

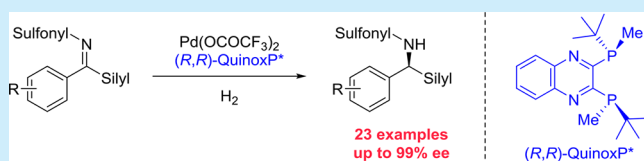
Synthesis of Chiral α -Aminosilanes through Palladium-Catalyzed Asymmetric Hydrogenation of Silylimines

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S Supporting Information

ABSTRACT: The asymmetric hydrogenation of silylimines was first developed by using a palladium complex of a P-stereogenic diphosphine ligand as the catalyst, affording the valuable chiral α -aminosilanes with quantitative conversions and excellent enantioselectivities (up to 99% ee).



Chiral organosilicon compounds are famous for their unique properties as carbon isosteres in pharmaceutical chemistry. Among them, chiral α -aminosilanes have been the most attractive examples for their utilization as mimics of natural α -amino acids in several protease inhibitors as well as chiral reagents for the synthesis of various valuable compounds.¹ In view of this, significant progress have been made for the enantioselective synthesis of chiral α -aminosilanes. The initial asymmetric methodologies include lithiation–silylation of cyclic amides,² reverse aza-Brook rearrangements of *N*-silylamines,³ addition of silyl anions to chiral sulfinimines,⁴ and MVP-type reduction of silylimines,⁵ which require stoichiometric chiral reagents. Recently, a number of copper-catalyzed asymmetric approaches have been developed, such as silylation of aldimines,⁶ hydroamination of vinylsilanes,⁷ and addition of Grignard reagents to arylsilylimines.⁸ However, uneconomic silicon-, nitrogen-, or carbon-containing reagents are always needed (Scheme 1). Thus, an efficient and green method for the construction of chiral α -aminosilanes is still highly desired.

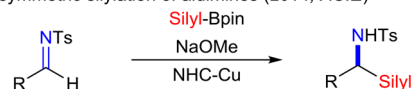
Among all of the methods for the construction of chiral compounds, asymmetric hydrogenation (AH) is one of the most efficient and green technologies.⁹ The transition-metal-catalyzed AH of vinyl and acyl silanes have been developed for the synthesis of chiral unfunctionalized silanes and α -hydroxyl silanes, respectively.¹⁰ However, the asymmetric hydrogenation of silylimines for the synthesis of chiral α -aminosilanes has not been solved, probably due to the low reactivity of the substrates and the instability of the corresponding products. Along with our continuing research on AH,¹¹ herein we disclose for the first time the highly efficient asymmetric hydrogenation of silylimines catalyzed by the palladium complex of a P-stereogenic diphosphine ligand QuinoxP* (Scheme 1).

Initially, a model substrate **1a**, which can be readily prepared by the reaction of acylsilane with tosylamine in the presence of triethylamine and TiCl_4 ,^{5b,10a} was tested in Pd-catalyzed asymmetric hydrogenation using our previously reported axial-chiral diphosphine ligand (*R*)-C10-BridgePhos.¹² Using

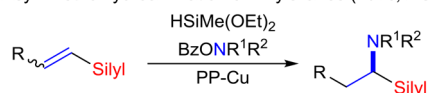
Scheme 1. Method for the Synthesis of Chiral α -Aminosilanes

Previous works:

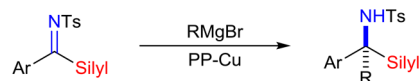
Asymmetric silylation of aldimines (2014, ACIE)



Asymmetric hydroamination of vinylsilanes (2015, ACIE)

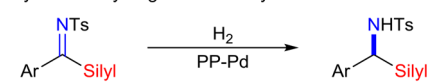


Asymmetric alkylation of silylimines (2016, NCOM)



This works:

Asymmetric hydrogenation of silylimines



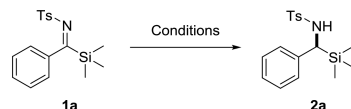
$\text{Pd}(\text{OAc})_2$ as the Pd precursor and trifluoroethanol as the solvent, the desired product **2a** was obtained in complete conversion with moderate enantioselectivity of 65% ee (Table 1, entry 1). Encouraged by this result, more axial-chiral diphosphine ligands were tested.

(*R*)-BINAP afforded similar results (entry 2), while the electron-rich (*R*)-MeO-BIPHEP and (*R*)-SegPhos showed almost no catalytic activity (entries 3 and 4). The ligand (*R*)-DTBM-SegPhos bearing *t*-Bu substituents gave a full conversion but low enantioselectivity of 33% ee (entry 5). We then turned our interest to other types of diphosphine ligands such as (*S,S*)-ChiraPhos, (*R,S_p*)-JosiPhos, and (*R,R*)-Me-DuPhos (entries 6–8). Only the palladium complex of

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Table 1. Condition Optimization



Reaction scheme: 1a (an imine with a Ts group and a silyl group) reacts under conditions to form 2a (the corresponding amine).

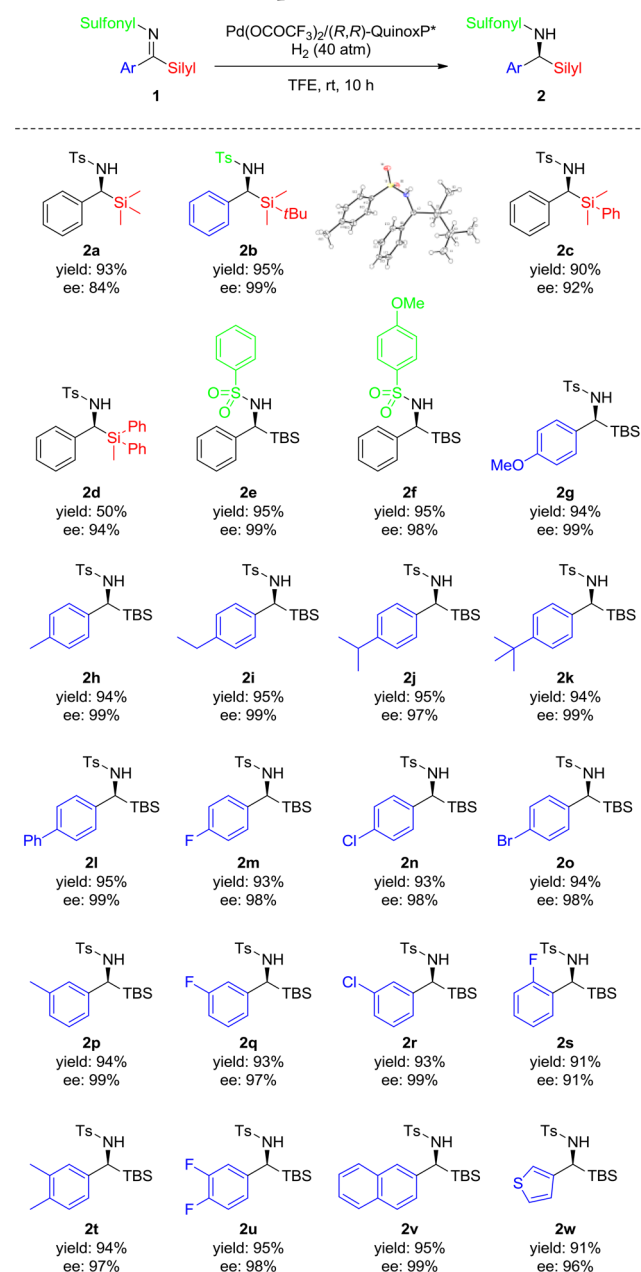
entry ^a	ligand	solvent	conv ^b (%)	ee ^c (%)
1	C10-BridgePhos	TFE	99	65
2	BINAP	TFE	99	58
3	MeO-BIPHEP	TFE	NR	
4	SegPhos	TFE	trace	
5	DTBM-SegPhos	TFE	99	33
6	ChiraPhos	TFE	trace	
7	JosiPhos	TFE	99	18
8	Me-DuPhos	TFE	NR	
9	DuanPhos	TFE	NR	
10	BipheP*	THF	99	67
11	BenzP*	TFE	99	84
12	QuinoxP*	TFE	99	84
13 ^d	QuinoxP*	TFE	NR	
14 ^e	QuinoxP*	TFE	70	85
15	QuinoxP*	MeOH	<10	
16	QuinoxP*	<i>i</i> PrOH	NR	
17	QuinoxP*	DCM	NR	
18	QuinoxP*	toluene	NR	

^aConditions: 1a (0.1 mmol), ligand (0.0022 mmol), Pd(OCOCH₃)₂ (0.002 mmol), H₂ (40 atm), solvent (2 mL), rt, 10 h, unless otherwise noted. ^bThe conversions were calculated from ¹H NMR spectra. ^cThe ee's were determined by HPLC using chiral columns. ^dPdCl₂ was used instead of Pd(OCOCH₃)₂. ^ePd(OCOCH₃)₂ was used instead of Pd(OCOCH₃)₂.

JosiPhos showed catalytic activity and obtained the hydrogenated product with 18% ee (entry 7). Some P-stereogenic diphosphine ligands were chosen and evaluated in this reaction (entries 9–11). No product was detected when the hydrogenation was catalyzed by the palladium complex of (*R*,*S*_p)-DuanPhos (entry 9). The ligand (*R*_p,*R*_p,*S*_a)-BipheP* recently developed in our group¹³ showed high activity and good enantioselectivity (entry 10). To our delight, the palladium complex of (*R*,*R*)-BenzP* and (*R*,*R*)-QuinoxP*¹⁴ promoted the hydrogenation to obtain product 2a with better enantioselectivities (entries 11 and 12). The more stable and available ligand QuinoxP* was chosen for the further optimization. We then turned our attention to examine the effect of Pd precursor on reactivity and enantioselectivity (entries 13 and 14). PdCl₂ showed almost no catalytic activity,

while Pd(OCOCH₃)₂ with weakly coordinating anions provided similar enantioselectivity but lower activity compared to Pd(OCOCH₃)₂. Almost no product can be detected using other solvents such as MeOH, *i*-PrOH, DCM, and toluene (entries 15–18).

With the optimized conditions, the effect of silyl and sulfonyl groups was examined (Scheme 2). The substrates 1a–d bearing different silyl groups were converted to 2a–d in good to excellent enantioselectivities. The substrate 1b bearing a bulky *tert*-butyldimethylsilyl (TBS) substituent gave the product 2b with highest enantioselectivity (99% ee). Further exploration of the sulfonyl groups showed an obvious influence

Scheme 2. Substrate Scope^a

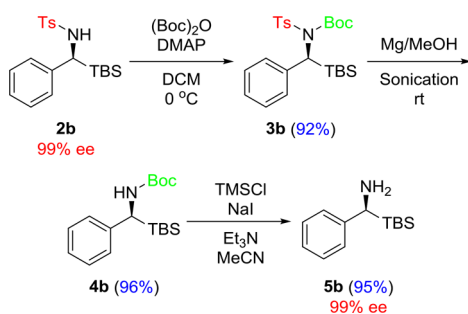
^aConditions: 1 (0.1 mmol), (*R,R*)-QuinoxP* (0.0022 mmol), Pd(OCOCH₃)₂ (0.002 mmol), H₂ (40 atm), TFE (2 mL), rt, 10 h. Isolated yields were recorded. The ee's were determined by HPLC using chiral columns.

on the reaction. High yields and enantioselectivities were obtained for the substrates **1e,f** possessing phenylsulfonyl or 4-methoxyphenylsulfonyl groups, while no hydrogenated product was obtained for substrate possessing a 4-(trifluoromethyl)phenylsulfonyl group. When the hydrogen pressure was reduced from 40 to 15, 5, and even 1 atm, all of the hydrogenation of **1b** could be finished in 10 h with a slightly decreasing enantioselectivity from 99.6% ee to 99.4%, 98.9%, and 98.5% ee.

A wide range of arylsilylimines bearing Ts and TBS substituents were tested (Scheme 2). Substrates with electron-donating (**1g–k**) or electron-withdrawing (**1l–o**) substituents on the *para*-position of the aryl groups can be successfully hydrogenated to give the corresponding amines **2g–o** with excellent ee's. Electron-withdrawing substituents reduced the enantioselectivities slightly as shown on substrates **2m–o**. Changing the substituents from the *para*-position to the *meta*-position on the aryl groups has almost no effect on the enantioselectivities as shown for the products **2p–r** compared to **2h**, **2m**, and **2n**. However, substrate **2s** with a strong electron-withdrawing fluoro substituent in the *ortho*-position was obtained in a slightly lower ee of 91%. The substrates **1t,u** bearing dimethyl or difluoro substituents on the *meta*- and *para*-positions were all fully reduced to **2t,u** with satisfactory enantioselectivities. Furthermore, the substrates processing other aryl groups such as naphthyl and thienyl (**1v–w**) were also applicable in this system to afford **2v–w** quantitatively with 99% and 98% ee's, respectively. A benzylsilylimine has also been synthesized and hydrogenated under the above conditions. However, no product was detected. Substrate **1v** was also completely hydrogenated in 20 h using higher S/C (200/1) with no decrease in enantioselectivity. Further reducing the S/C to 500/1 was accomplished by using BenzP* with a slight decrease in enantioselectivity (98% ee).

Deprotection of tosyl group produces the free α -aminosilanes and ensures the further applications of this methodology. To the best of our knowledge, there is no report concerning on the cleavage of Ts–N bond bearing a fragile C–Si bond.^{6,8} We also encountered difficulties with this reaction after many failures using the common reagents such as base, acid, sodium naphthalide, thioanisole, and SmI₂. Fortunately, we finally found an indirect way to solve this problem. The Ts–N bond was activated after introduction of a Boc group on the N atom and was smoothly disconnected by treatment with Mg/MeOH reagent. After removal of the Boc group, the free α -aminosilanes was obtained in high yield and with retained optical purity (Scheme 3).

Scheme 3. Deprotection of Tosyl Group



The favored and disfavored transition states are shown (Figure 1). According to the single-crystal structure of **1b**, the

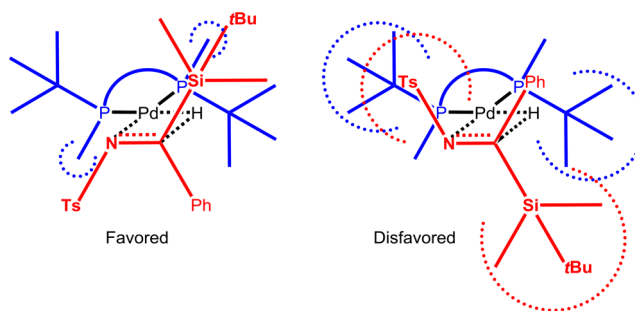


Figure 1. Proposed stereochemical model for the Pd-catalyzed asymmetric hydrogenation of **1b**. The red imine is positioned on top of the blue Pd complex.

Ts group is located opposite to the more bulky TBS group (compared to the Ph group). In the favored transition state, the more sterically hindered Ts group (compared to the lone pair electrons) and TBS group (compared to Ph) on the substrate is adjacent to the smaller Me group (compared to *t*-Bu) on the ligand. In the disfavored transition state, the more bulky *t*-Bu groups on the ligand become their adjacent groups, which leads to a higher energy barrier for the approach of substrate to the catalyst. Thus, the product **2b** was predicted to be (*S*)-configuration, which was consistent with the results of X-ray crystallography.

In summary, asymmetric hydrogenation of a new kind of substrate, *N*-sulfonyl arylsilylimines, was realized for the first time. Catalyzed by the palladium complex of a P-stereogenic diphosphine ligand QuinoxP*, the chiral α -aminosilanes, as the mimics of natural α -amino acids, were obtained in high yields and with excellent enantioselectivities. A challenging deprotection of tosyl group was developed to produce the free α -aminosilanes and ensure the further applications of this methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04073.

Synthetic details for substrates, procedures for hydrogenation reactions, and spectra of NMR and HPLC data (PDF)

Accession Codes

CCDC 1448051 and 1502280 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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