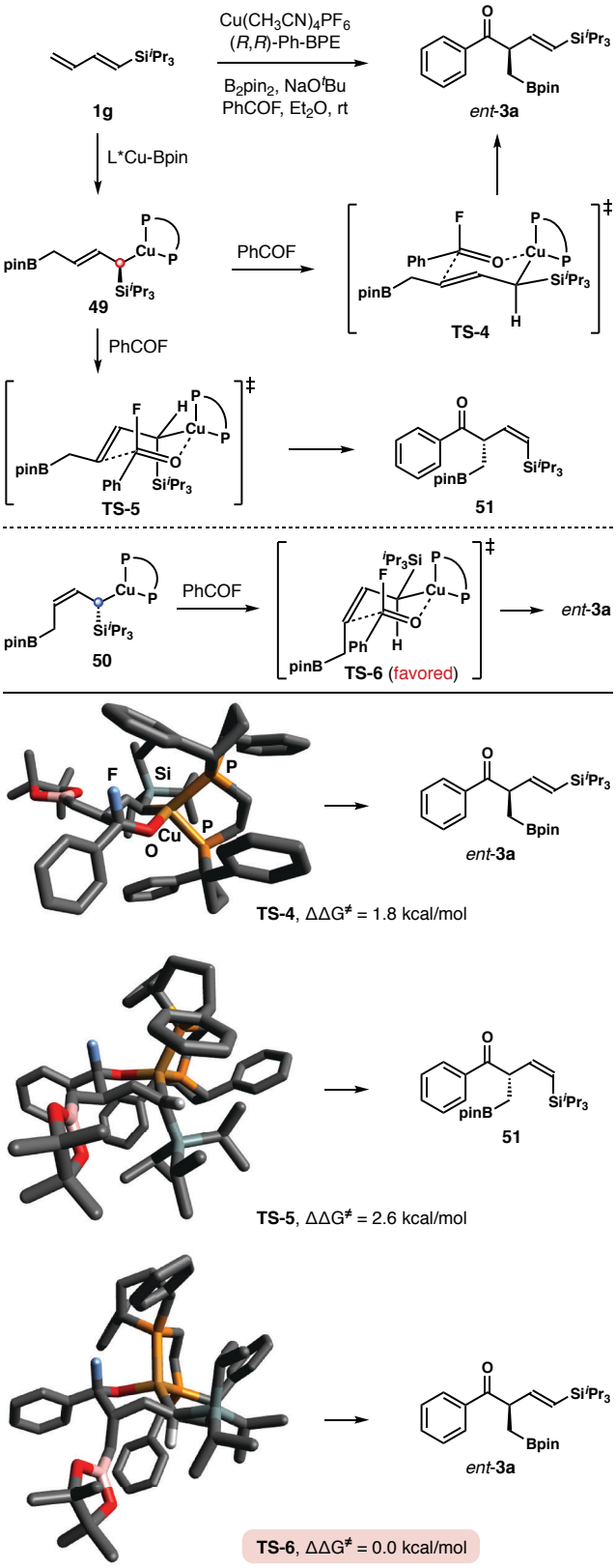
forms ketone **2**. The competing transition state **TS-2** via *re* face addition gives ketone **48**. The reaction of allylcopper **47** with the acyl fluoride should proceed via **TS-3** preferentially through minimization of $A^{1,3}$ allylic strain to deliver ketone **48** as well.[29] Transition state **TS-1** leading to ketone **2** is favored likely owing to the pseudoaxial orientation of the $SiMe_2Ph$ group to minimize the steric interaction. In comparison, the competing transition states **TS-2** and **TS-3** suffer the nonbonding steric interactions between pseudoequatorially positioned $SiMe_2Ph$ group and the ligand on copper (shown with red arrows in **TS-2** and **TS-3**), and therefore are disfavored. In addition, the exceptional optical purities (98-99% ee) of ketones **2** indicate the borocupration step that forms allylic copper **44** intermediate is highly enantioselective, because the optical purity of copper species **45** (derived from **44**) dictates the enantiomeric excess of ketones **2** as the reactions of **45** with acyl fluorides proceed with a chirality transfer process.

Scheme 7. Reaction Pathway Analyses of Dienylsilane 1a



In the case of $^{i}Pr_3Si$-substituted diene **1g** with the same (*R*,*R*)-Ph-BPE as the ligand, products *ent*-**3** with an *E*-alkene unit are formed. Assuming the reactions also proceeded through a chairlike transition state,[34] the *E*-alkene group in *ent*-**3** indicates that the $^{i}Pr_3Si$- group occupies a pseudoequatorial position in the reaction transition state. For the two potentially reactive intermediates, α-silyl allylcopper **49** and **50**, the reaction of **49** with benzoyl fluoride via transition state **TS-4** gives *E*-product *ent*-**3a** (Scheme 8). By contrast, the reaction of **49**

Scheme 8. Reaction Pathway Analyses of Dienylsilane 1g



via transition state **TS-5** leads to *Z*-product **51**, which is not a favorable reaction pathway as the formation of any *Z*-product was not detected. Meanwhile, the reaction of *Z*-α-silyl-allyl copper **50** with benzoyl fluoride also produces *E*-isomer *ent*-**3a** via transition state **TS-6**. To discern which allylic copper

species, **49** or **50**,[38] is involved in the reaction, or both intermediates are involved, we compared the energies of transition states **TS-4**, **TS-5** and **TS-6** using computation studies. The density functional theory (DFT) studies were performed at the ωB97xd/6-31G* density functional level of theory for structure optimization and energy calculation. As shown in Scheme 8, the results from computation studies suggest that **TS-6**, the reaction transition state of *Z*-allyl copper intermediate **50** with benzoyl fluoride, has the lowest energy. Transition state **TS-4**, which features allyl addition to benzoyl fluoride with *E*-allyl copper intermediate **50**, is 1.8 kcal/mol higher in energy than **TS-6**. Although transition state **TS-4** also leads to the formation of the same product *ent*-**3a** as **TS-6**, it is deemed to be a minor reaction pathway at most. Meanwhile, the addition to benzoyl fluoride with *E*-allyl copper **50** via **TS-5**, which leads to *Z*-isomer **51**, has the highest activation barrier ($\Delta\Delta G^{\neq} = 2.6$ kcal/mol). Such an energy difference is in good accord with the observed experimental data where the formation of any *Z*-isomer was not detected in reactions using diene **1g**.

Based on these data, we propose that the initial addition of L*Cu-Bpin complex to diene **1** forms a γ-silyl allylic copper intermediate (e.g., **44**, Scheme 7). This step generates a stereogenic center α to the Cu, and it is the enantio-determining step. However, this initial adduct is not reactive toward the addition to acyl fluorides. Instead, it equilibrates with α-silyl allylcopper species (e.g., **45**–**47**, Scheme 7, or **49**–**50**, Scheme 8) via reversible 1,3-metallo shifts. Depending on the nature of the silyl group of dienes **1** and the ligand on Cu, the reaction of acyl fluorides operates under the Curtin-Hammett principle to give either *Z*-isomers **2** or *E*-isomers **3** through either *E*-allylcopper **45** or *Z*-allylcopper **50**, respectively.[39] It is remarkable that the different silyl groups of dienes **1** could drastically impact the nature of reactive intermediate α-silyl allylcopper species and the stereoselectivities of the reactions.

CONCLUSIONS

In summary, we developed a diastereoselective and enantiodivergent syntheses of (*Z*)- or (*E*)-β,γ-unsaturated ketones from 1,3-butadienyl silanes.[40] The nature of the silyl group of the dienes not only dictates the reactive allylic copper intermediates (**45** or **50**) in the reactions with acyl fluorides, but also has a significant impact on the face-selective addition to acyl fluorides to control the *E*/*Z*-selectivities and enantioselectivities of the products. Under the developed catalytic systems, the reactions of acyl fluorides with $PhMe_2Si$-substituted 1,3-diene gave (*Z*)-β,γ-unsaturated ketones bearing an α-tertiary stereocenter with high *Z*-selectivities and excellent enantioselectivities, while reactions with $^{i}Pr_3Si$-substituted 1,3-diene formed (*E*)-β,γ-unsaturated ketones with high optical purities and excellent *E*-selectivities. Computational studies were conducted to provide the support to these fundamentally important discoveries. The products generated from the reactions contain three functional groups with orthogonal chemical reactivities, which can undergo a variety of transformations to afford synthetically valuable intermediates. Synthetic applications of this method are currently ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.
# These authors contributed equally.

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REFERENCES

1. (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-oriented synthesis, step economy, and drug design. *Acc. Chem. Res.* **2008**, *41*, 40. (b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010. (c) Gao, Y.; Ma, D. In pursuit of synthetic efficiency: Convergent approaches. *Acc. Chem. Res.* **2021**, *54*, 569. (d) Peters, D. S.; Pitts, C. R.; McClymont, K. S.; Stratton, T. P.; Bi, C.; Baran, P. S. Ideality in context: Motivations for total synthesis. *Acc. Chem. Res.* **2021**, *54*, 605.

2. (a) Davies-Coleman, M. T.; Garson, M. J. Marine polypropionates. *Nat. Prod. Rep.* **1998**, *15*, 477. (b) Rohr, J. A new role for polyketides. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847. (c) Feng, J.; Kasun, Z. A.; Krische, M. J. Enantioselective alcohol C–H functionalization for polyketide construction: Unlocking redox-economy and site-selectivity for ideal chemical synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 5467.

3. (a) Sugawara, K.; Nishiyama, Y.; Toda, S.; Komiyama, N.; Hatori, M.; Moriyama, T.; Sawada, Y.; Kamei, H.; Konishi, M.; Oki, T. Lactimidomycin, a new glutarimide group antibiotic production, isolation, structure and biological activity. *J. Antibiot.* **1992**, *45*, 1433. (b) Ju, J.; Seo, J.-W.; Her, Y.; Lim, S.-K.; Shen, B. New lactimidomycin congeners shed insight into lactimidomycin biosynthesis in *Streptomyces Amphibiosporus*. *Org. Lett.* **2007**, *9*, 5183. (c) Chen, M.; Wu, Y.; He, Y.; Xu, Y.; Li, Y.; Li, D.; Feng, T.; Yu, L.; Hong, B.; Jiang, W.; Si, S. Identification of trichostatin derivatives from *Streptomyces sp.* CPCC 203909. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 562. (d) Kudo, K.; Ozaki, T.; Shin-ya, K.; Nishiyama, M.; Kuzuyama, T. Biosynthetic origin of the hydroxamic acid moiety of trichostatin A: Identification of unprecedented enzymatic machinery involved in hydroxylamine transfer. *J. Am. Chem. Soc.* **2017**, *139*, 6799. (e) Liu, W.; Jannu, V. G.; Liu, Z.; Zhang, Q.; Jiang, X.; Ma, L.; Zhang, W.; Zhang, C.; Zhu, Y. Heterologous expression of the trichostatin gene cluster and functional characterization of N-methyltransferase TsnB8. *Org. Biomol. Chem.* **2020**, *18*, 3649. (f) Jung, J. A.; Lee, H. J.; Song, M. C.; Hwangbo, A.; Beom, J. Y.; Lee, S. J.; Park, D. J.; Oh, J. H.; Ha, S.-J.; Cheong, E.; Yoon, Y. J. Biosynthesis of nonimmunosuppressive prolylFK506 analogues with neurite outgrowth and synaptogenic activity. *J. Nat. Prod.* **2021**, *84*, 195. (g) Fujita, K.; Ikuta, M.; Nishimura, S.; Sugiyama, R.; Yoshimura, A.; Kakeya, H. Amphiol, an antifungal fungal pigment from *Pseudogymnoascus sp.* PF1464. *J.*

Nat. Prod. **2021**, *84*, 986. (h) Ju, F.; Kuang, Q.-X.; Li, Q.-Z.; Huang, L.-J.; Guo, W.-X.; Gong, L.-Q.; Dai, Y.-F.; Wang, L.; Gu, Y.-C.; Wang, D.; Deng, Y.; Guo, D.-L. Aureonitol analogues and orsellinic acid esters isolated from *Chaetomium elatum* and their antineuroinflammatory activity. *J. Nat. Prod.* **2021**, *84*, 3044.

4. (a) Xu, L.; Zhang, S.; Li, P. Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules. *Chem. Soc. Rev.* **2015**, *44*, 8848. (b) Sandford, C.; Aggarwal, V. K. Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. *Chem. Commun.* **2017**, *53*, 5481. (c) Zhang, C.; Hu, W.; Morken, J. P. α-Boryl organometallic reagents in catalytic asymmetric synthesis. *ACS Catal.* **2021**, *11*, 10660.

5. For a recent review, see: Cano, R.; Zakarian, A.; McGlacken, G. P. Direct asymmetric alkylation of ketones: Still unconquered. *Angew. Chem., Int. Ed.* **2017**, *56*, 9278.

6. (a) Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M. Asymmetric syntheses via metalated chiral hydrazones: Overall enantioselective α-alkylation of acyclic ketones. *Tetrahedron* **1984**, *40*, 1345. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. The SAMP-/RAMP-hydrazone methodology in asymmetric synthesis. *Tetrahedron* **2002**, *58*, 2253.

7. (a) Lim, D.; Coltart, D. M. Simple and efficient asymmetric α-alkylation and α,α-bisalkylation of acyclic ketones by using chiral N-amino cyclic carbamate hydrazones. *Angew. Chem. Int. Ed.* **2008**, *47*, 5207. (b) Wengryniuk, S. E.; Lim, D.; Coltart, D. M. Regioselective asymmetric α,α-bisalkylation of ketones via complex-induced *syn*-deprotonation of chiral *N*-amino cyclic carbamate hydrazones. *J. Am. Chem. Soc.* **2011**, *133*, 8714.

8. (a) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. Catalytic asymmetric vinylation of ketone enolates. *Org. Lett.* **2001**, *3*, 1897. (b) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. Palladium-catalyzed enantioselective α-arylation and α-vinylation of oxindoles facilitated by an axially chiral P-stereogenic ligand. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

9. (a) Dai, X.; Strotman, N. A.; Fu, G. C. Catalytic asymmetric Hiyama cross-couplings of racemic α-bromo esters. *J. Am. Chem. Soc.* **2008**, *130,* 3302. (b) Lou, S.; Fu, G. C. Enantioselective alkenylation via nickel-catalyzed cross-coupling with organozirconium reagents. *J. Am. Chem. Soc.* **2010**, *132*, 5010. (c) Xiong, P.; Hemming, M.; Ivlev, S. I.; Meggers, E. Electrochemical enantioselective nucleophilic α-C(sp3)–H alkenylation of 2-acyl imidazoles. *J. Am. Chem. Soc.* **2022**, *144*, 6964. (d) Ueda, Y.; Masuda, Y.; Iwai, T.; Imaeda, K.; Takeuchi, H.; Ueno, K.; Gao, M.; Hasegawa, J.; Sawamura, M. Photoinduced copper-catalyzed asymmetric acylation of allylic phosphates with acylsilanes. *J. Am. Chem. Soc.* **2022**, *144*, 2218.

10. For selected other methods: (a) Kim, H.; MacMillan, D. W. C. Enantioselective organo-SOMO catalysis: the α-vinylation of aldehydes. *J. Am. Chem. Soc.* **2008**, *130*, 398. (b) Skucas, E.; MacMillan, D. W. C. Enantioselective α-vinylation of aldehydes via the synergistic combination of copper and amine catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 9090. (c) Stevens, J. M.; MacMillan, D. W. C. Enantioselective α-alkenylation of aldehydes with boronic acids via the synergistic combination of copper (II) and amine catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 11756. For a recent example of borylative coupling of allenes, $B_2(pin)_2$, and nitriles, see: (d) Zhang, S.; del Pozo, J.; Romiti, F.; Mu, Y.; Torker, S.; Hoveyda, A. H. Delayed catalyst function enables direct enantioselective conversion of nitriles to NH_2-amines. *Science* **2019**, *364*, 45. For recent studies on borylative coupling of dienes, $B_2(pin)_2$, and carbonyl compounds, see: (e) Feng, J.-J.; Xu, Y.; Oestreich, M. Ligand-controlled diastereodivergent, enantio- and regioselective copper-catalyzed hydroxyalkylboration of 1,3-dienes with ketones. *Chem. Sci.* **2019**, *10*, 9679. (f) Feng, J.-J.; Oestreich, M. Tertiary α-silyl alcohols by diastereoselective coupling of 1,3-dienes and acylsilanes initiated by enantioselective copper-catalyzed borylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 8211.

11. (a) Wang, M.; Khan, S.; Miliordos, E.; Chen, M. Enantioselective syntheses of homopropargylic alcohols via asymmetric allenylboration. *Org. Lett.* **2018**, *20*, 3810. (b) Wang, M.; Khan, S.; Miliordos, E.; Chen, M. Enantioselective allenylation of aldehydes via Brønsted acid catalysis. *Adv. Synth. Catal.* **2018**, *360*, 4634. (c) Gao, S.; Chen, M. Enantioselective *syn*- and *anti*-alkoxyallylation of aldehydes via Brønsted acid catalysis. *Org. Lett.* **2018**, *20*, 6174. (d) Gao, S.; Chen, J.; Chen, M. (*Z*)-α-Boryl-crotylboron reagents via *Z*-selective alkene isomerization and application to stereoselective syntheses of (*E*)-δ-boryl-*syn*-homoallylic alcohols. *Chem. Sci.* **2019**, *10*, 3637. (e) Wang, M.; Gao, S.; Chen, M. Stereoselective syntheses of (*E*)-γ', δ-bisboryl-substituted *syn*-homoallylic alcohols via chemoselective aldehyde allylboration. *Org. Lett.* **2019**, *21*, 2151. (f) Chen, J.; Gao, S.; Gorden, J. D.; Chen, M. Stereoselective syntheses of γ-boryl substituted *syn*-β-alkoxy- and *syn*-β-amino-homoallylic alcohols via a regio- and stereoselective allene diboration and aldehyde allylboration reaction sequence. *Org. Lett.* **2019**, *21*, 4638. (g) Chen, J.; Gao, S.; Chen, M. Stereoselective syntheses of γ,δ-bifunctionalized homoallylic alcohols and ethers via chemoselective allyl addition to aldehydes. *Org. Lett.* **2019**, *21*, 9893. (h) Gao, S.; Chen, M. Enantioselective syntheses of 1,4-pentadien-3-yl carbinols via Brønsted acid catalysis. *Org. Lett.* **2020**, *22*, 400. (i) Chen, J.; Chen, M. Enantioselective syntheses of (*Z*)-6′-boryl-*anti*-1,2-oxaborinan-3-enes via a dienylboronate protoboration and asymmetric allylation reaction sequence. *Org. Lett.* **2020**, *22*, 7321. (j) Liu, J.; Chen, M. Enantioselective *anti*- and *syn*-(borylmethyl)allylation of aldehydes via Brønsted acid catalysis. *Org. Lett.* **2020**, *22*, 8967. (k) Gao, S.; Duan, M.; Houk, K. N.; Chen, M. Chiral phosphoric acid dual-function catalysis: asymmetric allylation with α-vinyl allylboron reagents. *Angew. Chem. Int. Ed.* **2020**, *59*, 10540. (l) Gao, S.; Duan, M.; Shao, Q.; Houk, K. N.; Chen, M. Development of α, α-disubstituted crotylboronate reagents and stereoselective crotylation via Brønsted or Lewis acid catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 18355. (m) Gao, S.; Duan, M.; Liu, J.; Yu, P.; Houk, K. N.; Chen, M. Stereochemical control via chirality pairing: stereodivergent syntheses of enantioenriched homoallylic alcohols. *Angew. Chem. Int. Ed.* **2021**, *60*, 24096.

12. (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. Aminodifluorosulfinium tetrafluoroborate salts as stable and crystalline deoxofluorinating reagents. *Org. Lett.* **2009**, *11*, 5050. (b) Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. Base-free nickel-catalysed decarbonylative Suzuki–Miyaura coupling of acid fluorides. *Nature*, **2018**, *563*, 100. (c) The reactions with activated esters such as TFE esters and aryl esters did not form a detectable amount of products.

13. Gao, S.; Chen, M. α-Silicon effect assisted Curtin–Hammett allylation using allylcopper reagents derived from 1,3-dienylsilanes. *Chem, Sci.* **2019**, *10*, 7554.

14. (a) Dale, J. A.; Mosher, H. S. Nuclear magnetic resonance enantiomer regents. Configurational correlations via nuclear magnetic resonance chemical shifts of diastereomeric mandelate, O-methyl mandelate, and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons. *Nat. Protoc.* **2007**, *2,* 2451.

15. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

16. Bartoli, G.; Bellucci, M. C.; Bosco, M. Marcantoni, E.; Sambri, L. Internal Lewis acid coordination as a powerful tool to promote highly stereoselective alkylation of α-alkyl-β-hydroxy ketones with Grignard reagents. *Chem. Eur. J.* **1998**, *4*, 2154.

17. (a) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R. The role of the α-stereogenic center in the control of stereoselection in the reduction of α-alkyl-β-hydroxy ketones: A highly diastereoselective protocol for the synthesis of 1,2-*syn*-2-alkyl-1,3-diols. *Chem. Eur. J.* **2000**, *6*, 2590. (b) Huang, Y.; Smith, K. B.; Brown, M. K. Copper-catalyzed borylacylation of activated alkenes with acid chlorides. *Angew. Chem. Int. Ed.* **2017***, 56,* 13314.

18. Liu, H.; Li, H.; Luo, N.; Wang, F. Visible-light-induced oxidative lignin C–C bond cleavage to aldehydes using vanadium catalysts. *ACS Catalysis* **2020,** *10*, 632.

19. (a) Rychnovsky, S. D.; Skalitzky, D. J. Stereochemistry of alternating polyol chains: ^{13}C NMR analysis of 1,3-diol acetonides. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. ^{13}C NMR chemical shift correlations in 1,3-diol acetonides. Implications for the stereochemical assignment of propionate-derived polyols. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. Configurational assignment of polyene macrolide antibiotics using the [^{13}C] acetonide analysis. *Acc. Chem. Res.* **1998**, *31*, 9.

20. Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *anti*-Diastereo- and enantioselective carbonyl (hydroxymethyl)allylation from the alcohol or aldehyde oxidation level: Allyl carbonates as allylmetal surrogates. *J. Am. Chem. Soc.* **2010**, *132*, 4562.

21. (a) Maity, J. K.; Ghosh, R.; Drew, M. G. B.; Achari, B.; Mandal, S. B. Introduction of vinyl and hydroxymethyl functionalities at C-4 of glucose-derived substrates: Synthesis of spirocyclic, bicyclic, and tricyclic nucleosides. *J. Org. Chem.* **2008**, *73*, 4305. (b) Guo, Y.-A.; Lee, W.; Krische, M. J. Enantioselective synthesis of oxetanes bearing all-carbon quaternary stereocenters via iridium-catalyzed C-C bond-forming transfer hydrogenation. *Chem. Eur. J.* **2017**, *23*, 2557.

22. Mlynarski, S. N.; Karns, A. S.; Morken, J. P. Direct stereospecific amination of alkyl and aryl pinacol boronates. *J. Am. Chem. Soc.* **2012**, *134*, 16449.

23. Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. Enantiospecific sp^2–sp^3 coupling of secondary and tertiary boronic esters. *Nat. Chem.* **2014**, 6, 584.

24. (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. A convenient stereoselective synthesis of substituted alkenes via hydroboration-iodination of alkynes. *J. Am. Chem. Soc.* **1967**, *89*, 3652. (b) Armstrong, R. J.; Aggarwal, V. K. 50 Years of Zweifel olefination: A transition-metal-free coupling. *Synthesis* **2017**, *49*, 3323.

25. (a) Zakarian, A.; Batch, A.; Holton, R. A. A Convergent total synthesis of hemibrevetoxin B. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. Hexafluoroisopropanol as a unique solvent for stereoselective iododesilylation of vinylsilanes. *Org. Lett.* **2008**, *10*, 1727. (c) Sidera, M.; Costa, A. M.; Vilarrasa, J. Iododesilylation of TIPS-, TBDPS-, and TBS-substituted alkenes in connection with the synthesis of amphidinolides B/D. *Org. Lett.* **2011**, *13*, 4934.

26. Stille, J. K.; Groh, B. L. Stereospecific cross-coupling of vinyl halides with vinyl tin reagents catalyzed by palladium. *J. Am. Chem. Soc.* **1987**, *109*, 813.

27. (a) Hayashi, M.; Ohara, H.; Ohno, M.; Sakakibara, H.; Satoi, S.; Harada, K.; Suzuki, M. Mycinamicins, new macrolide antibiotics. V. Isolation and structures of new 16-membered aglycones, mycinolide IV and protomycinolide IV. *J. Antibiot.* **1981**, *34*, 1075. (b) Suzuki, K.; Matsumoto, T.; Tomooka, K.; Matsumoto, K.; Tsuchihashi, G.-i. Stereocontrolled first total synthesis of mycinolide IV. *Chem. Lett.* **1987**, 113. (c) Asai, T.; Morita, S.; Shirata, N.; Taniguchi, T.; Monde, K.; Sakurai, H.; Ozeki, T.; Oshima, Y. Structural diversity of new C13-polyketides produced by *Chaetomium mollipilium* cultivated in the presence of a NAD^+-dependent histone deacetylase inhibitor. *Org. Lett.* **2012**, *14*, 5456. (d) Wang, C.-X.; Ding, R.; Jiang, S.-T.; Tang, J.-S.; Hu, D.; Chen, G.-D.; Lin, F.; Hong, K.; Yao, X.-S.; Gao, H. Aldgamycins J–O, 16-membered macrolides with a branched octose unit from *Streptomycetes* sp. and their antibacterial activities. *J. Nat. Prod.* **2016**, *79*, 2446.

28. (a) Chinchilla R.; N´ajera, C. Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084. (b) Negishi, E.-i.; Qian, M.; Zeng, F.; Anastasia L.; Babinski, D. Highly satisfactory alkynylation of alkenyl halides via Pd-catalyzed cross-coupling with alkynylzincs and its critical comparison with the Sonogashira alkynylation. *Org. Lett.* **2003**, *5*, 1597.

29. Hoffmann, R. W. Allylic 1,3-strain as a controlling factor in stereoselective transformations. *Chem. Rev.* **1989**, *89*, 1841.

30. (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. Asymmetric acylation reactions of chiral imide enolates. The first direct approach to the construction of chiral β-dicarbonyl synthons. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. Diastereoselective aldol reactions using β-keto imide derived enolates. A versatile approach to the assemblage of polypropionate systems. *J. Am. Chem. Soc.* **1990**, *112*, 866.

31. Mamone, P.; Grünberg, M. F.; Fromm, A.; Khan, B. A.; Gooßen, L. J. $Pd(\mu\text{-}Br)(P^tBu_3)]_2$ as a highly active isomerization catalyst: Synthesis of enol esters from allylic ester. *Org. Lett.* **2012**, *14*, 3716.

32. (a) Perry, G. J. P.; Jia, T.; Procter, D. J. Copper-catalyzed functionalization of 1,3-dienes: Hydrofunctionalization, borofunctionalization, and difunctionalization. *ACS Catal.* **2020**, *10*, 1485. (b) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. Copper-catalyzed borylative difunctionalization of π-systems. *ACS Catal.* **2020**, *10*, 11578.

33. (a) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. Copper(I)-catalyzed asymmetric monoborylation of 1,3-dienes: synthesis of enantioenriched cyclic homoallyl- and allylboronates. *J. Am. Chem. Soc.* **2010**, *132*, 1226. (b) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. Highly selective copper-catalyzed hydroboration of allenes and 1,3-dienes. *Chem. Eur. J.* **2013**, *19*, 7125. (c) Gao, S.; Wang, M.; Chen, M. Syntheses of unsymmetrical 1,4-bifunctional allylboron reagents via Cu-catalyzed highly regio- and stereoselective 1,4-protoboration of dienylboronates and analysis of the origin of chemoselective aldehyde *syn*-(hydroxymethyl)allylation. *Org. Lett.* **2018**, *20*, 7921.

34. Shibasaki, M.; Kanai, M. Asymmetric synthesis of tertiary alcohols and α-tertiary amines via Cu-catalyzed C−C bond formation to ketones and ketimines. *Chem. Rev.* **2008**, *108*, 2853.

35. Chen, J.; Miliordos, E.; Chen, M. Highly diastereo- and enantioselective synthesis of 3,6'-bisboryl-anti-1,2-oxaborinan-3-enes: an entry to enantioenriched homoallylic alcohols with a stereodefined trisubstituted alkene. *Angew. Chem. Int. Ed.* **2021**, *60*, 840.

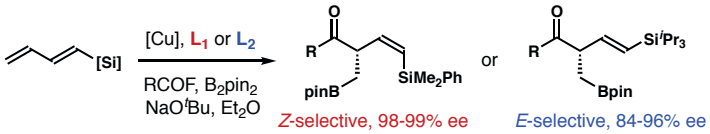
36. (a) Zimmerman, H. E.; Traxler, M. D. The stereochemistry of the Ivanov and Reformatsky reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Hoffmann, R. W. Diastereogenic addition of crotylmetal compounds to aldehydes. *Angew. Chem., Int. Ed.* **1982**, *21*, 555.

37. The electronic stabilization from the α-silyl group could lower the energy of transition state in the reactions of acyl fluorides with allylcopper species **45** and **47**. The reactions with aryl or alkyl-substituted dienes gave a complex mixture of products.

38. We attempted to identify intermediates **49** and **50** in stoichiometric reactions using ^1H NMR studies. However, such efforts have not been successful.

39. (a) Seeman, J. I. Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin-Hammett/Winstein-Holness kinetics. *Chem. Rev.* **1983**, *83*, 83. (b) Halpern, J. Mechanism and stereoselectivity of asymmetric hydrogenation. *Science* **1982**, *217*, 401. (c) Landis, C. R.; Halpern, J. Asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate catalyzed by [1,2-bis(phenyl-o-anisoyl)phosphino)ethane]rhodium(I): kinetics, mechanism and origin of enantioselection. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

40. For selected references on catalytic allylation using dienes, see: (a) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. Chiral-anion-dependent inversion of diastereo- and enantioselectivity in carbonyl crotylation via ruthenium-catalyzed butadiene hydrohydroxyalkylation. *J. Am. Chem. Soc.* **2012**, *134*, 20628. (b) Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. CuH-Catalyzed enantioselective ketone allylation with 1,3-dienes: scope, mechanism, and applications. *J. Am. Chem. Soc.* **2019**, *141*, 5062. (c) Gao, S.; Chen, M. Catalytic carboboration of dienylboronate for stereoselective synthesis of (*E*)-γ′,δ-bisboryl-*anti*-homoallylic alcohols. *Chem. Commun*. **2019**, *55*, 11199.


[Si]
[Cu], L1 or L2
RCOF, B2pin2
NaOtBu, Et2O
R
O
pinB
SiMe2Ph
or
R
O
Si iPr3
Bpin
Z-selective, 98-99% ee
E-selective, 84-96% ee