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Bifunctional thiosquaramide catalyzed asymmetric reduction of dihydro-β-carbolines and enantioselective synthesis of (−)-coerulescine and (−)-horsfiline by oxidative rearrangement†

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Tetrahydro-β-carboline (THBC) is a tricyclic ring system that can be found in a large number of bioactive alkaloids. Herein, we report a simple and efficient method for the synthesis of enantiopure THBCs through a chiral thiosquaramide (**11b**) catalyzed imine reduction of dihydro-β-carbolines (**17a–f**). The *in situ* generated Pd–H employed as hydride source in the reaction of differently substituted chiral THBCs (**18a–f**) afforded high selectivities (*R* isomers, up to 96% ee) and good isolated yields (up to 88%). Moreover, the chiral thiosquaramide used also afforded exceptional catalyst activity in the syntheses of (−)-coerulescine (**5**) and (−)-horsfiline (**6**) with excellent enantioselectivities up to 98% and 93% ee, respectively, *via* an enantioselective oxidative rearrangement approach.

Introduction

Reduction of the C=N bond in cyclic systems is a fundamental and important reaction in the area of modern organic synthesis.[1] Moreover, asymmetric reduction of the C=N bond promoted by organocatalysts is a very valuable aspect in organic stereoselective synthesis.[2] Generally, transition metal complexes with chiral bulky ligands are used for this type of transformation[3] and a few protocols are known in biocatalysis,[2c,4] as well as for chiral auxiliary assisted reduction of imines.[5] The preparation of enantioselective secondary amines, important chiral drug molecules and/or asymmetric reduction of imines is an important topic in academic research as well as from an industrial point of view.[6] Nowadays, widespread development has been witnessed in the asymmetric synthesis of tetrahydro-β-carboline (THBC) skeletons.[7] Furthermore, there is a constant search in the development of new approaches for asymmetric synthesis using chiral organocatalysis. Because the unique tricyclic system, THBCs play key role in their bioactivities,[8] for example: reserpine[4a,9] is an indole alkaloid which is an alternative drug for treating hypertension. The LY23728 (**1**)[3d,10] a simple THBC has been reported as first 5-HT$_{2B}$-selective antagonist and harmicine[4a,11] (**2**) is a rare tetracyclic pyrrolidine framework with strong antileishmania activity. Few other THBCs are competitive selective inhibitors of the monoamine oxidase type A (MAO-A) enzyme[12] and also potent reuptake inhibitors of serotonin and epinephrine with greater selectivity for serotonin.[12] Not only because of their bioactivity, THBCs are valuable intermediates in the production of potential drug candidates. For example, the chiral THBCs like **18c** and **18f** are key intermediates for the synthesis of active quinolactacin B[13] (**3**) and the potent PDE5 inhibitor like pyrroloquinolone RWJ387273 (**4**),[14] respectively (Fig. 1).

Another synthon afforded by THBCs are spirooxindoles, which show unique spiro-cyclic frameworks at the C3-position of the oxindole core.[15] The spirooxindole derivatives are playing important role in the recent drug discovery.[16] The structurally rigid spiro-cyclic system may be a reason for the good affinity towards three-dimensional proteins to exhibit

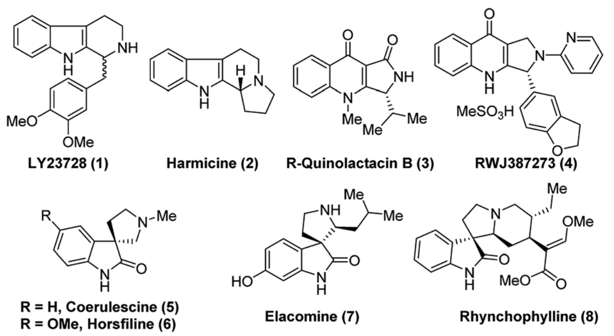

Fig. 1 Representative examples of bioactive THBCs (**1–4**) and some natural spirooxindoles (**5–8**).

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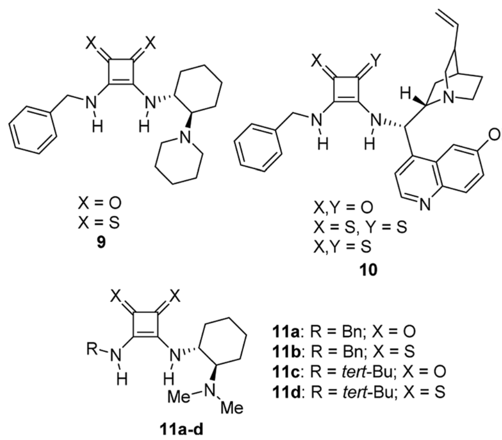
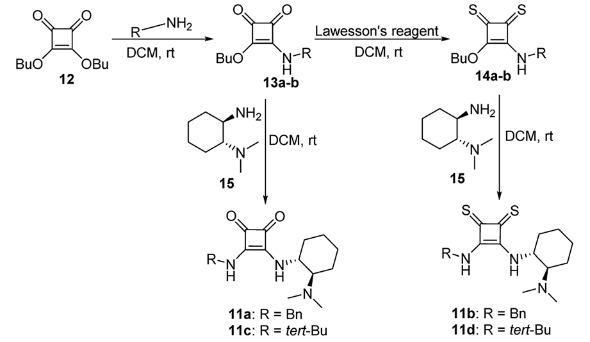
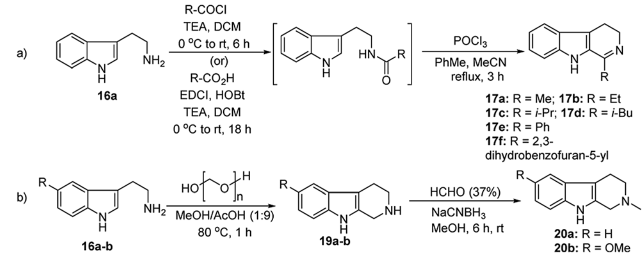


Fig. 2 Few known chiral squaramides and thiosquaramides (**9–11**) and the organocatalysts employed in this work (**11a–d**).



Scheme 1 Synthesis of chiral thiosquaramide (**11a–d**).



Scheme 2 Synthesis of (a) DHBCs **17a–f** and (b) *N*-methyl THBCs **20a–b**.

bioactivities.[15,17–23] For example, the (−)-horsfiline (**6**) is used as an intoxicating snuff,[24] spirotryprostatin A[25] inhibits G_2M progression of mammalian tsFT210 cells, rhynchophylline (**8**) shows potency against various cancer cell lines,[26] corynoxine and corynoxine B show prominent activity in preventing or treating Parkinson's disease.[27] These bioactivities of spirooxindole derivatives have augmented attention in organic chemists from academia as well as industry to develop various synthetic routes,[28] especially in the asymmetric manner for the synthesis of chiral spirooxindoles.[15,29]

On the other hand, the chiral squaramides[30] and thiosquaramides[31] have proven to be excellent catalysts in the asymmetric organocatalysis. However, due to the high solubility in non-polar solvents like toluene, DCM, DCE and THF, the thiosquaramides have established as exceptional chiral organocatalysts.[31] Whereas the squaramides are excellent catalysts in polar solvents.[31] Rawal group developed various squaramides and thiosquaramides as chiral organocatalysts and witnessed high enantioselectivities with thiosquaramides in Michael additions of barbituric acids to nitroalkenes.[31a] Recently, stereoselective double Michael addition of 2-(3*H*)-furanone to nitroolefins,[32] as well as asymmetric Michael additions of aldehydes to nitroolefins for synthesis of chiral pyrrolidines showed high enantio- and diastereoselectivities.[33] Inspired by Rawal's conclusions with chiral bifunctional thiosquaramides and other consequences from recent articles, we have synthesized a known squaramide and thiosquaramide based chiral organocatalysts **11a–d** (Fig. 2). In this work, the aim was to establish chiral protocols to construct bioactive natural products from DHBCs to afford enantiopure THBCs using chiral organocatalysts in asymmetric reduction reactions. The palladium hydride[11] (PdH) was generated in an *in situ* reaction of catalytic $PdCl_2$ with excess of Et_3SiH and utilized as hydride source in the asymmetric imine reduction. The chiral THBCs **18a–f** were obtained with excellent selectivities (up to 96% ee) and good yields (up to 88%). The catalytic efficiency of chiral thiosquaramide in an oxidative rearrangement was also examined to produce (−)-coerulescine (**5**) and (−)-horsfiline (**6**). Surprisingly, the products were observed with high enantioselectivities reaching 98% and 93%, respectively. Moreover, the chiral HPLC and polarimetry analyses proved the *R* configuration of all the products (**18a–f**), **5** and **6**.

Results and discussion

We have synthesized the chiral squaramides **11a** and **11c** and thiosquaramides **11b** and **11d** employing literature protocols[31a] (Scheme 1), **17a–f** and **20a–b** were prepared as displayed in Scheme 2. From our previous experience[11] and other literature reports,[34] we choose the PdH as hydride source that showed good enantioselectivity in similar approaches, which can be generated *in situ* by treatment of catalytic $PdCl_2$ (15 mol%) and excess of Et_3SiH. Initially, the asymmetric reduction of imine **17b** employing **11a–d** (10 mol%) was performed in 1,2-dichloroethane (DCE) and THF for 2 h at 0 °C. The reaction mixtures were analyzed by chiral HPLC, which shown the chiral THBC **18b** in 53%, 88%, 40%, and 62% ee in case of DCE, and 50%, 70%, 38% and 60% ee in THF with **11a**, **11b**, **11c** and **11d** respectively in moderate yields (entries 1–8, Table 1). It is observed that the thiosquaramide **11b** catalyzed well compared with **11a**, **11c** and **11d**. Thiosquaramides seem to be good catalysts for this reaction, it may be due to the poor solubility of squaramides that afforded low catalysts activity. Further, 5 mol% of **11b** was utilized to test the catalytic efficiency and achieved only 85% ee with low yield (45%, entry 9, Table 1). However, the selectivity and yield improved dramatically when the reaction was performed up to 24 h at 0 °C (entry 10, Table 1)

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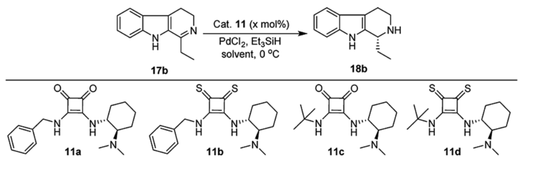
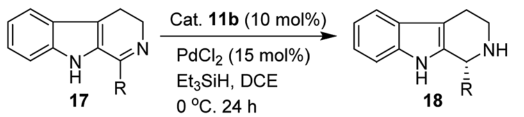
Table 1 Chiral thiosquaramide (**11a–d**) catalyzed reduction of imine (**17b**)[a]

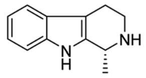


Entry	Catalyst	Mol%	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**11a**	10	DCE	2	30[d]	53
2	**11b**	10	DCE	2	60[d]	88
3	**11c**	10	DCE	2	34[d]	40
4	**11d**	10	DCE	2	55[d]	62
5	**11a**	10	THF	2	27[d]	50
6	**11b**	10	THF	2	55[d]	70
7	**11c**	10	THF	2	30[d]	38
8	**11d**	10	THF	2	53[d]	60
9	**11b**	5	DCE	2	45[d]	85
10	**11b**	10	DCE	24	85	92
11	**11b**	15	DCE	24	85	92
12	**11b**	10	THF	24	80	73
13	**11b**	10	MeOH	24	Trace	—
14	**11b**	10	DCM	24	82	80
15	**11b**	10	Water/DCM	24	Trace	—

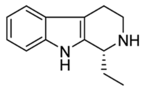
[a] Reactions were performed using **17b** (1 mmol), **11** (mol%), $PdCl_2$ (15 mol%) Et_3SiH (4 mmol) solvent, for the given time. [b] Isolated yield. [c] The enantiomeric excess (ee) was determined by chiral HPLC. [d] Imine **17b** was recovered and the yield calculated by isolated product amount.

Table 2 Chiral thiosquaramide (**11b**) catalyzed reduction of imine **17a–f**[a]

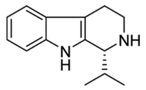




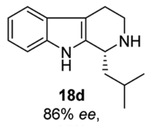
18a
95% *ee*[b],
73%[c]



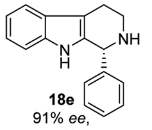
18b
92% *ee*,
85%



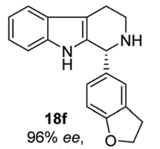
18c
93% *ee*,
88%



18d
86% *ee*,
65%



18e
91% *ee*,
75%



18f
96% *ee*,
70%

[a] Reactions were performed using **17** (1 mmol), **11b** (10 mol%), $PdCl_2$ (15 mol%) Et_3SiH (4 mmol) in DCE, for the 24 h. [b] The enantiomeric excess (ee) was determined by chiral HPLC. [c] Isolated yield.

with catalyst **11b** (10 mol%). Further increment in catalyst load (15 mol%) was ineffective on selectivity as well as yield (entry 11, Table 1). These observations indicate just 10 mol% of catalyst load is sufficient for the asymmetric imine reduction. Furthermore, the reaction was also examined in other solvents such as MeOH, DCM and water/DCM systems (entries 13–15, Table 1). Moderate selectivities (73% ee and 80% ee) and good yields (80% and 82%) were observed in aprotic solvents THF and DCM (entries 12 and 14, Table 1). Whereas only traces of products were observed in the protic solvents like MeOH as well as water/DCM systems (entries 13 and 15, Table 1). Based on the above methodology outcomes, the asymmetric imine reduction tool was fixed as 10 mol% of thiosquaramide catalyst (**11b**) in DCE as solvent for 24 h at 0 °C.

With the proven reaction conditions in hand, a series of DHBCs **17a–f** with different substituents were explored (Table 2). Thus, DHBCs evenly undergone asymmetric reduction in presence of catalytic chiral thiosquaramide (**11b**) and $PdCl_2$/Et_3SiH, and we observed the chiral THBCs in good yields and enantioselectivities (**18a–f**, Table 2). Typically, substituents at C1 position of the DHBCs slightly altered the enantioselectivities. For example, the imine (**17a**) with methyl group gave the chiral THBC (**18a**) with good selectivity (95% ee) and moderate yield (73%). Moreover, chiral THBCs (**18b** and **18c**) with ethyl and isopropyl groups also shown significant selectivities (92% ee and 93% ee, respectively) and high yields (85% and 88%), as depicted in Table 2. However, the 1-isobutyl THBC (**18d**) was obtained with slightly low selectivity (86% ee, Table 2), which may be explained due to an unfavorable transition state of isobutyl DHBC (**17d**) with chiral catalyst as proposed in Fig. 3. Despite, the chiral 1-phenyl THBC (**18e**) that displayed moderate selectivity (91% ee, Table 2), gratifyingly the 2,3-dihydrobenzofuranyl THBC (**18f**) demonstrated high enantioselectivity (96% ee, Table 2).

Furthermore, we also explored an alternative enantiomeric oxidative rearrangement of THBC. Several approaches for the syntheses of chiral quinolactacins[13] and RWJ387273 [14] were described. Quinolactacins shows activity against tumor necrosis factor production, and RWJ387273 exhibited promising male erectile dysfunction (MED) PDE5 inhibition. However, the key step in both the syntheses approaches was the asymmetric reduction of imine to corresponding amines. Generally, most of the reports applied Noyori asymmetric transfer hydrogenation of cyclic imine (**17c** and **17f**) to the total synthesis of chiral quinolactacin B (**3**) and potential PDE5 inhibitor RWJ387273 (**4**). Although the Noyori hydrogenation[35] is an excellent methodology, which includes Ru catalyst and extremely flammable hydrogen gas, considering the cost effect, mildness of protocol and environmental point of view, it is proposed a new formal synthetic route for the *R*-quinolactacin B (**3**) and potential PDE5 inhibitor RWJ387273 (**4**), as depicted in Scheme 3.

Next following our interest in complex structures, it was explored the conversion of *N*-methyl tetrahydro-β-carbolines to spirooxindoles through a bifunctional activity of organocatalyst **11a–d**. Thus, the conversion from *N*-methyl tetrahydro-β-carboline **20a** to spirooxindole **5** have been carried out using *N*-bromosuccinimide (NBS, 1 equiv., Scheme 2) and isolated products with satisfactory yields (58–85%) after 20 min reaction time, as depicted in Table 3. In the catalytic activity optimization, initially we tested 10 mol% of thiosquaramides **11a–d** for

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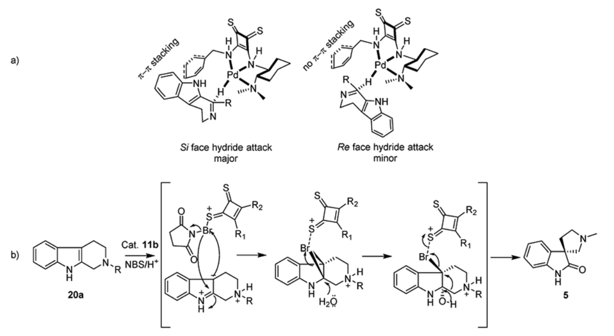
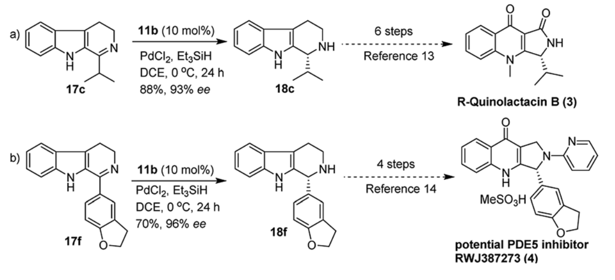


Fig. 3 Plausible mechanism for the approach (major *Si* face and minor *Re* face) of hydride to the DHBC **17** in the presence of chiral thiosquaramide catalyst (**11b**), and the catalyzed oxidative rearrangement.

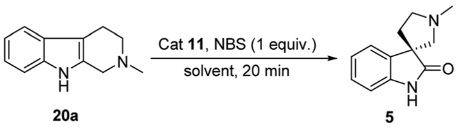


Scheme 3 Formal synthesis of (*R*)-quinolactacin (**3**) and potential PDE5 inhibitor RWJ387273 (**4**) through **11b** catalyzed asymmetric reduction of **17c** and **17f**.

the asymmetric synthesis of spirooxindole **5** in THF/water/AcOH (1 : 1 : 1). The reaction mixtures were analysed by chiral HPLC and evidenced that all the catalysts **11a–d** catalysed the reaction considerably (78%, 98%, 69% and 85% ee respectively, entries 1–4, Table 3). However, reaction with **11b** gave excellent selectivity and good yield (98% ee and 85%, entry 2, Table 3). We considered **11b** as suitable catalyst for this reaction, further tested with 5 mol% and we noticed only 68% ee (entry 9, Table 3). This reaction was found to be optimal with 10 mol% of **11b**. However, the asymmetric reactions without AcOH afforded only racemic mixtures even after 24 h (entries 5–8, Table 3). This may be due to the low solubility of **20a** in the absence of AcOH, which may be needed to protonate the basic nitrogen to soluble in the solvent mixture. It might indicate that the asymmetric oxidative rearrangement may require protonation to the nitrogen atom at β-position of carboline to form the stable transition state with thiosquaramide catalyst leading to yield the product in an enantioselective manner. Product **5** was not observed without the use of aqueous solvent mixtures (entries 12 and 13, Table 3). Hence, we examined solvent mixtures such as THF/water (1 : 1), DCE/water (1 : 1), THF/water/AcOH (1 : 1 : 1), DCE/water/AcOH (1 : 1 : 1) and identified that the chiral reaction was slightly efficient in THF/water/AcOH (98% ee, entry 2, Table 3) than in DCE/water/AcOH (87% ee, entry 11, Table 3). The reaction temperature also affected drastically the enantioselectivities and witnessed good selectivity at 0 °C, while poor selectivities were observed at room temperature (entry 10, Table 3). Reactions carried out at temperatures below −10 °C (−20 to −78 °C) did not give the desired product.

Based on above results, it was fixed the protocol as 1 equivalent of NBS, 10 mol% of thiosquaramide catalyst **11b**, THF/water/AcOH (1 : 1 : 1) as solvent system, and reaction temperature at 0 °C for 20 min to give the key spirooxindole for the asymmetric synthesis of (−)-coerulescine (**5**) in 98% ee and 85% yield. Furthermore, after reaching the optimal reaction

Table 3 Asymmetric oxidative rearrangement reaction optimization[a]



Entry	Catalyst	Mol%	Solvents	Temp. (°C)	Yield (%)	ee[b] (%)
1	**11a**	10	THF/water/AcOH (1 : 1 : 1)	0	83	78
2	**11b**	10	THF/water/AcOH (1 : 1 : 1)	0	85	98
3	**11c**	10	THF/water/AcOH (1 : 1 : 1)	0	78	69
4	**11d**	10	THF/water/AcOH (1 : 1 : 1)	0	80	85
5[c]	**11b**	10	THF/water (1 : 1)	rt	65	Racemic
6[c]	**11b**	10	DCE/water (1 : 1)	rt	60	Racemic
7[c]	**11b**	10	THF/water (1 : 1)	0	63	Racemic
8[c]	**11b**	10	DCE/water (1 : 1)	0	58	Racemic
9	**11b**	5	THF/water/AcOH (1 : 1 : 1)	0	80	68
10	**11b**	10	THF/water/AcOH (1 : 1 : 1)	rt	83	78
11	**11b**	10	DCE/water/AcOH (1 : 1 : 1)	0	84	87
12	**11b**	10	THF	0	—	—
13	**11b**	10	DCE	0	—	—

[a] All the reactions were performed using tetrahydro-β-carboline **20a** (1 equiv.), NBS (1 equiv.) for 20 min. [b] The enantiomeric excess (ee) was determined by chiral HPLC. [c] The reaction was stirred for 24 h.

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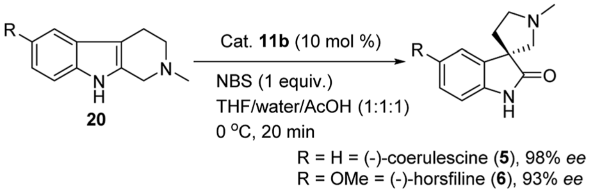

Scheme 4 Thiosquaramide **11b** catalyzed asymmetric synthesis of (−)-coerulescine (**5**) and (−)-horsfiline (**6**).

conditions, we also explored a short synthesis of (−)-horsfiline (**6**) with 93% ee and 90% yield, as shown in Scheme 4.

Conclusions

In conclusion, we have synthesized four known squaramides and thiosquaramide based organocatalysts (**11a–d**) and **11b** was identified as excellent organocatalyst for the asymmetric imine reduction. Under the optimized conditions, considerable yields (65–88%) and good enantioselectivities (88–96%) were observed for the synthesis of chiral tetrahydro-β-carbolines (**18a–f**). All THBCs were obtained with *R* configuration that could be explained by *Si* face approach of hydride in the transition state, as rationalized in Fig. 3. Moreover, formal syntheses of *R*-quinolactacin (**3**) and potential PDE5 inhibitor RWJ387273 (**4**) *via* asymmetric reduction of **17c** and **17f**, which can be avoided through metal catalyst and hazardous reagents. Additionally, we perform a chiral thiosquaramide **11b** catalyzed enantioselective synthesis of natural spirooxindoles (−)-coerulescine (**5**) and (−)-horsfiline (**6**) through enantioselective rearrangement in a short approach, which afforded good yield and high enantioselectivities (up to 98% ee) in the direct oxidative rearrangement.

Conflicts of interest

There are no conflicts to declare.

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