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PAPER

Metal-free Tandem Cyclization/Hydrosilylation to Construct Tetrahydroquinoxalines

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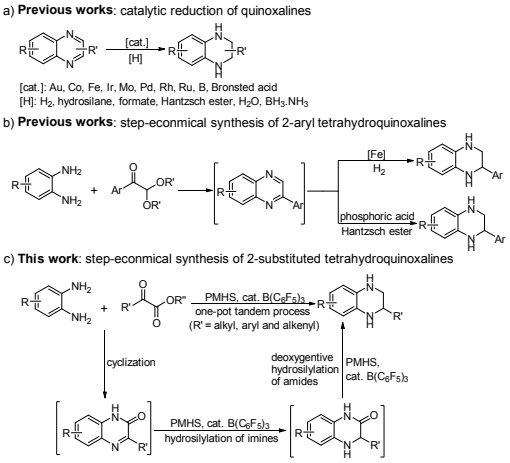
A one-pot tandem procedure involving cyclization and sequential hydrosilylation of imines and amides under the catalysis of $B(C_6F_5)_3$ has been developed for the step-economical construction of 1,2,3,4-tetrahydroquinoxalines directly from readily available 1,2-diaminobenzenes and α-ketoesters and cheap, safe polymethylhydrosiloxane (PMHS). This metal-free approach provides various products in good to excellent yields, and displays a wide range of substrate scope and high degree of functional group tolerance even to reduction-sensitive moieties. The choice of hydrosilanes is critical to the catalysis, and PMHS proved to be optimal. Decreasing the amount of PMHS could enable the reaction to stop at 3,4-dihydroquinoxalin-2(1*H*)-one stage. The procedure is convenient and scalable, and neither a dried solvent nor an inert atmosphere is required. Moreover, the enantioselective construction of these products were explored, and promising results were achieved.

Introduction

Tetrahydroquinoxalines constitute the core structures of numerous bioactive natural products and synthetic compounds.[1,2] Accordingly, the development of efficient protocols for the synthesis of these heterocycles has received considerable interest in the past several decades, and remains to be of great appeal today.[3] Among these known methods, the direct reduction of quinoxalines represents one of the most frequently adopted strategies for the preparation of tetrahydroquinoxalines.[4] In the past several decades, tremendous progress has been made towards the selective reduction of quinoxalines into tetrahydroquinoxalines with cheap molecular hydrogen in the presence of homogeneous or heterogeneous transition-metal catalysts (Scheme 1a).[5-8] Meanwhile, catalytic reduction of quinoxalines with formates,[9a-h] Hantzsch esters,[9i,j] hydrosilanes,[9k] water[9l,m] and ammonia borane[9n] as hydrogen donors has also been successfully achieved (Scheme 1a). Despite these impressive achievements, it should be pointed out that most of these known reports necessitated the prior preparation and purification of quinoxaline substrates, and the step-economic synthesis of tetrahydroquinoxalines via in situ generation of quinoxalines from readily available starting materials has been less studied. In 2013, Beller et al. disclosed a tandem process consisting of cyclization of phenylglyoxal and 1,2-phenylenediamine and catalytic asymmetric hydrogenation of the in situ generated 2-phenylquinoxaline to provide 2-phenyl tetrahydroquinoxaline in high yields and enantioselectivities (Scheme 1b).[7q] Shortly after, Shi and co-workers reported an asymmetric organocatalytic tandem reaction of cyclization/transfer hydrogenation for the step-economical construction of various chiral 2-aryl tetrahydroquinoxalines from aryl glyoxals and 1,2-phenylenediamines (Scheme 1b).[9j]



Scheme 1. Catalytic synthesis of 1,2,3,4-tetrahydroquinoxalines.

Deoxygenative reduction of the amide moiety of 3,4-dihydroquinoxalin-2(1*H*)-ones represents another useful route to 1,2,3,4-tetrahydroquinoxalines,[10] but this transformation has been

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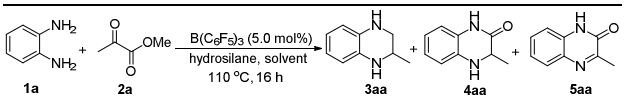
almost completely overlooked most likely due to the lack of efficient and practical catalytic methods for amide reduction. Although catalytic hydrogenation is an ideal choice for selective reduction of amides into amines, it is still in its infancy.[11] In contrast, the operationally simple catalytic hydrosilylation of amides has been subjected to intensive studies, and a variety of catalytic systems based on Rh,[14a-e] Ru,[14f-i] Ir,[14j] Mo,[14k-m] Pt,[14n,o] In,[15a,b] Zn,[15c-e] Cu,[15f] Co,[15g] Fe,[16] B[17] and even the simple bases [18] have been developed for the efficient reduction of amides into amines. In particular, $B(C_6F_5)_3$ and its analogues, which exhibited remarkable catalytic performance in the metal-free reduction of aldehydes, ketones, imines, olefins, alkynes, ethers and N-heteroarenes with hydrosilanes as the reductants via frustrated Lewis pairs,[19,20] has proved to be quite effective to catalyze hydrosilylation of various primary, secondary and tertiary amides into the corresponding amines.[21] Moreover, Fu and co-workers revealed that $B(C_6F_5)_3$ could efficiently catalyze N-alkylation of amines with readily available carboxylic acids and PMHS, and the transformation is believed to proceed through the in situ generation of an amide intermediate followed by a catalytic reduction of the amide to the amine with PMHS.[22a] Ingleson and co-workers reported that $B(C_6F_5)_3$ could perform well in wet solvent to catalyze the reductive amination of aldehydes and ketones with amines using Me_2PhSiH as the reductant.[22b,c] Very recently, Otte et al. described the tandem Meinwald rearrangement-reductive amination of epoxides with anilines and silanes under $B(C_6F_5)_3$ catalysis.[22d]

Since $B(C_6F_5)_3$ is known to be capable of catalysing the reduction of both the in situ formed amides and imines with hydrosilanes, we envisaged that it would be possible to enable the one-pot tandem construction of 1,2,3,4-tetrahydroquinoxalines directly from the easily accessible 1,2-diaminobenzenes and α-ketoesters by using $B(C_6F_5)_3$ as the catalyst. This would involve the initial cyclization reaction of the amine with the ketoester to in situ generate quinoxalin-2(1*H*)-ones followed by the sequential catalytic hydrosilylation of the resulting imine and amide moieties of quinoxalin-2(1*H*)-ones. Following our previous studies on catalytic reduction of N-heteroaryl compounds,[7g,7m,9c,9f,23] herein we would like to report the development of such a one-pot tandem process for the step-economical synthesis of 1,2,3,4-tetrahydroquinoxalines, which combines cyclization with subsequent sequential hydrosilylation of imines and amides with PMHS under the catalysis of $B(C_6F_5)_3$ (Scheme 1c). This metal-free protocol features high yields, broad substrate scope, wide functional group tolerance and simple operational procedure. Moreover, the reaction could be halted at the 3,4-dihydroquinoxalin-2(1*H*)-one stage by decreasing the amount of PMHS. Finally, promising initial results for the enantioselective construction of these products have been accomplished.

Results and discussion

Our investigations started with the reaction of 1,2-diaminobenzene (**1a**) and ethyl 2-oxopropanoate (**2a**) in the presence of catalytic amount of $B(C_6F_5)_3$ at 110 °C (Table 1; also see Supporting Information for more details). With THF as the solvent and $PhSiH_3$ as the reductant, the first reaction gave the target product 2-methyl-1,2,3,4-tetrahydroquinoxaline (**3aa**) in 67% yield together with 3-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4aa**) (25%) and a small amount of 3-methylquinoxalin-2(1*H*)-one (**5aa**) (Table 1, entry 1). Clearly, the cyclization of **1a** with **2a** to produce **5aa** and the following hydrosilyation of **5aa** into **4aa** proceeded well under the current conditions, but the efficiency of the deoxygenative reduction of the amide group of **4aa** needed to be improved. Considering that the choice of hydrosilanes could affect the reaction efficiency, the performance of different hydrosilanes was then examined. Although Ph_2SiH_2, Et_3SiH, $(EtO)_3SiH$, $EtMe_2SiH$ and TMDS (tetramethyldisilazane) all exhibited reductive reactivity (Table 1, entries 2-7), the inexpensive and non-toxic PMHS provided the best **3aa** yield of 80% (Table 1, entry 8). Subsequently a brief screening of various solvents revealed that replacing THF with nBu$_2$O, toluene or MTBE led to better yields of **3aa** (Table 1, entries 10-12), but the use of 1,4-dioxane, CH_3CN or DMF as the solvent was detrimental (Table 1, entries 9, 13, 14). Toluene furnished the highest **3aa** yield (94%) with minimal amount of side products, and was thus selected as the choice of solvent for further studies (Table 1, entry 11). When the catalyst loading, reaction temperature or the amount of PMHS was lowered, the yield of **3aa** decreased as well (Table 1, entries 15-17). Notably, BPh_3 and bis(2-chlorophenyl)(hydroxy)borane, which have been reported to efficiently catalyse hydrosilylation of amides,[18c,d] turned out to be ineffective in the current reaction (Table 1, entries 18 and 19). Finally a control experiment showed that $B(C_6F_5)_3$ catalyst was indispensable for this transformation (Table 1, entry 20). It should be stressed that the reaction is operationally simple, and neither a dried solvent nor an inert atmosphere is required.

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3aa 4aa 5aa

Entry	Solvent	Hydrosilane	**3aa** (%)[b]	**4aa** (%)[b]	**5aa** (%)[b]
1	THF	PhH_3Si	67	25	3
2	THF	Ph_2H_2Si	73	20	4
3	THF	Et_3HSi	68	20	8
4	THF	$(EtO)_3HSi$	62	27	10
5	THF	$EtMe_2HSi$	71	23	4
6	THF	$PhMe_2HSi$	73	22	2
7	THF	TMDS	42	50	3
8	THF	PMHS	80	13	2
9	dioxane	PMHS	78	12	8
10	nBu$_2$O	PMHS	88	10	<1
11	toluene	PMHS	94 (91)	3	<1
12	MTBE	PMHS	83	10	4
13	CH_3CN	PMHS	62	25	10
14	DMF	PMHS	4	3	85
15[c]	toluene	PMHS	88	9	<1
16[d]	toluene	PMHS	86	12	<1
17[e]	toluene	PMHS	83	13	<1

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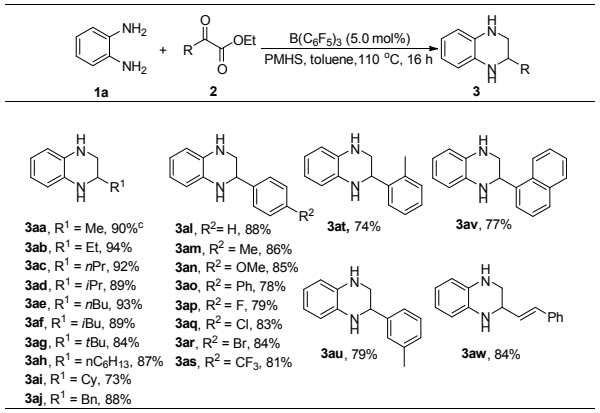
18[f]	toluene	PMHS	<1	<1	95
19[g]	toluene	PMHS	7	41	50
20[h]	toluene	PMHS	nd	nd	98

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.275 mmol), $B(C_6F_5)_3$ (5.0 mol%), PMHS (1.0 mmol), solvent (1.5 mL) at 110 °C for 16 h. nd: not detected. Yield of isolated product was given in parenthesis. [b] Yield determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] $B(C_6F_5)_3$ (4.0 mol%) was employed. [d] Reaction temperature 80 °C. [e] PMHS (0.75 mmol) was used. [f] BPh_3 (5.0 mol%) was employed. [g] Bis(2-chlorophenyl)(hydroxy)borane (5.0 mol%) was employed. [h] No $B(C_6F_5)_3$.

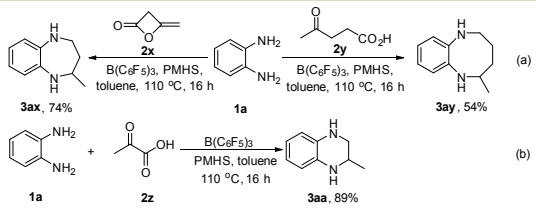
With the optimized reaction conditions in hand, the scope of this reaction with respect to α-ketoester **2** was first explored. As shown in Table 2, the reaction of a wide range of α-alkyl substituted α-ketoesters (**2b**-**2j**) proceeded smoothly, furnishing the corresponding products (**3ab**-**3aj**) in good to excellent yields. Both linear and branched alkyl groups were found to be compatible with the reaction conditions, but the presence of bulky alkyl groups resulted in lower reactivity due to the steric hindrance (**3ad**, **3af**, **3ag**, **3ai**). Ethyl 3,3,3-trifluoro-2-oxopropanoate (**2k**) reacted in a similar fashion to give **3ak** in 71% yield. Likewise, α-aryl substituted α-ketoesters (**2l**-**2u**) proved to be viable reaction partners to provide the desired products (**3al**-**3au**) in high yields with good tolerance of functional groups regardless of the nature of the substituents on the aryl ring. It is notable that the synthetically valuable halide substituents including F (**3ap**), Cl (**3aq**) and Br (**3ar**) remained untouched during the reaction process, thus offering the opportunity for further elaboration. When ethyl 2-(naphthalen-1-yl)-2-oxoacetate (**2v**) was employed, the product **3av** was obtained in 77% yield. It is worth noting that the protocol was applicable to ethyl (*E*)-2-oxo-4-phenylbut-3-enoate (**2w**) to deliver the target product **3aw** in 84% yield with the sensitive C=C bond kept intact throughout the reaction. To showcase the scalability of this methodology, a gram-scale reaction of **1a** (10.0 mmol) and **2a** (11.0 mmol) was performed, and **3aa** was isolated in 90% yield under the standard conditions.

Table 2 Synthesis of tetrahydroquinoxalines from **1a** and α-ketoesters.[a,b]



[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.275 mmol), $B(C_6F_5)_3$ (5.0 mol%), PMHS (1.0 mmol), toluene (1.5 mL) at 110 °C for 16 h. [b] Isolated Yield. [c] **1a** (10.0 mmol) was employed.

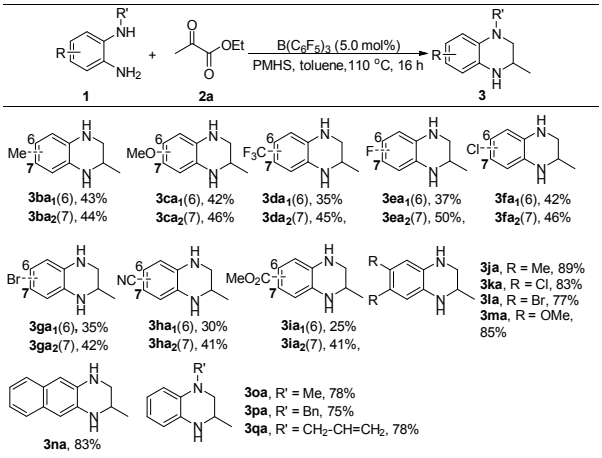
Furthermore, the biomass-derived acetyl ketene (**2x**) and levulinic acid (**2y**) also worked well, giving rise to the seven- and eight-membered products **3ax**[24]and **3ay** in 74% and 54% yields, respectively (Scheme 2a). Interestingly, the current catalytic system could also catalyse the reaction of **1a** with pyruvic acid (**2z**) to afford **3aa** in 90% yield (Scheme 2b).



Scheme 2. Reactions of acetyl ketene (**2x**), levulinic acid (**2y**) and pyruvic acid (**2z**).

We next turned our attention to the reactions of different 1,2-diaminobenzenes **1** with **2a** under the optimized reaction conditions. A range of 4-substituted 1,2-diaminobenzenes (**1b**-**1i**) containing electron-donating and electron-withdrawing substituents underwent smooth reaction with **2a** to generate mixture of separable C6- and C7-substituted regioisomers (**3ba$_1$**-**3ia$_1$**,**3ba$_2$**-**3ia$_2$**) in favour of the latter in 66-90% yields. The electron-rich 4-substituted 1,2-diaminobenzenes generally exhibited better reactivity. Importantly, the reaction was tolerant of a variety of valuable functional groups such as OMe, CF_3, F, Cl, Br, and even the reducible CN and CO_2Me groups. The symmetrical 1,2-diaminobenzenes (**1j**-**1n**) also successfully engaged in the transformation, affording the corresponding products (**3ja**-**3na**) in high yields. The N1-substituted benzene-1,2-diamines (**1o**-**1q**) participated well in this reaction, and the desired products (**3oa**-**3qa**) were isolated in 75-78% yields. It is noteworthy that the reducible allyl moiety in substrate **1q** remained intact during the reaction.

Table 3 Synthesis of tetrahydroquinoxalines from 1,2-diaminobenzenes and **2a**.[a,b]



[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.275 mmol), $B(C_6F_5)_3$ (5.0 mol%), PMHS (1.0 mmol), toluene (1.5 mL) at 110 °C for 16 h. [b] Isolated Yield.

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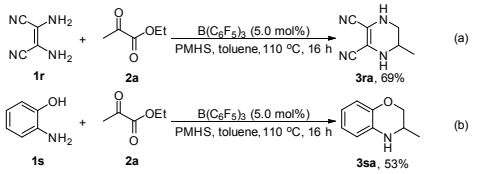
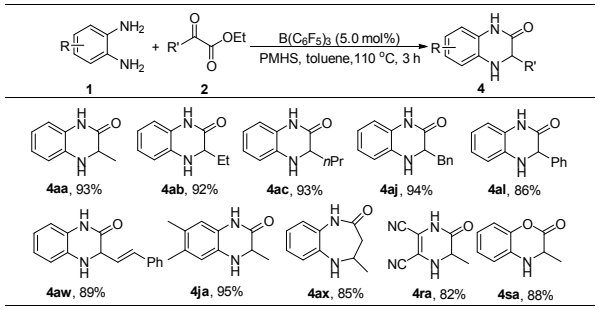
Furthermore, the reaction of **2a** with 2,3-diaminomaleonitrile (**1r**) and 2-aminophenol (**1s**) led to the formation of **3ra** and **3sa** in 69% and 53% yields (Scheme 3), respectively, thus further demonstrating the power of the current catalytic system.



Scheme 3. Reactions of 2,3-diaminomaleonitrile (**1r**) and 2-aminophenol (**1s**).

Considering that the reaction involves the intermediary of an amide, the potential of this catalytic system for the preparation of 3,4-dihydroquinoxalin-2(1*H*)-ones was also investigated. It was found that the reaction of **1a** with **2a** could deliver **4aa** as the sole product in 93% yield when the amount of PMHS was reduced to 1.5 equivalents (Table 4). Similarly, other 2-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones (**4ab**,**4ac**,**4aj**,**4al**,**4aw**,**4ja**) could be obtained in good to excellent yields. Notably, acetyl ketene (**2x**) also underwent ready reaction with **1a** to provide the corresponding product **4ax** in 88% yield, and 2,3-diaminomaleonitrile (**1r**) and 2-aminophenol (**1s**) could be used, affording the corresponding products **4ra** and **4sa** in 82% and 88% yields, respectively.

Table 4 Synthesis of 3,4-dihydroquinoxalin-2(1H)-ones.[a,b]



[a] Reaction conditions: **1** (0.25 mmol), **2** (0.275 mmol), $B(C_6F_5)_3$ (5.0 mol%), PMHS (0.375 mmol), toluene (1.5 mL) at 110 °C for 3 h. [b] Isolated Yield.

With an aim to shed light on the reaction mechanism, the kinetic profile of the reaction between **1a** and **2a** was monitored. As shown in Figure 1, **1a** was completely transformed into **5aa** within 1 h. The following hydrosilylation of **5aa** into **4aa** started before the total consumption of **1a**. Finally deoxygenative reduction of the amide moiety of **4aa** led to the formation product **3aa**. Obviously, **4aa** and **5aa** are the intermediates of the reaction. HRMS analysis of the reaction system of **1a** and **2a** under standard conditions confirmed the generation of **4aa** and **5aa** during the reaction. Furthermore, formation of propane-1,2-diol or ethyl 2-hydroxypropanoate was not observed by HRMS analysis, indicating that the reduction of **2a** by PMHS did not occur. Additional studies revealed that the reaction of **1a** and **2a** in the absence of $B(C_6F_5)_3$ and PMHS gave almost identical yield of **5aa** to that obtained in the presence of 5.0 mol% $B(C_6F_5)_3$ (Scheme 4a). Still further, when the separately synthesized **5aa** and **4aa** were treated with PMHS under the standard conditions, the target product **3aa** was isolated in excellent yields (Scheme 4b,c). These results clearly suggest that the role of $B(C_6F_5)_3$ in the current transformation is to catalyze the reduction of **5aa** and **4aa** with PMHS.

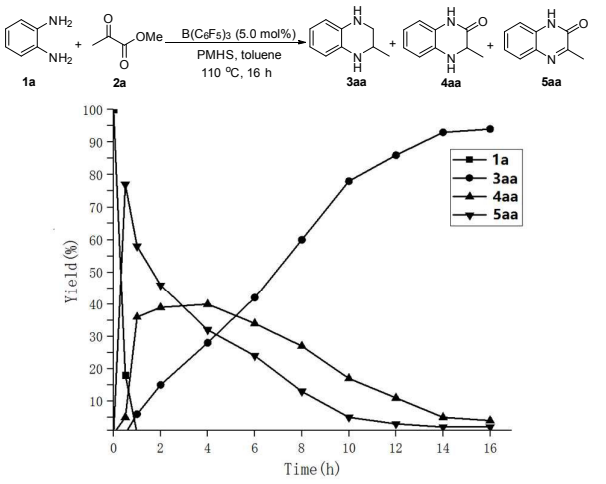
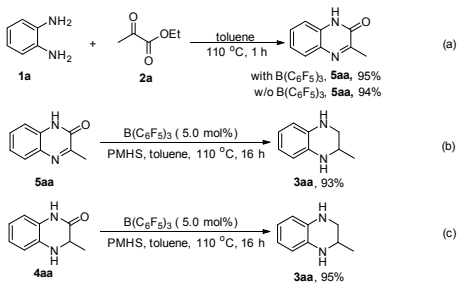


Fig. 1 Kinetic profile for the reaction of **1a** with **2a** under standard reaction conditions. Yields were determined by ^1H NMR with CH_2Br_2 as an internal standard.



Scheme 4. Mechanistic studies.

Based on the above mechanistic studies and the previous reports,[19-22] a reaction pathway is proposed. As shown in Scheme 5, the starting materials **1** and **2** initially undergo cyclization to form the quinoxalinone **5**. Meanwhile, $B(C_6F_5)_3$ abstracts a hydride from the hydrosilane to give the borane-silane complex **A.** The transfer of silylium cation of **A** to **5** leads to the formation of intermediate **B** possessing a borohydride anion. The following hydride attack gives rise to the silylated amine **C**. **C** is protonated by water to afford the 3,4-dihydroquinoxalin-2(1*H*)-one **4** and the hydroxysilane. The silylium cation of **A** then activates the C=O bond of **4** to generate the intermediate **D**,[21] which is subsequently attacked by a hydride to form the corresponding O-silylated N,O-acetal **E**. Reduction of **E** by **A**, presumably via the intermediary of an iminium species **F**, the affords the product **3**.

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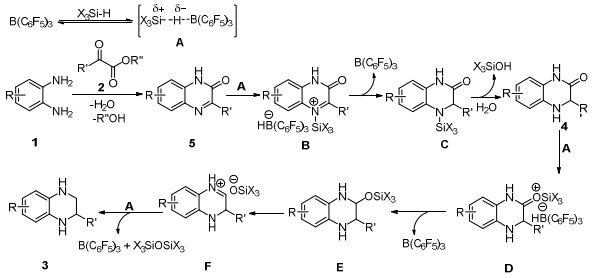
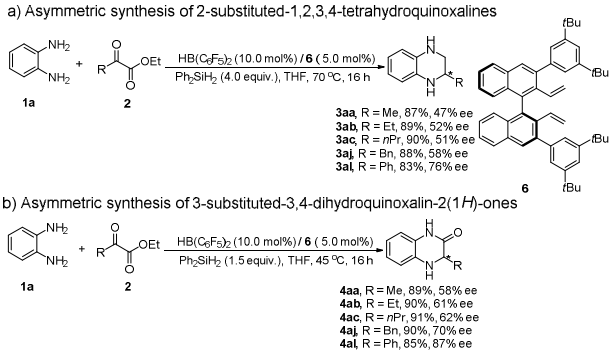


Scheme 5. Proposed reaction pathway

Finally we carried out a preliminary exploration of the enantioselective synthesis of these heterocycles. Inspired by the recent reports from the group of Du on the application of chiral borane catalysts generated by the *in situ* hydroboration of chiral dienes with $HB(C_6F_5)_2$ for symmetric reduction of imines and quinoxalines with hydrosilanes and hydrogen,[7r,25] we examined the reaction of **1a** and **2a** under similar catalysis, with the catalyst formed in situ from the hydroboration of chiral dienes. After a brief screening of the reaction conditions (Table S7 in Supporting Information), it was found that **3aa** could be obtained in 87% yield with 47% ee under the optimal reaction conditions (Scheme 6a). Likewise, the reactions of **1a** with **2b**, **2c**, **2j** and **2l** provided the corresponding products in 83-90% yields with 47-76% ee values. Further investigations showed that decreasing the amount of the reducing agent Ph_2H_2Si to 1.5 equivalents and lowering the reaction temperature to 45 °C resulted in the formation of 3,4-dihydroquinoxalin-2(1*H*)-ones in high yields with moderate to good ee values (Scheme 6b). The lower ee values of **3** may result from the higher temperature used for the reduction of amide moiety.



Scheme 6. Asymmetric synthesis of 1,2,3,4-tetrahydroquinoxalines and 3,4-dihydroquinoxalin-2(1*H*)-ones.

Conclusions

In conclusion, we have developed a new and efficient one-pot tandem protocol for the step-economic synthesis of 2-substituted 1,2,3,4-tetrahydroqinoxalines directly from readily available 1,2-diaminobenzenes and α-ketoesters under $B(C_6F_5)_3$ catalysis with cheap, safe PMHS as the reductant. The reaction scope is broad, and a number of functional groups including the reducible moieties are tolerated. The choice of hydrosilane is shown to be crucial for a high catalytic activity and selectivity. Moreover, 3-substituted-3,4-dihydroquinoxalin-2(1*H*)-ones could be efficiently prepared simply by reducing the amount of PMHS. The enantioselective version of this transformation has also been demonstrated. This operationally simple protocol offers a practical and environmentally friendly alternative to the currently known methods for the reduction of qinoxalines and quinoxalin-2(1*H*)-ones.

Experimental

General

All experiments were carried out in air, and all commercially available chemicals including organic solvents were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 100.6 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks, and coupling constants (J) were reported in Hertz.

General procedure for the synthesis of tetrahydroquinoxalines

To an oven-dried screw-capped pressure tube were sequentially added 1,2-diaminobenzene **1** (0.25 mmol), α-ketoester **2** (0.275 mmol), $B(C_6F_5)_3$ (6.4 mg, 5.0 mol%), PMHS (0.06 mL, 1.0 mmol) and toluene (1.5 mL). Then the reaction mixture was stirred at 110 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (5.0 mL). Then water (5.0 mL) was added to the reaction mixture, which was extracted with EtOAc three times (5.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and hexane to give the corresponding pure product.

General procedure for the synthesis of 3,4-dihydroquinoxalin-2(1*H*)-ones

To an oven-dried screw-capped pressure tube were sequentially added 1,2-diaminobenzene **1** (0.25 mmol), α-ketoester **2** (0.275 mmol), $B(C_6F_5)_3$ (6.4 mg, 5.0 mol%), PMHS (22.5 μL, 0.375 mmol) and toluene (1.5 mL). Then the reaction mixture was stirred at 110 °C for 3 h. After cooling to room temperature, the mixture was diluted with EtOAc (5.0 mL). Then water (5.0 mL) was added to the reaction mixture, which was then extracted with EtOAc three times (5.0 mL each). The combined organic phases were dried over Na_2SO_4, then filtered and evaporated under reduced pressure. After the removal of volatile materials by rotary evaporation, the resultant mixture was purified by silica gel column chromatography using a mixture of EtOAc and hexane to give the corresponding pure product.

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Graphical Abstract:

Metal-free Tandem Cyclization/Hydrosilylation to Construct Tetrahydroquinoxalines

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$B(C_6F_5)_3$-catalyzed tandem cyclization/hydrosilylation for the step-economical construction of 1,2,3,4-tetrahydroquinoxalines from readily available starting materials has been developed.