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Communication

Enantioselective Rh-Catalyzed Hydroboration of Silyl Enol Ethers

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ABSTRACT: The asymmetric hydroboration of alkenes has proven to be among the most powerful methods for the synthesis of chiral boron compounds. This protocol is well suitable for activated alkenes such as vinylarenes and alkenes bearing directing groups. However, the catalytic enantioselective hydroboration of O-substituted alkenes has remained unprecedented. Here we report a Rh-catalyzed enantioselective hydroboration of silyl enol ethers (SEEs) that utilizes two new chiral phosphine ligands we developed. This approach features mild reaction conditions and a broad substrate scope as well as excellent functional group tolerance, and enables highly efficient preparation of synthetically valuable chiral borylethers.

The ability to selectively and efficiently manipulate carbon−boron bonds into carbon−carbon or carbon−heteroatom bonds can greatly simplify and expedite synthetic routes, thus leading to numerous applications of alkyl boronates in medicinal chemistry, materials science, and the synthesis of natural products and fine chemicals.[1] The hydroboration of alkenes as one of the most straightforward and reliable synthetic methods for the preparation of alkyl boronates has been well developed.[2] However, the catalytic asymmetric version of this reaction still have important limitations. For instance, the alkenes are largely limited to C-substituted alkenes (X = H, Figure 1a),[3] such as vinylarenes,[4] electron deficient alkenes (X = CN, ketone, ester, amide, etc.),[5] and the ones with a directing group (X = DG).[6] Catalytic enantioselective hydroborations of heteroatom-substituted alkenes are rarely explored (X = B, N, Si, P, S),[7] and the heteroatom-substituted alkenes employed previously typically have a conjugated electron-withdrawing group. For example, S- and P-substituted alkenes participated in the asymmetric hydroboration in the form of α,β-unsaturated sulfones[7g] and phosphonates,[7f] respectively. With regard to O-substituted alkenes,[8] their asymmetric catalytic hydroboration is yet to be reported to our knowledge (X = O, Figure 1a), but it is highly anticipated given that the desired chiral β-hydroxy boronic esters and their derivatives could serve as multifaceted precursors to various high-value chemical products.[9]

The catalytic enantioselective hydroboration of O-substituted alkenes will meet various issues according to our experience in the borylation of O-substituted alkenes,[10] which makes it challenging (Figure 1b). The first issue would be the undesired cleavage of the C−O bond via oxidative addition of the C−O bond or β-O elimination to form alkene **I** in the presence of borane.[10a] The resulting alkene can further react with borane to furnish a hydroboration product or undergo dehydrogenative borylation to afford vinylboronate **II**.[10b] In addition, the O-substituted alkene can also go through deconjugative isomerization and hydroboration to give boronate **III**.[10c] The control of the regioselectivity and enantioselectivity would be another great challenge based on

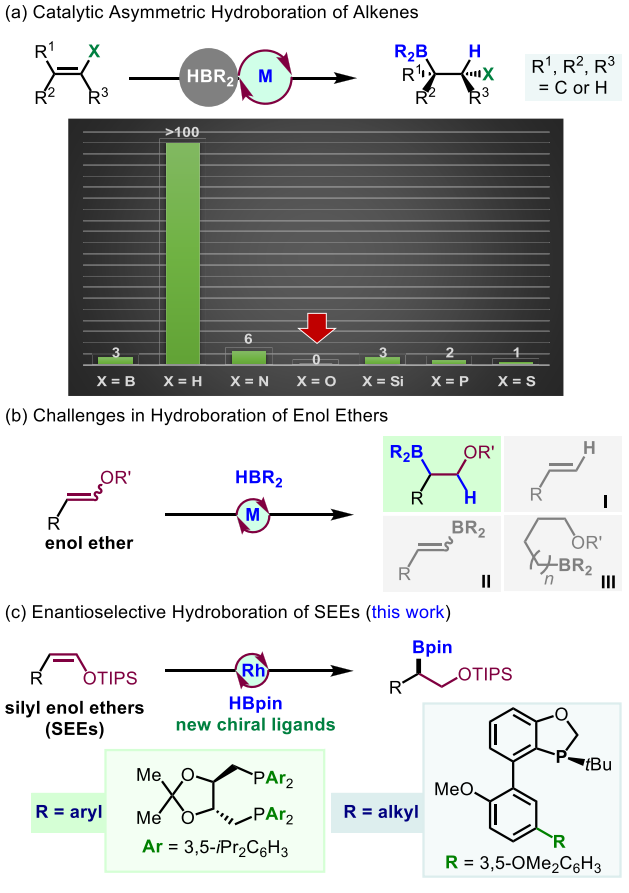

Figure 1. (a) Catalytic asymmetric hydroboration of alkenes. (b) Challenges in hydroboration of enol ethers. (c) Enantioselective Rh-catalyzed hydroboration of SEEs.

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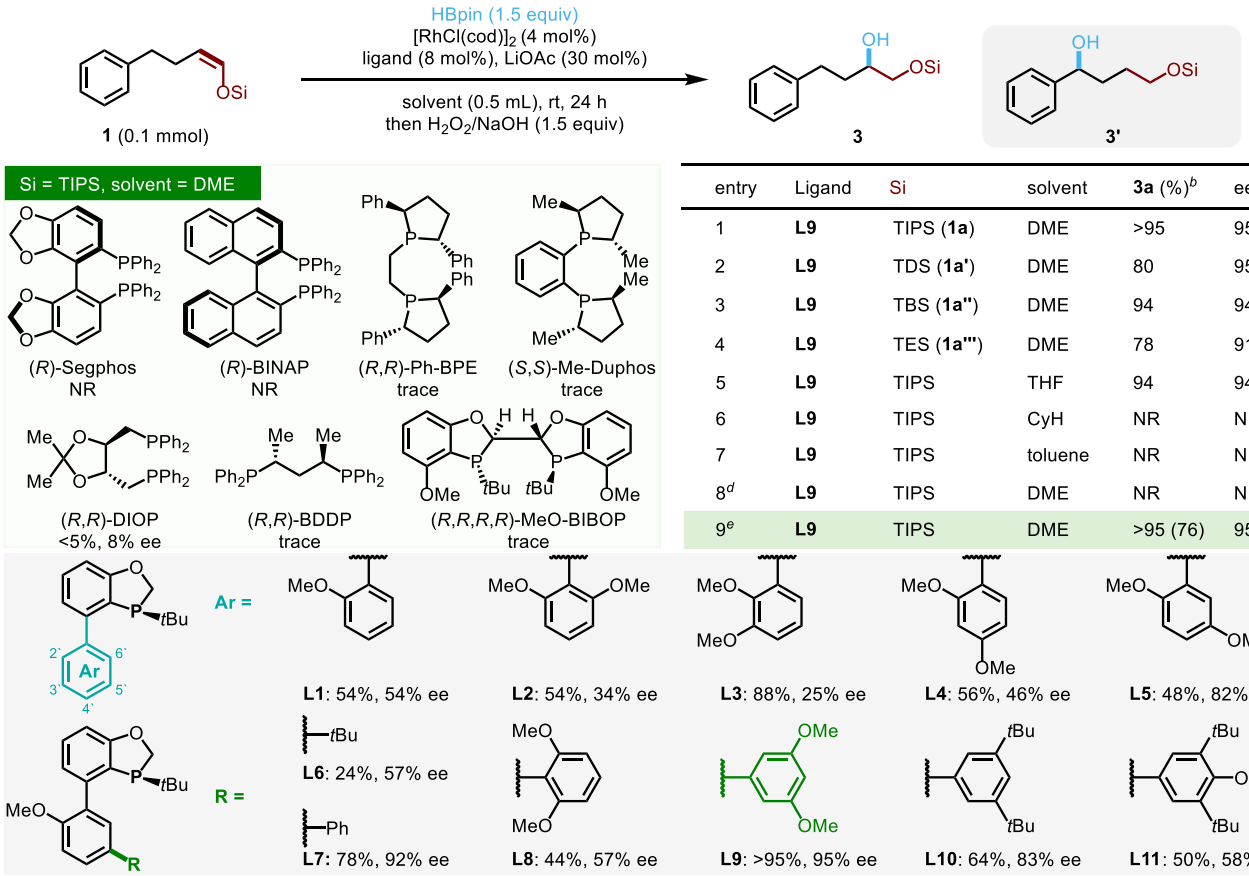
Table 1. Reaction Condition Optimization[a]



entry	Ligand	Si	solvent	**3a** (%)[b]	ee (%)[c]
1	**L9**	TIPS (**1a**)	DME	>95	95
2	**L9**	TDS (**1a'**)	DME	80	95
3	**L9**	TBS (**1a''**)	DME	94	94
4	**L9**	TES (**1a'''**)	DME	78	91
5	**L9**	TIPS	THF	94	94
6	**L9**	TIPS	CyH	NR	NR
7	**L9**	TIPS	toluene	NR	NR
8[d]	**L9**	TIPS	DME	NR	NR
9[e]	**L9**	TIPS	DME	>95 (76)	95

[a]Reactions conditions: **1** (0.1 mmol), HBpin (1.5 equiv), $[RhCl(cod)]_2$ (4 mol %), ligand (8 mol %), LiOAc (30 mol %), solvent (0.5 mL), rt, 24 h. [b]^{1}H NMR yield. [c]Ee were determined by chiral HPLC. [d]Without LiOAc. [e]T = 40 °C. cod = 1,5-cyclooctadiene, DME = dimethoxyethane, THF = tetrahydrofuran, TIPS = triisopropylsilyl, TDS = thexyldimethylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

the previous hydroboration of enol ethers.[8] To overcome these issues, silyl enol ethers would be an ideal starting point due to their ready availability, ease of deprotection, and the adjustable steric hindrance of silyl groups,[11] which would be crucial to avoid the undesired C−O bond cleavage and isomerization. Herein, we reported the first Rh-catalyzed asymmetric hydroboration of silyl enol ethers, allowing access to chiral *β*-borylethers in high yields and ee's (Figure 1c).

To explore the possibility of catalytic asymmetric hydroboration of O-substituted alkenes, silyl enol ether **1a** was selected as the model substrate. Initially, chiral bidentate phosphine ligands were investigated in the presence of $[RhCl(cod)]_2$, HBpin, and LiOAc. (*R*)-Segphos and (*R*)-BINAP resulted in no reaction. In addition, the more electron-rich ligands including Ph-BPE, Me-Duphos, DIOP, BDDP, and MeO-BIBOP gave a trace amount of hydroboration product **3a**[12] along with large quantities of undesired **3a′**,[10c] although full conversions were observed. We next turned our attention to monodentate phosphine ligands. To our delight, the desired product **3a** was exclusively obtained in moderate ee (54% and 34%) without the formation of **3a′**, when the commercially available ligands **L1** and **L2** were employed.[13] Encouraged by these delightful results, we then focused on the ligand modification. As shown in Table 1, the position of substituents has great impact on the enantioselectivity (**L2** → **L5**), and the ee was improved to 82% by fine-tuning the two methoxy groups to 2′- and 6′-positions (**L5**). Although the enantioselectivity was decreased to 57% when the methoxy was replaced with a *tert*-butyl group (**L6**), the ligand **L7** gave a much higher enantioselectivity (92% ee) with full conversion. The further ligand modification revealed that the steric ligands such as **L8**, **L10**, and **L11** led to a decrease in enantiomeric excess, and the ligand **L9** with a 3,5-dimethoxyphenyl group was the best for this asymmetric hydroboration of silyl enol ethers. The investigation of silyl groups indicated that increasing the steric bulk improved the enantioselectivity (entries 1−4, Table 1). The effect of solvents was also evaluated. The ee was slightly decreased in the THF (entry 5), while nonpolar solvents such as hexane and toluene gave no reaction (entries 6−7). Notably, no conversion was observed in the absence of LiOAc (entry 8). Furthermore, the hydroboration product **3a** was obtained in 76% isolated yield at elevated temperature (40 °C) without erosion of the ee (95% ee, entry 9).

With the optimal reaction conditions in hand, we examined the scope of silyl enol ethers for this Rh-catalyzed enantioselective hydroboration in the presence of the chiral ligand **L9**. As demonstrated in Table 2, a wide range of silyl enol ethers successfully participated in this asymmetric hydroboration to give the desired products in good yields and excellent enantioselectivities. A variety of aromatic substituents including phenyl groups with different functional groups such as $-CF_3$, −F, and $-NH_2$ (**3b−e**), furan (**3f**), thiophene (**3g**), protected and unprotected indoles (**3h−i**), and naphthalene (**3j**) were tolerated, affording the correspond-

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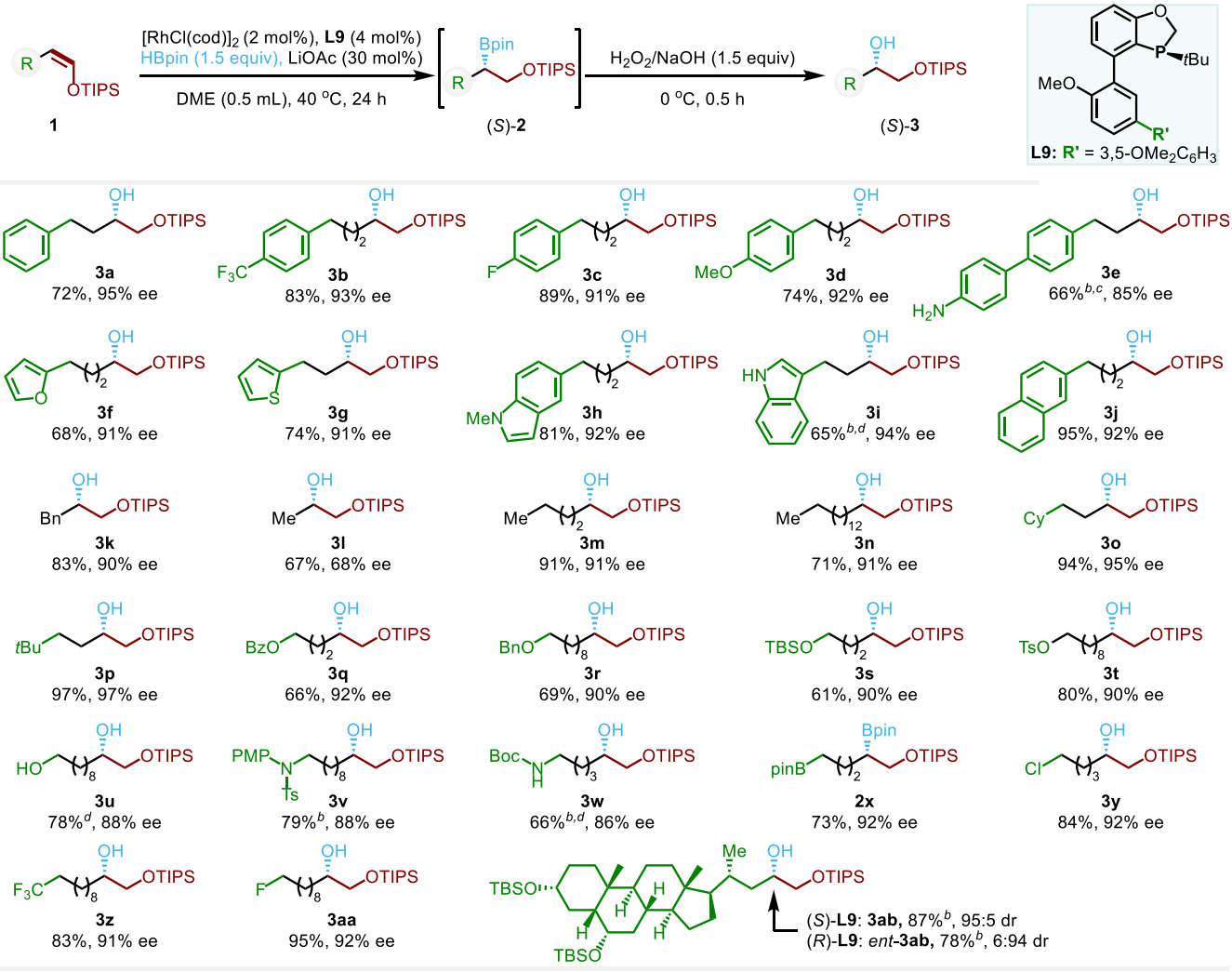
Table 2. Scope of Alkyl Silyl Enol Ethers[a]



[a]Reactions conditions: **1** (0.2 mmol), HBpin (1.5 equiv), $[RhCl(cod)]_2$ (2 mol %), **L9** (4 mol %), LiOAc (30 mol %), DME (0.5 mL), 40 °C, 24 h; isolated yield. [b]$[RhCl(cod)]_2$ (4 mol %), **L9** (8 mol %), 30 °C, 48 h. [c]HBpin (3.5 equiv). [d]HBpin (2.5 equiv).

ing diols in good yields and excellent ee's. The optimized conditions were also applicable to benzyl substituted substrate to afford **3k** in 90% ee and 83% yield without the occurrence of double-bond isomerization/hydroboration.[10c] Gratifyingly, methyl silyl enol ether was competent to furnish the desired product **3l** in high efficiency albeit with moderate enantioselectivity due to the small size of the methyl group. Noticeably, both products **3m** and **3n** were obtained in 91% ee, regardless of the chain length. The reaction is amenable to secondary and tertiary alkyl groups (**3o**−**p**). It is worth noting that numerous functional groups were tolerated, such as −OBz (**3q**), −OBn (**3r**), −OTBS (**3s**), −OTs (**3t**), −OH (**3u**), sulfamide (**3v**), −NHBoc (**3u**), −Bpin(**2x**), −Cl (**3y**), $-CF_3$ (**3z**), and −F (**3aa**), affording the corresponding products in 88−92% ee. Particularly noteworthy, the silyl enol ether derived from cholic acid reacted smoothly to give product **3ab** and *ent*-**3ab** in good yields and diastereoselectivities.

The enantioselective hydroboration of *Z*-aryl substituted silyl enol ethers was then investigated. Under the standard reaction conditions for the alkyl SEEs (entry 9, Table 1), diol **3ac** was produced in only 50% ee. However, pleasingly, the enantiomeric excess was improved to 95% when the reaction was conducted in toluene at −20 °C in the presence of **L12**. The scope of aryl substituted SEEs was then explored. As shown in Table 3, a series of aryl SEEs with various substituents at different positions on the phenyl group all reacted smoothly to deliver the diols in high yields and ee. The reaction of the substrates with substituents at the *ortho*-, *meta*-, or *para*-position all proceeded efficiently to generate the desired products **3ad**−**af** in 92−96% ee. It is worth mentioning that a diverse set of functional groups were compatible with the established reaction conditions, including electron-donating and electron-withdrawing groups, such as $-NMe_2$ (**3ag**), −OBn (**3ai**), acetal (**3aj**), phenyl (**3ak**), −F (**3al**), −Bpin (**3ao**), and $-CF_3$ (**3ap**). The susceptible functionalities, like −Cl (**3am**), −Br (**3an**), and −CN (**3aq**), were readily accommodated. Moreover, aryl substituents other than the phenyl, such as indole, furan, pyridine, and naphthalene, could be successfully incorporated into the products (**3as**−**av**). Finally, the substrate prepared from *β*-estradiol was suitable to provide the products **3aw** and *ent*-**3aw** in good yields and diastereoselectivities.

Next, we sought to extend this strategy to enantioselective hydroboration of *E*/*Z* mixtures of silyl enol ethers given that

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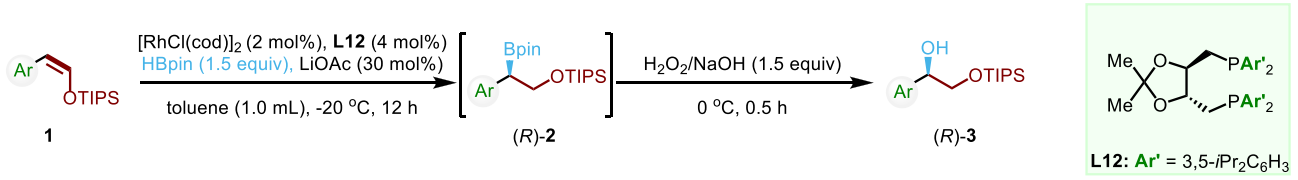
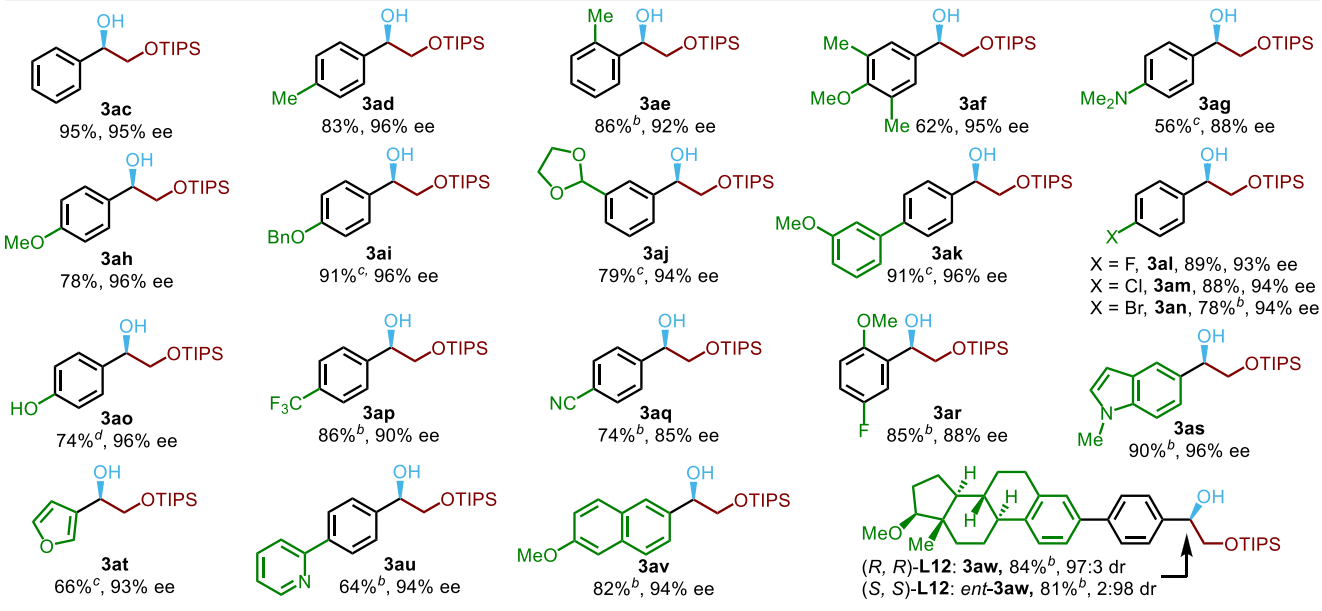
Table 3. Scope of Aryl Silyl Enol Ethers[a]





[a]Reactions conditions: **1** (0.3 mmol), HBpin (1.5 equiv), $[RhCl(cod)]_2$ (2 mol %), (*R*,*R*)-3,5-*i*Pr_2-DIOP (4 mol %), LiOAc (30 mol %), toluene (1.0 mL), −20 °C, 12 h; isolated yield. [b]AgOAc as base. [c]The reaction was performed for 18 h. [d]The substrate is **1ao** (see Supporting Information for details).

SEEs are typically synthesized as a mixture of *E*/*Z* isomers.[11a] Additionally, the *E* and *Z* isomers may give opposite enantioselectivities,[14] making asymmetric hydroboration of *E*/*Z* mixtures of SEEs challenging. As demonstrated in Table 4, we first treated (*E*)-**1a** with the standard conditions shown in Table 2. Delightfully, the desired **3a** was isolated in 70% yield and 85% ee, and showed the same (*S*)-configuration as *Z*-**1a** did. Additionally, the enantioselectivity of **3a** could be improved when the ratio of *E*-**1a**/*Z*-**1a** decreased. This method was proved to be compatible with a broad range of *E*/*Z* mixtures of SEEs (synthesized from the corresponding aldehydes, ratios from 1/14.7 to 1/1.2). It is noteworthy that substituents such as *p*-methoxyphenyl (**3d**), thienyl (**3g**), −OBz (**3q**), −OTBS (**3s**), −Bpin (**2x**), −Cl (**3y**), and pyridyl (**3ax**) were well tolerated, furnishing the products in good yields and enantioselectivities. However, the standard reaction conditions used in Tables 2 and 3 were unsuitable for the *E*-aryl substituted silyl enol ethers, which led to low enantioselectivities (see Supporting Information). To our delight, the hydroboration of *E*-aryl substituted SSEs could give moderate enantioselectivities when (*S*,*S*)-Me-Duphos was used as the ligand. For instance, the product **3ac** was obtained in 79% yield and 69% ee in the presence of (*S*,*S*)-Me-Duphos (eq 1, Figure 2a).

To better understand the reason why both *Z*- and *E*-isomers gave the product **3** in the (*S*)-configuration, a couple of control experiments are worthy of note. First, to figure out whether the same configuration obtained was caused by the isomerization between *Z*- and *E*-isomers, pure *E*-**1a** and *Z*-**1a** were subjected to the standard conditions used in Table 2 and quenched after 2 h, providing the product **3a** in 23% and 46% yields (eqs 2 and 3, Figure 2a), respectively. In addition, the substrate **1a** was recovered in the form of a mixture of *Z*- and *E*-isomers, suggesting the isomerization occurred during the reaction of hydroboration. However, based on these results, we cannot conclude that the isomerization is responsible for the resulting same configuration in view of the different ee's obtained from the *E*-and *Z*-isomers (85% for *E*-**1a** and 95% for *Z*-**1a**). To obtain more information, DFT calculations were carried out. We hypothesize that the origin of enantioselectivity observed in the hydroboration reactions is closely related to the insertion of a silyl enol ether substrate molecule into a [Rh]−H bond. In the presence of LiOAc and HBpin, it is reasonable to assume that a [Rh]−H active species can be formed from the precatalyst $[RhCl(COD)]_2$. According to the reaction conditions (Rh:phosphine = 1:1) together with an early report of an X-ray crystal structure of a closely related rhodium norbornene complex,[7c] we consider [(COD)LRhH] as the active species for the insertion. On the basis of this assumed active species, we performed DFT calculations (at the level of ωB97X-D) to obtain the barriers for the insertion reactions of the substrates *Z*-**1a** and *E*-**1a** with [(COD)**L9**RhH] by considering insertion taking place at both faces of each substrate molecule's double bond.

We first calculated the insertion of *Z*-**1a** and located a pair of transition state structures that would eventually lead to the *S*- and *R*-products, respectively. The two structures show an energy difference of 4.0 kcal/mol, favoring the experimentally

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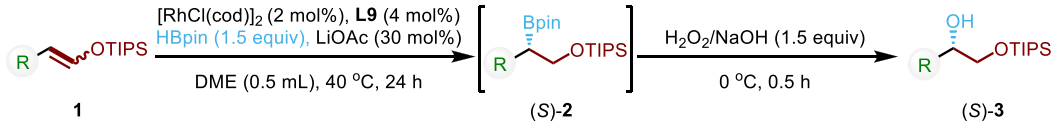
Table 4. Scope of *E*/*Z*-Silyl Enol Ethers[a]



SEEs	Products	SEEs	Products
1a (*E* only) (*E*/*Z* = 1/1) (*E*/*Z* = 1/9) (*Z* only)	**3a** 70%, 85% ee; 68%, 90% ee; 68%, 92% ee; 72%, 95% ee	**1q** (*E*/*Z* = 1/14.7) (*Z* only)	**3q** 71%, 92% ee; 66%, 92% ee
1d (*E*/*Z* = 1/1.2) (*Z* only)	**3d** 80%, 88% ee; 74%, 92% ee	**1s** (*E*/*Z* = 1/8.2) (*Z* only)	**3s** 62%, 90% ee; 61%, 90% ee
1g (*E*/*Z* = 1/1.9) (*Z* only)	**3g** 68%, 88% ee; 74%, 91% ee	**1x** (*E*/*Z* = 1/6.4) (*Z* only)	**2x** 65%, 92% ee; 73%, 92% ee
1o (*E*/*Z* = 1/8.9) (*Z* only)	**3o** 89%, 94% ee; 94%, 95% ee	**1y** (*E*/*Z* = 1/8.4) (*Z* only)	**3y** 87%, 89% ee; 84%, 92% ee
		1ax (*E*/*Z* = 1/1.1)	**3ax** 76%[b], 88% ee

[a]Reaction conditions: **1** (0.2 mmol), HBpin (1.5 equiv), [RhCl(cod)]$_2$ (2 mol %), **L9** (4 mol %), LiOAc (30 mol %), DME (0.5 mL), 40 °C, 24 h; isolated yield. [b][RhCl(cod)]$_2$ (4 mol %), **L9** (8 mol %), 30 °C, 48 h.

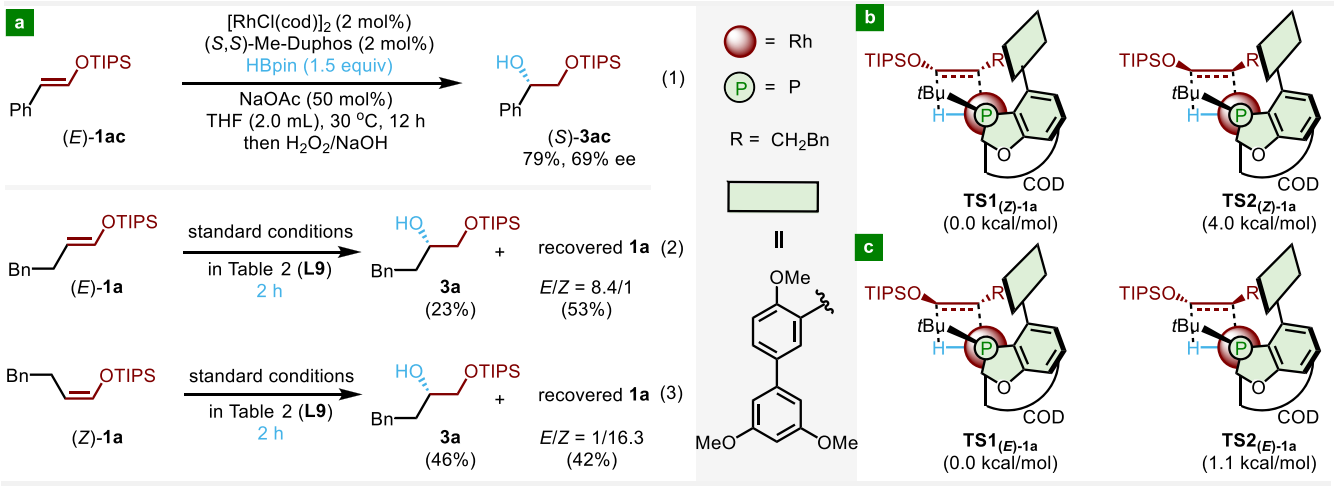


Figure 2. (a) Control experiments. (b and c) Structures calculated for the pair of transition states that would eventually lead to the *S*- and *R*-products for the insertion reactions of the substrates *Z*-**1a** and *E*-**1a** with [(COD)**L9**RhH]. The relative free energies are given in kcal/mol.

observed enantiomer. This DFT result gives reasonably/qualitatively good prediction regarding the experimentally obtained ee of 95%. The result also indicates that **L9** is able to create an excellent chiral pocket for the asymmetric hydroboration in the current catalytic system. Figure 2b schematically illustrates the structures calculated for the pair of transition states. Each structure adopts approximately a square-pyramidal geometry in which the phosphine ligand occupies the apical position. From the Newman projections shown in Figure 2b, we can see that the biaryl group on the phosphine ligand exerts the most steric influence that causes the enantiomeric discrimination. This conclusion is further supported by the calculations on the insertion of *E*-**1a**, in which the energy difference is reduced by 2.9 kcal/mol (1.1 versus 4.0 kcal/mol) (Figure 2c). The results also explain why both the *Z*- and *E*-silyl enol ethers afford the product with the same absolute configuration.

In addition to the pair of transition state structures shown in Figure 2a for the insertion reaction of *Z*-**1a**, we also located another pair of noticeably unstable transition state structures.

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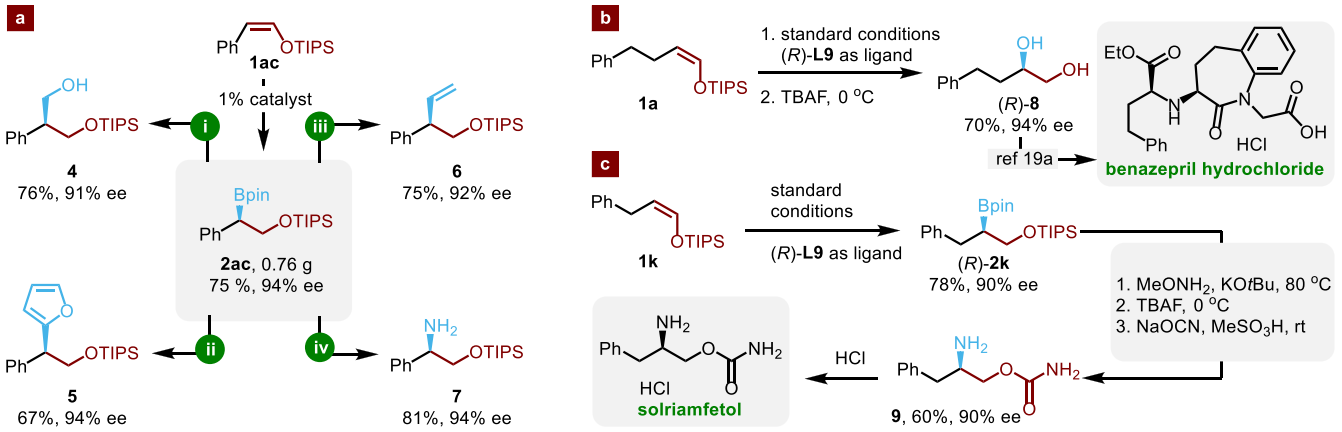

Figure 3. (a) Gram-scale reaction and synthetic applications. Reaction conditions: (i) bromochloromethane (2.5 equiv), *n*BuLi (2.3 equiv), −78 °C to rt, 2 h; NaOH (1.5 equiv), H_2O_2 (1.5 equiv). (ii) furan (1.5 equiv), *n*BuLi (1.5 equiv), NBS (1.5 equiv), −78 °C to rt, 15 h. (iii) vinylmagnesium bromide (4.0 equiv), I_2 (4.0 equiv), −78 °C, 0.5 h. (iv) $MeONH_2$ (3.0 equiv), *n*BuLi (3.0 equiv), −78 to 60 °C, 15 h. (b) Synthesis of benazepril hydrochloride. (c) Synthesis of solriamfetol.

These unstable structures were obtained by moving the apical (chiral) phosphine ligand to the opposite side of the square base, which are in fact the diastereomers of those presented in Figure 2b. For readers' convenience, these diastereomers are given in the SI (Figure S1). In view of the instability of these diastereomers, we did not carry out the corresponding calculations for *E*-**1a**.

To test the scalability of the reaction, we carried out a gram-scale reaction. With 1 mol % of the catalyst, the product **2ac** was isolated in 0.76 g and 94% ee. To demonstrate the robustness and practicability of this protocol, the transformations of **2ac** are outlined in Figure 3. The synthesis of one-carbon-homologated alcohol **4** was achieved in 76% yield via the Matteson reaction and subsequent oxidation.[15] The sp^2−sp^3 coupling of furan and **2ac** led to the formation of **5** in 67% yield and 94% ee.[16] Furthermore, the product **2ac** can undergo the alkenylation to provide the allylbenzene derivative **6**.[17] Finally, amination of **2ac** with $MeONH_2$ was carried out, providing the desired amination product **7** in 81% yield and 94% ee.[18] The synthetic utilities of this approach were further demonstrated by the synthesis of solriamfetol that acts as a dopamine and norepinephrine reuptake inhibitor and the key diol intermediate in the synthesis of benazepril hydrochloride (Figure 3b and c).[19]

In summary, we have developed a Rh-catalyzed asymmetric hydroboration of silyl enol ethers using two new phosphine ligands we developed to construct valuable chiral boronic esters in good yields and enantioselectivities. Both alkyl- and aryl-substituted silyl enol ethers are competent substrates. Importantly, the amenability of *E*/*Z* mixtures of alkyl SEEs in this approach is particularly attractive from the perspective of practical applicability. Control experiments and DFT calculations disclosed that the chiral ligand is responsible for the same configuration obatined from the *E* and *Z* isomers in the hydroboration. The utility of this method is illustrated by a gram-scale reaction and the transformations of borylether products. Enantioselective hydroborations of silyl enol ethers derived from ketones are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06697.

Experimental procedures, characterization and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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