How to cite: Angew. Chem. Int. Ed. 2023, e202305449
doi.org/10.1002/anie.202305449

Organic Chemistry

Borane-Catalyzed Tandem Cyclization/Hydrosilylation Towards Enantio- and Diastereoselective Construction of *trans*-2,3-Disubstituted-1,2,3,4-Tetrahydroquinoxalines

Zhenli Luo[+], Zhewei Li[+], Haoqiang Zhao[+], Ji Yang, Lijin Xu, Ming Lei,* Qinghua Fan, and Patrick J. Walsh**

Abstract: Recent years have witnessed marked progress in the efficient synthesis of various enantioenriched 1,2,3,4-tetrahydroquinoxalines. However, enantio- and diastereoselective access to *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines remains much less explored. Herein we report that a frustrated Lewis pair-based catalyst generated via in situ hydroboration of 2-vinylnaphthalene with $HB(C_6F_5)_2$ allows for the one-pot tandem cyclization/hydrosilylation of 1,2-diaminobenzenes and 1,2-diketones with commercially available $PhSiH_3$ to exclusively afford *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines in high yields with excellent diastereoselectivities (>20:1 dr). Furthermore, this reaction can be rendered asymmetric by using an enantioenriched borane-based catalyst derived from $HB(C_6F_5)_2$ and a binaphthyl-based chiral diene to give rise to enantioenriched *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines in high yields with almost complete diastereo- and enantiocontrol (>20:1 dr, up to >99% ee). A wide substrate scope, good tolerance of diverse functionality and up to 20-gram scale production are demonstrated. The enantio- and diastereocontrol are achieved by the judicious choice of borane catalyst and hydrosilane. The catalytic pathway and the origin of the excellent stereoselectivity are elucidated by mechanistic experiments and DFT calculations.

Introduction

■■Please provide academic titles (Prof., Dr.) for all authors■■

Enantioenriched 1,2,3,4-tetrahydroquinoxalines constitute backbones of numerous pharmaceutically active compounds that display a variety of pharmaceutical and biological activities,[1] such as antiproliferative activity, potent cholesteryl ester transfer protein inhibition, vasopressin V2 receptor antagonist and bromodomain and extra-terminal domain (BET) inhibition. As a result of their potential utility in medications, synthetic access to enantiomerically enriched chiral 1,2,3,4-tetrahydroquinoxalines has become the subject of intense research.[2–6] Among the reported approaches to this class of compounds, asymmetric reduction of quinoxalines with molecular hydrogen or hydrogen donors under transition-metal catalysis and organocatalysis has been developed.[3–5] Moreover, advances have been reported in the tandem one-pot synthesis of enantioenriched 1,2,3,4-tetrahydroquinoxalines via asymmetric reduction of quinoxalines, quinoxalinones or dihydroquinoxalines generated in situ from readily available starting materials.[4k,5c,6a–d] Most of these studies, however focused on the enantioselective synthesis of 2-substituted 1,2,3,4-tetrahydroquinoxalines. In contrast, enantio- and diastereoselective access to 2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines remains underdeveloped, because of challenges associated with controlling both relative and absolute stereochemistry in the creation of two vicinal stereogenic centers.

In general, the catalytic reduction of 2,3-disubstitued quinoxalines predominantly gives rise to the *cis*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxaline diastereomers.[7] The reduction can be rendered enantioselective through the action of enantioenriched catalyst (Scheme 1a and 1b).[4l,5d,6d] In contrast, enantio- and diastereoselective access to *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines has proven challenging. In 2011, Fan and co-workers first realized a Ru-catalyzed enantio- and diastereoselective hydrogenation of

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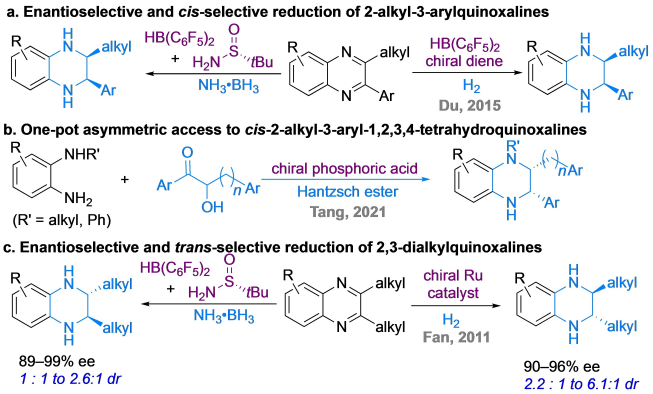
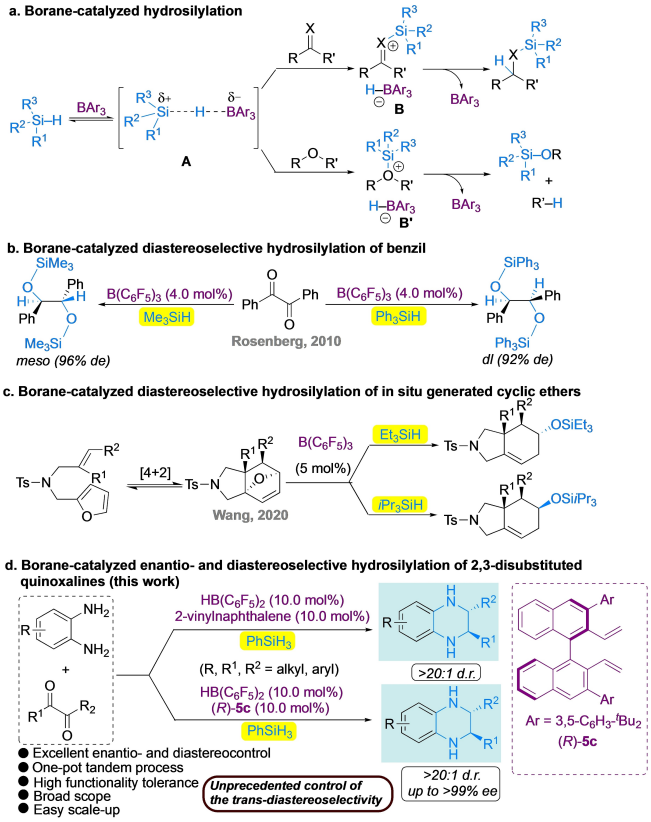


Scheme 1. Enantio- and diastereoselective syntheses of 2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines.

2,3-dialkyl quinoxalines to provide *trans*-2,3-dialkyl 1,2,3,4-tetrahydroquinoxalines with up to 99 % ee, but only modest *trans*-diastereoselectivities (2.2:1 to 6.1:1 dr, Scheme 1c) were obtained.[4e] Likewise, high enantioselectivities (up to >99 % ee), but low to modest *trans* diastereoselectivities (1:1 to 2.6:1 dr) were observed in the $HB(C_6F_5)_2$/(*R*)-*tert*-butanesulfinamide catalyzed asymmetric transfer hydrogenation of 2,3-dialkyl quinoxalines developed by Du and co-workers (Scheme 1c).[5d] Given that 1) stereoisomers exhibit different biological activities, 2) mixtures of stereoisomers are usually difficult to separate and 3) that the stereoselective synthesis of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines is difficult, there clearly exists incentive to develop efficient catalytic systems for highly enantio- and diastereoselective generation of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines.

Since its discovery in 1996, the borane-catalyzed transition metal-free Piers-type hydrosilylation has undergone extensive investigation and found broad applications in the reduction of unsaturated compounds.[8–15] The advantages of this approach are its high efficiency, convenience and mild reaction conditions. In particular, recent progress has enabled facile hydrosilylation of various *N*-heteroarenes.[7f,12] As shown in Scheme 2a, the borane-catalyzed Piers-type hydrosilylation generally starts via activation of the hydrosilane instead of the substrate by the borane catalyst to give the borane-silane complex **A**.[9,13] The reaction of **A** with the unsaturated compound or the ether results in the formation of ion pair **B** or **B′**. Finally, hydride transfer from the borohydride yields the corresponding reduction products with the release of the borane catalyst. As such, it is quite possible to tune the diastereoselectivity through judicious choice of the borane catalysts and hydrosilanes. Indeed, Rosenberg and co-workers revealed that $B(C_6F_5)_3$-catalyzed bis(hydrosilylation) of benzil with a small hydrosilane (Me_3Si–H) predominantly produced the *meso* (*anti*) product, but the large hydrosilane Ph_3Si–H favored the generation of the *dl* (*syn*) product (Scheme 2b).[14a] More recently, Wang and co-workers were also able to tune diastereoselectivity through choice of silane cone-angle in $B(C_6F_5)_3$-catalyzed diastereoselective hydrosilylation of in situ generated cyclic ethers (Scheme 2c).[14b] Inspired by these elegant works, we reasoned that the enantio- and diastereoselective hydrosilylation of 2,3-disubstituted quinoxalines to *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines might be possible through proper choice of hydrosilane reagent and borane catalyst.



Scheme 2. Borane-catalyzed diastereoselective hydrosilylation.

Continuing our pursuit of new synthetic methods for the synthesis of 1,2,3,4-tetrahydroquinoxalines,[5b,e,6b,7a] we first demonstrate proof-of-concept that 2,3-disubstituted quinoxalines can be reduced to *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines with excellent diastereoselectivity in the presence of $HB(C_6F_5)_2$ by proper choice of hydrosilane and catalytic amounts of styrene derivatives ($PhSiH_3$ and 2-vinylnaphthalene). Building upon these studies, a highly enantio- and diastereoselective hydrosilylation of 2,3-disubstituted quinoxalines to furnish *trans*-products is then introduced (Scheme 2d). The proper selection of borane catalyst and hydrosilane reductant is essential for achieving excellent enantio- and diastereoselectivity. To increase the synthetic efficiency, we used an in situ generation of the 2,3-disubstituted quinoxalines from readily available 1,2-diaminobenzenes and 1,2-diketones.

Results and Discussion

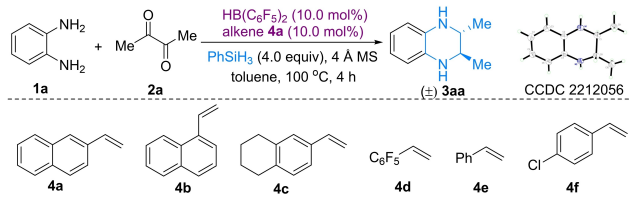
We commenced our study on the diastereoselective synthesis of *trans*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline

((±) **3aa**) from 1,2-diaminobenzene (**1a**) and 2,3-butanedione (**2a**). Thus, after extensive screening it was found that the reaction of **1a** and **2a** was best performed with in situ generated borane catalyst from $HB(C_6F_5)_2$ and 2-vinylnaphthalene (**4a**) using $PhSiH_3$ as the reductant and toluene as the solvent at 100 °C, affording exclusively the target *trans* product (±) **3aa** in 93 % isolated yield (>20:1 dr, as determined by ^{1}H NMR, Table1, entry1). The relative configuration of (±) **3aa** (CCDC: 2212056) was confirmed by single crystal X-ray crystallographic analysis.[15] The reaction proceeded much less diastereoselectively upon replacing 2-vinylnaphthalene (**4a**) with other aryl alkenes, such as 1-vinylnaphthalene (**4b**), 6-vinyl-1,2,3,4-tetrahydronaphthalene (**4c**), 1,2,3,4,5-pentafluoro-6-vinylbenzene (**4d**), styrene (**4e**) and 1-chloro-4-vinylbenzene (**4f**) (Table 1, entries 2–6). Interestingly, the use of **4c**, the partially hydrogenated derivative of **4a**, led to a dramatic drop in diastereoselectivity (Table 1, entry 3), demonstrating the importance of the extended π-system.

As hypothesized at the outset, the nature of the hydrosilane employed strongly affected the reaction diastereoselectivity. For example, when a trialkylhydrosilane, such as Et_3SiH, $(iPr)_3SiH$ or $EtMe_2SiH$, was employed, the preferential formation of the *cis* diastereoisomer was observed (Table 1, entries 7–9). Likewise, $(EtO)_3SiH$ delivered a mixture of *cis* and *trans* diastereoisomers favoring the former (Table 1, entry 10). Intriguingly, the use of arylhydrosilanes, like Me_2PhSiH and Ph_2SiH_2, reversed the diastereoselectivity to predominantly generate the *trans*-diastereoisomer with high diastereoselectivity (Table 1, entries 11 and 12), although less with Ph_3SiH (Table 1, entry 13). These results suggest that a phenyl substituent in the hydrosilane is crucial to the *trans* diastereoselectivity. Toluene emerged as the most suitable solvent, while other solvents, like THF, 1,4-dioxane and CH_3CN, were less effective with low levels of *trans* diastereoselectivity (Table 1, entries 14–16). Finally, catalytic $B(C_6F_5)_3$ and BPh_3 were also tested, but they favored the formation of the *cis*-diastereoisomer (Table 1, entries 17 and 18).

Under the optimized conditions, we explored the scope of this reaction (Table 2). First various 1,2-diaminobezenes were evaluated in the reaction with **2a**. Specifically, with 4-substituted 1,2-diaminobenzenes (**1b–1j**) the reactions proceeded to deliver the target *trans*-2,3-diakyl-1,2,3,4-tetrahydroquinoxalines ((±) **3ba–3ja**) in 74–95 % yields and producing a single detectable diastereomer (>20:1 dr). The reaction exhibited tolerance to a variety of electron-donating (Me, OMe) and electronegative and withdrawing functional groups (F, Cl, Br, CF_3, CN, CO_2Me and NO_2) on the aryl ring. Notably, the relative configuration of (±) **3ia** (CCDC: 2179563) was verified by single crystal X-ray crystallographic analysis.[15] Despite the steric hindrance, 3-

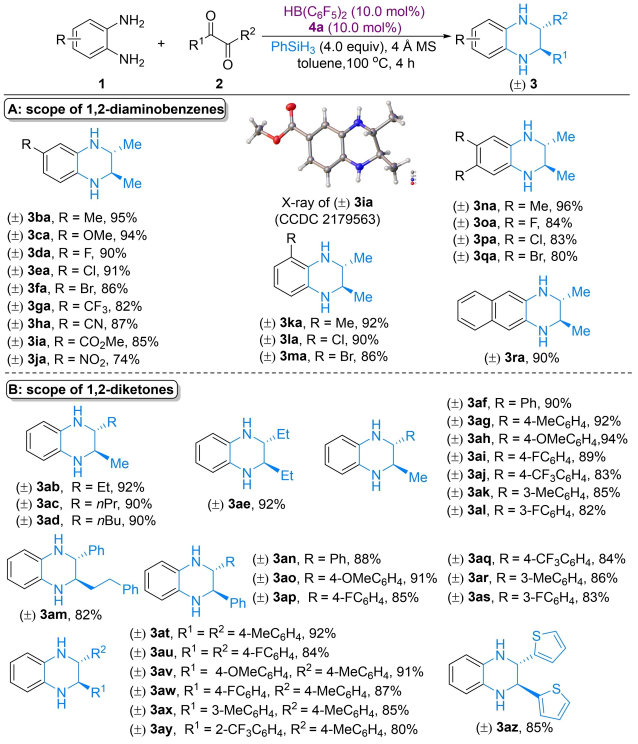
Table 1: Optimization of reaction conditions for synthesis of (±) **3aa** from **1a** and **2a**.[a]



Entry	Deviation	(±)**3aa** (%)[b]	*trans*/*cis*[b]
1	none	96 (93)[c]	>20:1
2	**4b** instead of **4a**	95	6.1:1
3	**4c** instead of **4a**	95	2.3:1
4	**4d** instead of **4a**	82	1.6:1
5	**4e** instead of **4a**	96	1.9:1
6	**4f** instead of **4a**	91	2.6:1
7	Et_3SiH instead of $PhSiH_3$	94	1:1.6
8	$EtMe_2SiH$ instead of $PhSiH_3$	95	1:1.9
9	$(iPr)_3SiH$ instead of $PhSiH_3$	82	1:4
10	$(EtO)_3SiH$ instead of $PhSiH_3$	88	1:2.3
11	Me_2PhSiH instead of $PhSiH_3$	96	19:1
12	Ph_2SiH_2 instead of $PhSiH_3$	94	11.5:1
13	Ph_3SiH instead of $PhSiH_3$	85	1.9:1
14	THF	93	7.3:1
15	1,4-dioxane	80	9:1
16	CH_3CN	85	3:1
17	$B(C_6F_5)_3$ (10.0 mol%) as the catalyst	96	>1:20
18	BPh_3 (10.0 mol%) as the catalyst	75	1:4.6

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), $HB(C_6F_5)_2$ (10.0 mol%), **4a** (10.0 mol%), 4 Å MS (30.0 mg), $PhSiH_3$ (0.8 mmol), toluene (1.0 mL), 100 °C, under N_2, 4 h. [b] Determined by ^{1}H NMR analyses of the crude reaction mixtures. [c] Isolated yield.

Table 2: Substrate scope for diastereoselective synthesis of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines.[a]

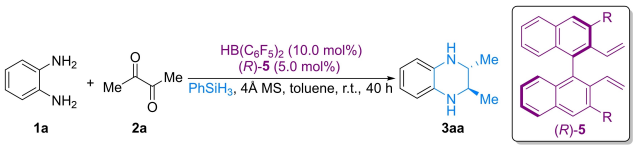


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), $HB(C_6F_5)_2$ (10.0 mol%), **4a** (10.0 mol%), 4 Å MS (30.0 mg), $PhSiH_3$ (0.8 mmol), toluene (1.0 mL), 100 °C, N_2, 4 h. Isolated yield. The ratio of diastereomers was determined by ^{1}H NMR analysis. Unless otherwise noted, >20:1 dr was observed.

substituted 1,2-diaminobenzenes (**1k**–**1m**) were equally suitable for this reaction, furnishing the desired *trans* products (**3ka**-**3ma**) in 86–92 % yields with >20:1 dr. Moreover, 4,5-disubstituted 1,2-diaminobenzenes (**1n**–**1q**) and naphthalene-2,3-diamine (**1r**) readily participated in the transformation to afford the corresponding *trans* products ((±) **3na**–**3ra**) in 80–96 % yields with >20:1 dr. The generality of this protocol was further showcased by its compatibility with diversely substituted 1,2-diketones. The 1,2-dialkyl-ethanediones (**2b**–**2e**) reacted with **1a** to afford the *trans* products ((±) **3ab**–**3ae**) in high yields with >20:1 dr. A series of aryl alkyl 1,2-diketones (**2f**–**2m**) proved to be viable in this transformation, and the corresponding products ((±) **3af**–**3am**) were formed in 82–94 % yields with >20:1 dr. This reaction was also amenable to differently substituted 1,2-diaryl-ethanediones (**2n**–**2y**) to exclusively furnish the target *trans* products ((±) **3an**–**3ay**) in 80–92 % yields. Finally, 1,2-di(thiophen-2-yl)ethane-1,2-dione (**2z**) was also tolerated, leading to the exclusive *trans*-formation of (±) **3az** in 85 % yield.

Next our attention turned to enantio- and diastereoselective access to *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines. Inspired by the axially chiral borane catalysts formed in situ from the hydroboration of $HB(C_6F_5)_2$ and the axially binaphthyl-based chiral dienes developed by Du,[4l,11d,h,16] a series of such catalysts were synthesized and screened at room temperature. As illustrated in Table 3, these reactions proceeded diastereoselectively to exclusively provide the desired chiral *trans* product **3aa** in good to excellent yields. The enantioselectivities, however, varied in response to the structure of the enantioenriched dienes. For example, using (*R*)-2,2′-divinyl-1,1′-binaphthalene ((*R*)-**5a**) resulted in the generation of **3aa** in 91 % yield with only 35 % ee. Further studies revealed that introduction of various aryl substituents at the 3,3′-positions of the 1,1′-binaphthyl moiety could substantially enhance the enantioselectivity without impacting the *trans*-diastereoselectivity. The enantioenriched diene (*R*)-**5c** led to the most enantioselective catalyst (99 % ee). Intensive screening of solvents, reaction temperatures and other reaction parameters disclosed that this enantio- and diastereoselective reaction was best conducted using $HB(C_6F_5)_2$ (10.0 mol%)/(*R*)-**5c** (5.0 mol%) to form the catalyst, 4 Å MS as the additive and $PhSiH_3$ (4.0 equiv) in toluene at room temperature for 40 h, affording **3aa** in 92 % yield with 99 % ee. Notably, the absolute configuration of **3aa** was determined to be (2*R*,3*R*) based on single-crystal X-ray analysis of (4-bromophenyl)(2,3-dimethyl-3,4-dihydroquinoxalin-1(2*H*)-yl)methanone **6a** (CCDC: 2203880) (Scheme 3).[15] The configurations of other *trans*-products were assigned by analogy.

Table 3: Evaluation of chiral dienes.[a]

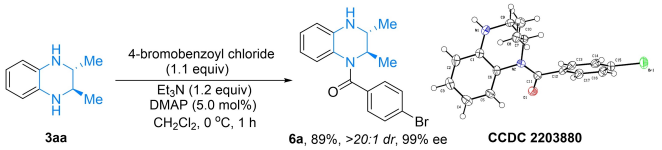


Entry	Entry	Entry	Entry	Entry
1	(*R*)-**5a**	H	91	35
2	(*R*)-**5b**	Ph	90	64
3	(*R*)-**5c**	3,5-$tBu_2C_6H_3$	92	99
4	(*R*)-**5d**	2-naphthyl	85	90
5	(*R*)-**5e**	2-$MeOC_6H_4$	93	85
6	(*R*)-**5f**	5-*t*Bu-2-$MeOC_6H_3$	90	84
7	(*R*)-**5g**	2,4,6-$Me_3C_6H_2$	89	88
8	(*R*)-**5h**	3,5-$(CF_3)_2C_6H_3$	88	85
9	(*R*)-**5i**	3,5-$TMS_2C_6H_3$	90	92
10	(*R*)-**5j**	4-MeC_6H_4	89	74
11	(*R*)-**5k**	4-PhC_6H_4	91	68
12	(*R*)-**5l**	3-MeC_6H_4	90	76
13	(*R*)-**5m**	2-MeC_6H_4	89	80
14	(*R*)-**5n**	5-*i*Pr-$_2$-$MeOC_6H_3$	92	82

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), $HB(C_6F_5)_2$ (10.0 mol%), (*R*)-**5** (5.0 mol%), 4 Å MS (30.0 mg), $PhSiH_3$ (0.8 mmol), toluene (1.0 mL), r.t., N_2, 40 h. [b] Yields of isolated products were provided. [c] The ee values were determined by HPLC using chiral stationary phase columns. Unless otherwise noted, >20:1 dr was obtained.

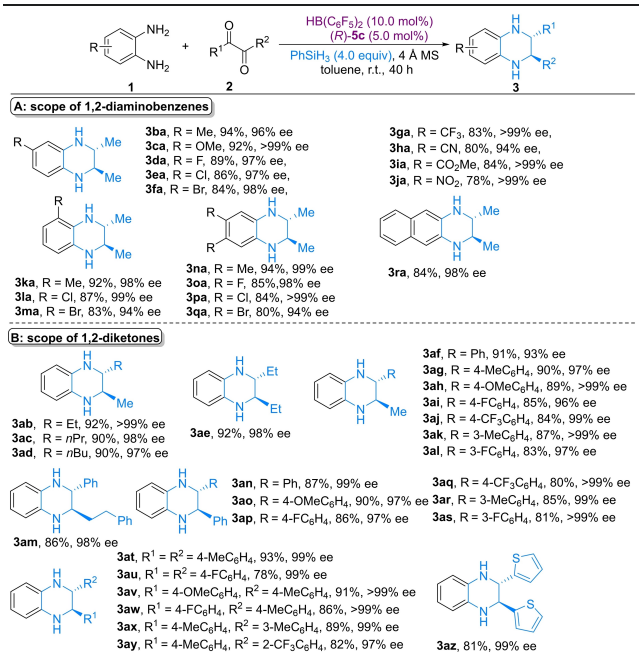
Table 4A, an array of 1,2-diaminobenzenes (**1b**–**1q**) reacted smoothly with **2a** regardless of the nature of the substituents on the aryl moiety, exclusively generating the corresponding *trans* products (**3ba**–**3qa**) in good to excellent yields with enantioselectivities between 94–>99 %. Likewise, naphthalene-2,3-diamine (**1r**) underwent the desired transformation to give **3ra** in 84 % yield with 98 % ee. Differently substituted 1,2-diketones were also viable substrates for this protocol (Table 4B). Diverse alkyl and aryl substituents attached to the carbonyl carbon were all compatible, affording products (**3ab**–**3ay**) in high yields with excellent enantiocontrol (93–>99 % ee). Surprisingly, the nature of the substrate substituents exerted negligible influence on the catalyst enantioselectivity. As expected, 1,2-di(thiophen-2-yl)ethane-1,2-dione (**2z**) was efficiently converted to the desired product **3az** in 81 % yield with 99 % ee.

The reactions can be readily scaled up without erosion of reactivity or stereoselectivity. As illustrated in Scheme 4a, the reaction of **1a** and **2a** on a 20-gram scale occurred smoothly under the catalysis of $HB(C_6F_5)_2$/**4a**, exclusively giving rise to (±) **3aa** in 90 % isolated yield with >20:1 dr. For the asymmetric version, the combination of (*R*)-**5c** and $HB(C_6F_5)_2$ enabled the gram-scale reaction of **1a** and **2a** to afford **3aa** in 88 % yield with >20:1 dr and 99 % ee. Further studies indicated that enantioenriched **3aa** underwent facile mono-*N*-functionalization and di-*N*-functionalization reac-

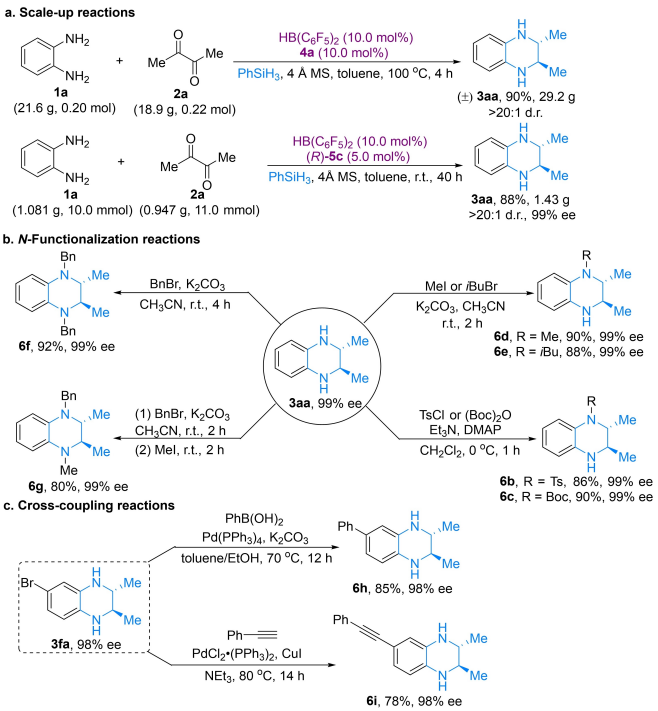


Scheme 3. Determination of the absolute configuration of **3aa**.

Table 4: Substrate scope for enantio- and diastereoselective synthesis of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines.[a]



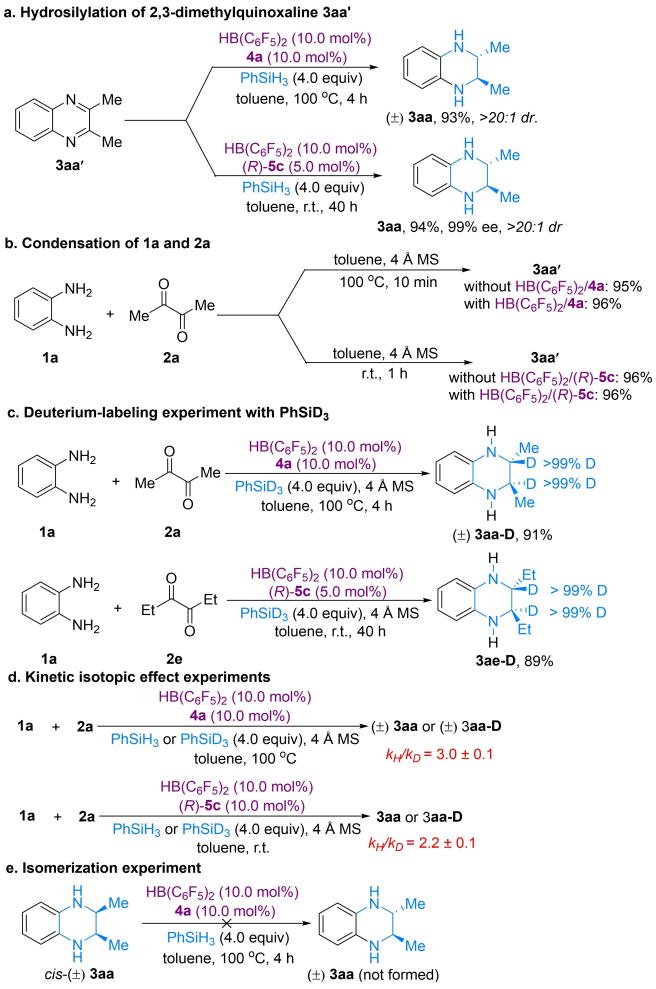
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.22 mmol), $HB(C_6F_5)_2$ (10.0 mol%), (*R*)-**5c** (5.0 mol%), 4 Å MS (30.0 mg), $PhSiH_3$ (0.8 mmol), toluene (1.0 mL), r.t., under N_2, 40 h. Isolated yield. The ratio of diastereomers was determined by ^1H NMR analysis. Unless otherwise noted, >20:1 dr was obtained. The ee values were determined by HPLC using chiral stationary phase columns.



Scheme 4. Synthetic utility.

tions to provide the chiral building blocks **6b**–**6g** in 80–92 % yields without compromising the enantio- and diastereopurity (Scheme 4b). Finally, enantioenriched **3fa** could be easily functionalized via Pd-catalyzed cross-coupling reactions to deliver **6h** and **6i** in 85 % and 78 % yields, respectively, with full retention of stereochemistry (Scheme 4c).

To elucidate the reaction mechanism, several additional experiments were conducted. First, high resolution mass spectrometry (HRMS) of the reaction mixture of **1a** and **2a** catalyzed by $HB(C_6F_5)_2$/**4a** or (*R*)-**5c** revealed the in situ generation of 2,3-dimethylquinoxaline **3aa′** (for details, see Supporting Information). Moreover, treatment of preformed **3aa′** with $PhSiH_3$ under $HB(C_6F_5)_2$/**4a** catalysis resulted in the exclusive generation of (±) **3aa** in 94 % yield with >20:1 dr, and asymmetric hydrosilylation of **3aa′** with $PhSiH_3$ using $HB(C_6F_5)_2$/(*R*)-**5c** catalysis proceeded readily to deliver **3aa** in 93 % yield with almost complete enantio- and diastereocontrol (Scheme 5a). These results validate the involvement of an in situ formed quinoxaline intermediate in this transformation. Interestingly, no formation of butane-2,3-diol was detected by HRMS analysis, suggesting that the reduction of **2a** by $PhSiH_3$ did not occur under the current conditions. Further studies revealed that the room temper-

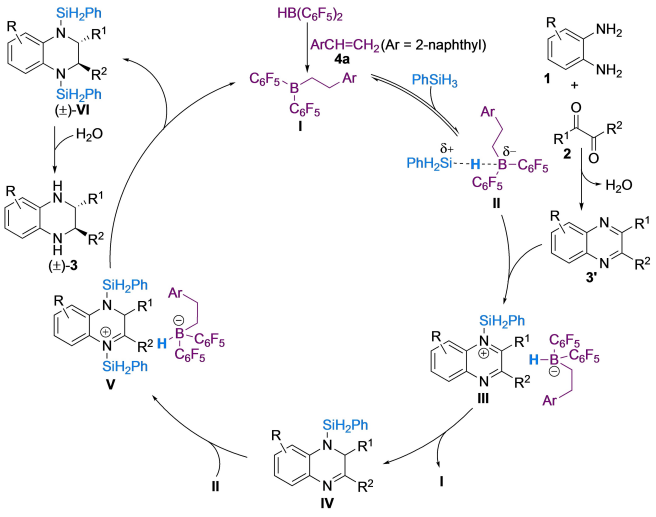


Scheme 5. Mechanistic studies.

ature reactions of **1a** and **2a** 1) without catalyst, 2) with $HB(C_6F_5)_3$/**4a** or 3) with $HB(C_6F_5)_3$/(*R*)-**5c** provided essentially the same yields of **3aa′** (Scheme 5b), indicating that the catalysts do not likely participate in the formation of **3aa′**. No deuteriation was detected when toluene-d_8 was used as the reaction medium, excluding the possibility of solvent participation in this reaction (for details, see Supporting Information). Replacing $PhSiH_3$ with D_3SiPh in the presence of the achiral and enantioenriched catalysts led to the formation of deuterated products (±) **3aa-D** and (*R*,*R*)-**3ae-D**, suggesting that the reactions indeed proceeded via hydrosilylation of the in situ formed C=N bonds and demonstrating the synthesis of the isotopomers (Scheme 5c). The parallel reactions between **1a** and **2a** with $PhSiH_3$ or $PhSiD_3$ with catalyst derived from **4a** or (*R*)-**5c** revealed kinetic isotope effect values of 3.0 ± 0.1 and 2.2 ± 0.1 (Scheme 5d), respectively, implying that the hydride reduction might be involved in the rate-limiting step. Finally, subjecting *cis*-**3aa** to the standard reaction conditions did not form the thermodynamically more stable *trans*-(±) **3aa** (Scheme 5e), thus ruling out the possibility of *cis*/*trans* isomerization in this transformation.

Based on the results attained from the above experiments and previous reports,[9–14] a mechanism for the borane-catalyzed diastereoselective generation of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines from 1,2-diketones and 1,2-diaminobenzenes is proposed. As shown in Scheme 6, hydroboration of 2-vinylnaphthalene (**4a**) with $HB(C_6F_5)_2$ yields the borane catalyst **I**, which activates $PhSiH_3$ to give the borane-hydrosilane complex **II**. The transfer of the silylium cation of **II** to 2,3-disubstituted quinoxaline **3′** generated in situ from 1,2-diaminobenzene **1** and 1,2-diketone **2** results in the formation of the ion pair intermediate **III** possessing a borohydride anion. The delivery of hydride to the C2-position of the quinoxalinium moiety affords the *N*-silylated dihydroquinoxaline intermediate **IV**. The silylium cation of **II** then activates the C=N bond of **IV** to generate the ion pair intermediate **V**, which subsequently undergoes diastereoselective hydride attack at the C3-position of the dihydroquinoxalinium moiety to give the *trans*-*N*-silylated-2,3-disubstituted-1,2,3,4-tetrahydroquinoxaline (±)-**VI** and regenerate the borane catalyst **I**. Finally, hydrolysis of (±)-**VI** provides (±)-**3**.

To gain further insights into the mechanism and the origin of the unusual diastereoselectivity, density functional theory (DFT) calculations were performed with 2,3-dimethylquinoxaline (**3aa′**) and the borane formed in situ from $HB(C_6F_5)_2$ and **4a** as the catalyst (for computational details see the Supporting Information). As shown in Figure 1, mono-hydrosilylation of 2,3-dimethylquinoxaline **3aa′** to give the *N*-silylated dihydroquinoxaline product (±)-**3aa″** proceeds via the optimized transition state **TS1**, which is favored by an attractive aromatic C–H/π interaction between the Si–Ph of the quinoxalinium moiety and the naphthalene ring of the borohydride anion. The interaction region indicator (IRI)[17] analysis of **TS1** illustrated by the green isosurfaces clearly supports the existence of such a non-bonding interaction. Figure 2a illustrates the structural geometries of two optimized **TSs** for the diastereoselective hydrosilylation of the C=N bond of (±)-**3aa″**. Here, **TS2** ($\Delta G^{\ddagger} = 6.8$ kcal/mol) leading to the *trans* product is favored over **TS2′** ($\Delta G^{\ddagger} = 8.2$ kcal/mol), which leads to the *cis*, by $\Delta G^{\ddagger} = 1.4$ kcal/mol. The calculated ratio of *trans*/*cis* is 10.1:1, which agrees well with the experimental value of >20:1. Notably, **TS2** is stabilized by C–H/π interaction between the two silyl benzene rings of the 3,4-dihydroquinoxalinium moiety with each other and with the naphthalene ring of the borohydride anion. In the case of **TS2′** this interaction is greatly weakened. This difference accounts for the preferential generation of *trans*-(±)-**3aa** over *cis*-**3aa**. IRI analysis of **TS2** and **TS2′** further verified that **TS2** affords stronger C–H/π interaction than **TS2′** (Figure 2b). Moreover, additional calculations disclosed that replacement of the naphthyl ring of the borohydride anion with a phenyl ring weakens this C–H/π interaction and is



Scheme 6. Proposed reaction mechanism.

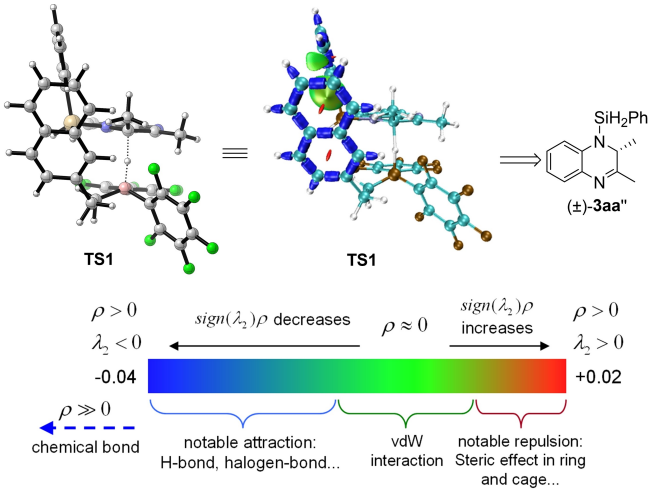


Figure 1. Optimized structure and IRI isosurface of transition state **TS1** for monohydrosilylation of **3aa′** (Isosurface maps of IRI = 1.0. Grid spacing for IRI is 0.08 Bohr).

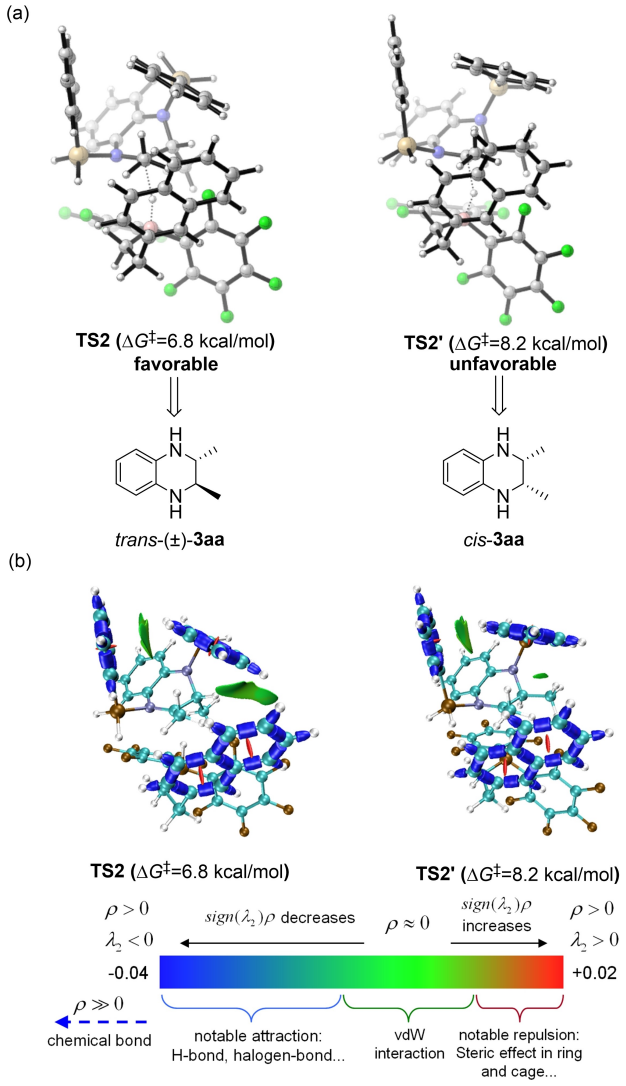


Figure 2. (a) The diastereoselectivity-determining transition states of **TS2** and **TS2′**; (b) IRI isosurface of **TS2** and **TS2′** (isosurface maps of IRI = 1.0. Grid spacing for IRI is 0.08 Bohr).

predicted to lower the *trans*/*cis* ratio to 2.3:1 (Figure S18 in the Supporting Information). This prediction is in good agreement with the experimental value of 1.9:1. This result demonstrates that the C–H/π interaction between the catalyst naphthyl ring and the Si–Ph is indeed the key factor controlling the excellent *trans* diastereoselectivity observed in this transformation.

On the basis of the above mechanistic studies and previous reports,[18] we proposed models of transition states (**TS3** and **TS4**) accounting for the stereoselectivity in the asymmetric hydrosilylation of **3aa′** (Figure 3). For the asymmetric hydrosilylation of **3aa′**, owing to the existence of a favorable C–H/π interaction between the silyl phenyl ring of the quinoxalinium moiety and the naphthyl ring of the borohydride anion in **TS3**, the hydride is transferred from the borane center to the *Si* face of the C=N moiety to give the *R*-configured product (*R*)-**3aa″**. This mono-hydrosilylated intermediate undergoes further reduction of the

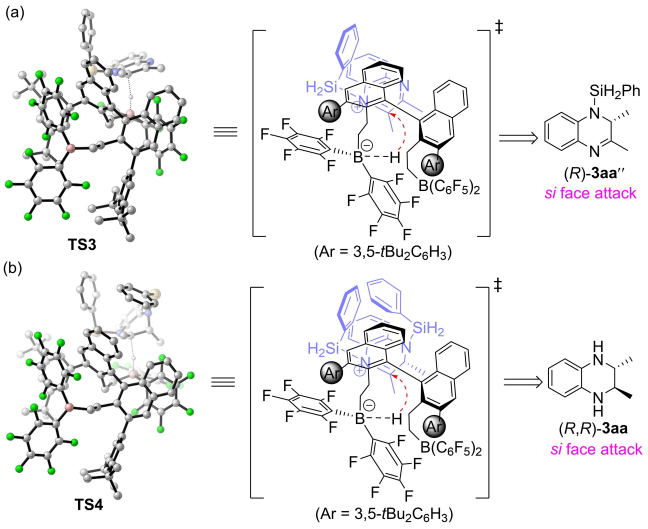


Figure 3. Proposed transition states for the production of (*R*)-**3aa″** and (*R*,*R*)-**3aa**. (The structures of **TS3** and **TS4** are not optimized using DFT method).

remaining C=N bond via **TS4**, in which the hydride preferentially adds to the *Si* face of the C=N moiety to deliver the *trans* product (*R*,*R*)-**3aa** as a result of the strength of the C–H/π interaction.

Conclusion

In conclusion, we have developed the first borane-catalyzed tandem protocol for diastereo- and enantioselective synthesis of *trans*-2,3-disubstitited 1,2,3,4-tetrahydroquinoxalines from 1,2-diaminobenzenes and 1,2-diketones with $PhSiH_3$ as the reducing agent. Proper selection of borane catalyst and hydrosilane is crucial for the enantio- and diastereocontrol in this transformation. The reaction catalyzed by a borane generated in situ from 2-vinylnaphthalene and $HB(C_6F_5)_2$ proceeded diastereoselectively to exclusively give *trans* 2,3-disubstitited 1,2,3,4-tetrahydroquinoxalines in high yields with almost complete diastereocontrol. Employing an enantioenriched borane derived from $HB(C_6F_5)_2$ and chiral diene (*R*)-**5c** as the catalyst resulted in the exclusive formation of *trans*-2,3-disubstitited 1,2,3,4-tetrahydroquinoxalines in high yields with excellent *trans* diastereoselectivities and up to >99 % ee. The protocol exhibits wide substrate scope and broad compatibility with functional groups and can be readily scaled. DFT investigations uncovered the *trans* diastereoselectivity originated from the C–H/π interaction between the two silyl benzene rings of the 3,4-dihydroquinoxalinium and the naphthalene ring of the borohydride anion. The present protocol represents a rare example of catalytic *trans*-hydrosilylation of *N*-heterocycles. We anticipate that the present method will find applications for the synthesis of enantioenriched 2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines and their derivatives with biological and medicinal activity.

Acknowledgements

Financial supports from National Natural Science Foundation of China (21372258 and 22073005), and the Beijing National Laboratory for Molecular Sciences (BNLMS201845) are gratefully acknowledged. P. J. W. acknowledges the US NSF (CHE-2154593). H. Z. thanks Renmin University of China, University of Pennsylvania and Beijing University of Chinese Medicine for generous support.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 1,2,3,4-Tetrahydroquinoxaline · Borane · Frustrated Lewis Pairs · Hydrosilylation · Quinoxaline

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Manuscript received: April 19, 2023
Accepted manuscript online: June 20, 2023
Version of record online: ■■, ■■

Research Articles

Organic Chemistry

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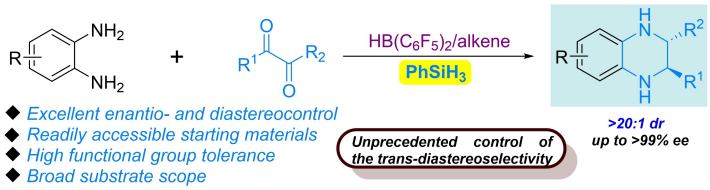
Borane-Catalyzed Tandem Cyclization/Hydrosilylation Towards Enantio- and Diastereoselective Construction of *trans*-2,3-Disubstituted-1,2,3,4-Tetrahydroquinoxalines



A one-pot tandem cyclization/hydrosilylation process applied to 1,2-diaminobenzenes and 1,2-diketones under borane catalysis with $PhSiH_3$ for the enantio- and diastereoselective synthesis of *trans*-2,3-disubstituted 1,2,3,4-tetrahydroquinoxalines is presented. Experimental studies and density functional theory calculations were conducted to explore the reaction mechanism. The diastereoselectivity was found to originate from a C–H/π interaction.

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