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Direct organocatalytic stereoselective transfer hydrogenation of conjugated olefins of steroids†‡

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Kinetically controlled and organocatalytic *syn*-selective transfer hydrogenation has been successfully demonstrated for the reduction of the enone functional group of various steroids. Herein, diastereoselective synthesis of many 5β-steroids have been reported through organocatalysis, which have broad medicinal and pharmaceutical applications. The mechanistic studies and the selectivity of the products clearly indicated that the catalyst **1b**·D-CSA is mild enough to activate the various chiral cyclic enones through iminium ion formation during the organocatalytic transfer hydrogenations with Hantzsch ester **2a** as a hydrogen source. Further, clear evidence for the selective formation of intermediate iminium species $[\mathbf{I}]^+$ have been characterized through on-line monitoring of controlled experiments by NMR and ESI-HRMS analyses.

Introduction

The Δ^4-3-ketosteroid functionality is present in many important steroid hormones, *e.g.*, testosterone, cortisone, and progesterone. An initial step in steroid hormone metabolism is the reduction of the Δ^4-ene, which in humans is mediated by steroid 5α-reductases (SRD5A1, SRD5A2) or steroid 5β-reductase (AKR1D1) to yield the corresponding 5α- or 5β-dihydrosteroids, respectively.

The enzyme 5β-reductase catalyzes the reduction of the Δ^4-double bond of cholesterol and many steroid hormones bearing the Δ^4-3-one moiety to 5β-dihydro-3-ones and thus plays a major role in the biosynthesis of bile acids and metabolism of many steroid hormones.[1] In contrast, enzyme 5α-reductase influences the biology and physiology of mammalian species by catalyzing the reduction of testosterone to 5α-dihydrotestosterone.[1] Thus the difference between these two enzymes lies in the selective reduction of the Δ^4-double bond leading to two distinct metabolisms.

In particular, 5β-reductase has been a topic of research for many decades, as it plays a vital role in bile acid homeostasis and its deficiency causes fatal effects like accumulation of bile acid intermediates in blood and urine.[2] In addition, it involves in the androgen, steroid hormone metabolic and cholesterol catabolic processes.[3] Chart 1 shows some important bile acids and steroid hormones which are synthesized *in vivo* through 5β-reductase catalysis.[4]

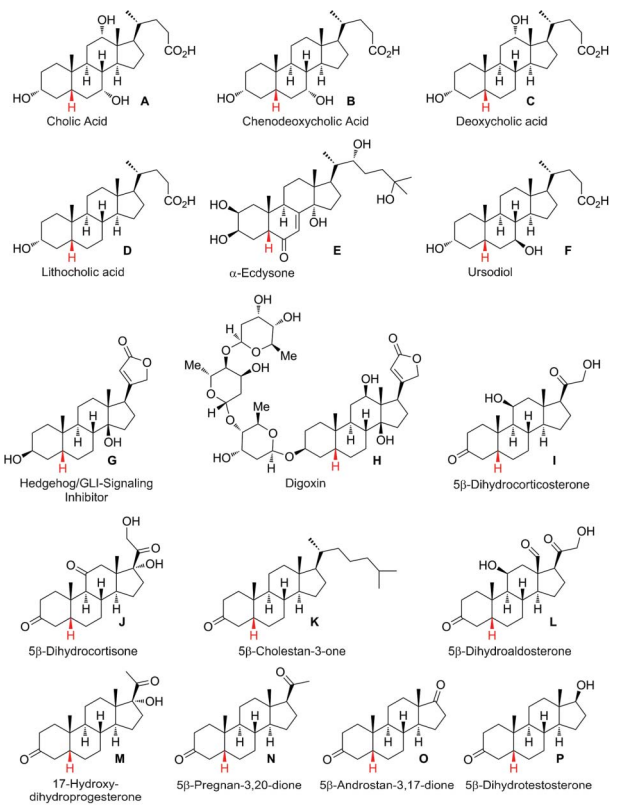

Chart 1 Biologically active 5β-dihydrosteroids synthesized through human steroid 5β-reductase catalysis.

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. CCDC 888376 and 888377. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra41519h

‡ This work is dedicated to Professor M. Periasamy (University of Hyderabad, India) on the occasion of his 60th birthday.

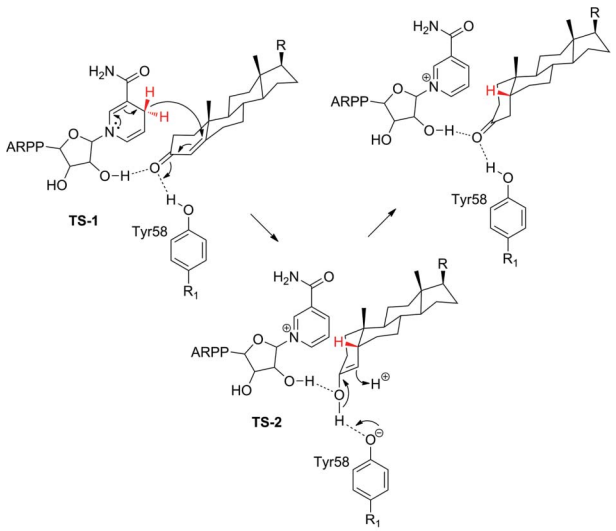


Fig. 1 Reaction mechanism of human steroid 5β-reductase catalysis.

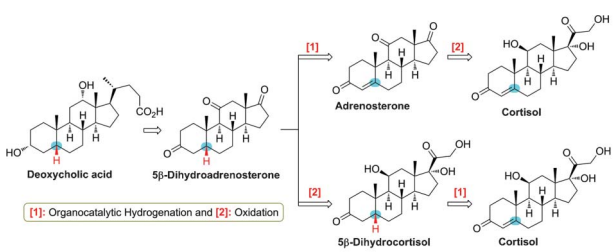
A brief mechanism by Penning *et al.* explains the activation of C-3 carbonyl of Δ^4-3-ketosteroids by the Tyr-58 residue, which has the ability to act as an acid. This facilitates the hydride transfer from NADPH to C-5 through the β-face, which determines the construction of a *cis*-A/B ring junction, and this is considered to be the rate-determining step. Subsequent enzyme or solvent bound protonation of C-4 yields the reduced *cis*-product (Fig. 1).[5]

From the bile acid family, deoxycholic acid (DCA) **C** plays a prime role in the absorption of fats in the intestine and it has been used as drug in a range of medicines.[6] Interestingly, DCA is not only an attractive component in medicinal chemistry, but also in nanotechnology and microlithography.[7] The stereoselective total synthesis of DCA is challenging task for organic chemists and the laboratory synthesis of DCA involves a decisive step of fixing the A/B ring junction as *cis* which is thermodynamically less stable.

Commercially available cortisol or adrenosterone are the two important precursors to commence the synthesis of DCA as shown in Scheme 1. The primary and important step in the synthetic strategy of DCA involves the stereoselective reduction of cortisol or adrenosterone to the thermodynamically less stable *cis*-A/B ring configuration. Surprisingly, only a few number of patents/papers are available for this selective reduction, and these used harsh reaction conditions which usually resulted in moderate selectivity.[8] To achieve a fruitful synthesis of DCA, the Δ^4-double bond has to be reduced stereoselectively under mild reaction conditions for which a retrosynthetic approach has been proposed as shown in Scheme 1. Revising the synthetic strategy is quite possible by changing the sequence of oxidation and organocatalytic transfer hydrogenation reactions to obtain 5β-dihydroadrenosterone, from which DCA can be synthesized through a few chemical transformations starting from cortisol (Scheme 1).

Recently, our group, Rueping *et al.*, List *et al.*, and MacMillan *et al.* have independently developed novel reactions based on the bio-mimetic reductions using the organic hydrides through amino acid catalysis.[9,10] Based on our preliminary investigation on the stereoselective transfer hydrogenation of bicyclic enones,[9k] herein we envisaged that adrenosterone and cortisol could be reduced to dihydroadrenosterone and dihydrocortisol, respectively under mild reaction conditions. With the evolution of organocatalysis as better bio-inspired catalysis, we envisioned that it would be feasible to activate the LUMO of the enone carbonyl through iminium formation and deliver the hydride to C-5 carbon stereoselectively, similar to the 5β-reducatase catalysis.

For the successful demonstration of kinetically controlled *syn*-selective transfer hydrogenation with small molecular systems, we developed the various hydrogenation conditions (1–11) with combination of amine catalyst, co-catalyst acid and hydrogen source as shown in Fig. 2. Interestingly, palladium-



Scheme 1 Retrosynthetic approach to DCA through organocatalysis.

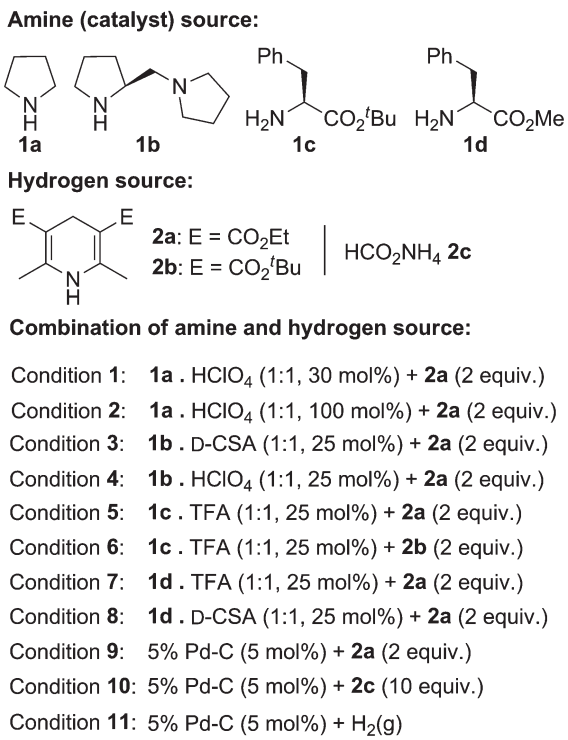
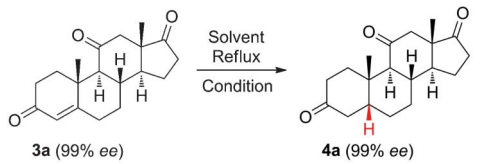


Fig. 2 Various hydrogenation conditions screened in this work.

Table 1 Reaction optimization for the transfer hydrogenation of adrenosterone **3a**[a]



3a (99% *ee*) **4a** (99% *ee*)

Entry	Condition	Solvent (0.1 M)	Time (h)	Yield (%)[b]	*de* of **4a** (%)[c,d]
1[e]	Condition 1	CH_3CN	72	—	—
2[e]	Condition 2	CH_3CN	72	<5	—
3[e]	Condition 3	CH_3CN	24	—	—
4[e]	Condition 4	CH_3CN	24	—	—
5	**Condition 5**	**CH_3CN**	**30**	**80**	**58**
6[f,g]	Condition 5	1,4-dioxane	72	76	70
7	Condition 5	THF	48	76	58
8	Condition 5	$CHCl_3$	72	40	48
9	Condition 6	CH_3CN	78	77	48
10[g]	Condition 7	CH_3CN	72	68	50
11[e,h]	Condition 8	CH_3CN	24	—	—
12[i,j]	Condition 9	EtOH	18	82	19
13[e]	Condition 9	3-picoline	48	—	—
14[e]	Condition 10	MeOH	72	—	—
15[i,k]	Condition 11	3-picoline	24	71	32

[a] See experimental section. [b] Yield refers to the column-purified product. [c] *de* was determined based on the NMR analysis. [d] Unless otherwise mentioned, *cis*-**4a** was obtained as the major diastereomer. [e] 60–70% of starting material was recovered. [f] Reaction was carried out in sealed tube at 60 °C. [g] Some unidentified compound was also formed. [h] Four equiv. of **2a** was used. [i] *trans*-**4a** was the major diastereomer. [j] Three equiv. of **2a** was used. [k] Reaction was carried out at 25 °C.

charcoal (Pd/C) was also used as catalyst in combination with organic hydrides as a hydrogen source (Fig. 2).[11,12]

Results and discussion

Reaction optimization for the *syn*-selective transfer hydrogenation of adrenosterone and cortisol

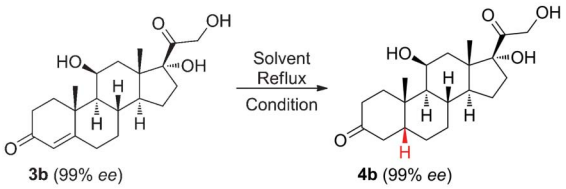
Studies towards direct organocatalytic *syn*-selective transfer hydrogenations were executed on adrenosterone **3a** and cortisol **3b** to generate the 5β-dihydroadrenosterone *cis*-**4a** and 5β-dihydrocortisol *cis*-**4b** respectively, by applying various reaction conditions as shown in Fig. 2. Herein, first we have chosen achiral amine pyrrolidine **1a** as the catalyst to study the designed reaction. In 1974, Pandit and co-workers reported the stereoselective transfer hydrogenation of α,β-unsaturated ketones through reaction of activated preformed pyrrolidinium salts with Hantzsch ester **2a**.[9l] Unfortunately, pyrrolidine/$HClO_4$ as catalyst for the transfer hydrogenation of **3a** with **2a** gave a disappointing result and also same thing happened when we used pyrrolidine/$HClO_4$ in 100 mol% (Table 1, entries 1–2). Based on our previous experience,[9k] we tested the diamine **1b** as the catalyst to study the designed transfer hydrogenation. The combination of diamine **1b** and co-catalyst D-CSA or $HClO_4$ with Hantzsch ester **2a** as a hydrogen source (Condition-3 and 4) in refluxing CH_3CN was also found to be inefficient to carry out the expected reduction reaction (Table 1, entries 3 and 4). When the primary amino acid **1c** with co-catalyst TFA was employed with 2 equiv. of **2a** (Condition-5) in refluxing CH_3CN for 30 h, the anticipated *cis*-**4a** was generated in 80% yield with 58% *de* (Table 1, entry 5). After understanding the ability of catalyst **1c** in the reduction of **3a**, various solvents and co-catalysts were investigated with the scope of increasing the diastereoselectivity.

Catalyst **1c**·TFA with **2a** as a hydrogen source (Condition-5) in 1,4-dioxane under sealed tube conditions at 60 °C, yielded **4a** in 76% yield with 70% *de* (Table 1, entry 6). Although selectivity is good, the longer reaction time (72 h) and some unidentified impurities associated with the product made the reaction condition inferior. Changing the solvent to THF and $CHCl_3$ under Condition-5 also did not help in improving the diastereoselectivity (Table 1, entries 7 and 8). Using bulkier hydrogen source **2b** (Condition-6) decreased the yield to 77% and *de* to 48% taking prolonged reaction times 72 h (Table 1, entry 9). The primary amine methyl ester **1d**·TFA (Condition-7) was also not found to be better than primary amine *tert*-butyl ester **1c**·TFA (Condition-5) in terms of *de* and reaction times (Table 1, entry 10). The reaction was found to not proceed at all, when catalyst **1d**·D-CSA (Condition-8) was employed with **2a** in CH_3CN (Table 1, entry 11). The reaction Condition-8 explains the importance of co-catalysts as well as the amine catalyst on the reduction of **3a** (Table 1).

After achieving only moderate selectivities with organocatalysts, the potential ability of Pd/C as catalyst for the transfer hydrogenation reactions was investigated to obtain the product **4a** with good selectivity. Interestingly, Hantzsch ester **2a** as the hydrogen source over 5 mol% of 5% Pd/C (Condition-9) in refluxing ethanol for 18 h furnished the *trans*-**4a** in 82% yield with 19% *de* (Table 1, entry 12). To obtain the anticipated selectivity, other basic solvents like 3-methylpyridine (3-picoline) were also tested. However solvent 3-picoline at 25 °C under Condition-9 did not yield the product **4a**, rather starting material was recovered as such (Table 1, entry 13). Switching over to a different hydrogen source, ammonium formate **2c** over Pd/C in refluxing methanol (Condition-10) also did not serve the purpose and only starting material was recovered (Table 1, entry 14). The similar trend of opposite selectivity was observed when neat hydrogen gas over Pd/C (Condition-11) was used in 3-picoline solvent at 25 °C to furnish the *trans*-**4a** in 71% yield with 32% *de* (Table 1, entry 15). The structure and stereochemistry of the product *cis*-**4a** was confirmed by NMR analysis.

Similar results were observed by Nishimura and co-workers[8d,8e] in their palladium black catalyzed hydrogenation of adrenosterone **3a** with atmospheric pressure of H_2 in different solvents at 25 °C and gave the concluding remarks that stereoselectivity to 5β is greatly controlled by the reaction medium and also the functional groups present in the steroids especially at C-11, C-17 and C-20 positions. As shown in Table 1, still further improvement was required in terms of *de*, as only moderate *de* was obtained so far. Hence, the reaction strategy was revised as already shown in Scheme 1. It was envisaged that cortisol **3b** would produce better *de* in hydrogenation reactions instead of adrenosterone **3a** due to the presence of the C-11 hydroxyl group. According to

Table 2 Reaction optimization for the transfer hydrogenation of cortisol **3b**[a]



3b (99% *ee*) **4b** (99% *ee*)

Entry	Condition	Solvent (0.1 M)	Time (h)	Yield (%)[b]	*de* of **4b** (%)[c,d]
1[e]	Condition 1	CH_3CN	72	—	—
2[e]	Condition 3	CH_3CN	48	—	—
3[e]	Condition 5	CH_3CN	72	—	—
4[f]	**Condition 9**	**EtOH**	**8**	**86**	**72**
5[e,f,g]	Condition 9	3-picoline	24	—	—
6[h]	**Condition 11**	**3-picoline**	**24**	**97**	**89**

[a] See experimental section. [b] Yield refers to the column-purified product. [c] *de* was determined based on the NMR analysis. [d] Unless otherwise mentioned, *cis*-**4b** was obtained as the major diastereomer. [e] 60–70% of starting material was recovered. [f] Three equiv. of **2a** was used. [g] Reaction was carried out at 80 °C. [h] Reaction was carried out at 25 °C.

Nishimura observations on palladium black catalyzed hydrogenation of functionalized steroids **3**, a C-11 oxo group has a more negative effect on obtaining high 5β-selectivity compared to the C-11 hydroxyl group due to electronic factors.[8d,8e]

With these observations in mind, the optimization for reduction of **3b** was initiated employing various conditions as shown in Fig. 2 and Table 2. Surprisingly, catalyst **1a**·$HClO_4$ (Condition-1), **1b**·D-CSA (Condition-3) and **1c**·TFA (Condition-5) with **2a** as a hydrogen source in refluxing CH_3CN for 48–78 h did not furnish **4b**, instead starting material was recovered (Table 2, entries 1–3). To our delight, Pd/C-mediated transfer hydrogenation with 3 equiv. of **2a** (Condition-9) in refluxing ethanol furnished the anticipated *cis*-**4b** in 86% yield with 72% *de* within 8 h (Table 2, entry 4). Surprisingly, the same reaction did not proceed in 3-picoline as solvent under Condition-9 at 80 °C and only starting material was recovered (Table 2, entry 5). However, the utilization of hydrogen gas over Pd/C in 3-picoline at 25 °C for 24 h yielded the *cis*-**4b** in 97% yield with improved (89%) *de* (Table 2, entry 6). Diastereomerically pure chiral (+)-*cis*-**4b** would be suitable starting material for the total synthesis of DCA as highlighted in the Scheme 1.

After careful examination of the efficiency of various hydrogenation conditions on **3a** and **3b**, we observed that achieving good *syn*-selectivity is totally controlled by C-11, C-17 and C-20 functional groups in the steroids **3a–b** along with hydrogen source, catalysts, solvents and reaction temperature. Already Nishimura and co-workers studied the Pd-catalyzed hydrogenation of various steroids **3** with H_2 gas in different solvents to achieve good to moderate 5β-selectivity, herein we relatively state that the second best optimization condition is Pd/C with 3 equiv. of **2a** (Condition-9) in refluxing ethanol to transform the **3b** to **4b**. This condition was found to be superior over Pd/C with hydrogen gas (Condition-11) due to the *in situ* generation of controlled number of active hydrogen molecules, which is suitable for the chemoselective reduction of functionalized 4-ene-3-ketosteroids (Table 3).

Synthesis of chiral 5β-dihydrosteroids through Pd-catalysis

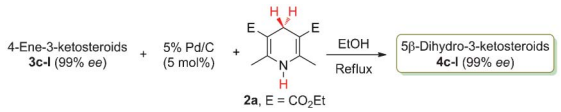
With optimized reaction conditions in hand, the generality of the novel Condition-9 (Pd/C with 3 equiv. of **2a**) was tested for the chemo- and stereoselective transfer hydrogenation of highly functionalized 4-ene-3-ketosteroids **3c–l** (Table 3). The presence of polar functional groups at C-11, C-17, C-20 and C-21 in **3c–l** was found to increase the 5β-selectivity without compromise in yield. The selectivity of the Pd/C-Hantzsch ester mediated transfer hydrogenation reactions was suitable to provide the anticipated *cis*-5β-dihydro-3-ketosteroids **4c–l** as the major products (Table 3). Interestingly, the reaction of non-activated double bond containing steroid androst-2-en-17-one **3f** with **2a** under Pd/C-catalysis furnished the androstan-17-one **4f** in good yield (Table 3, entry 4). This reaction would be a suitable example to explain the mechanism of transfer hydrogenation through Pd/C-**2a** (Condition-9).

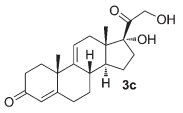
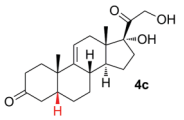
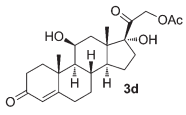
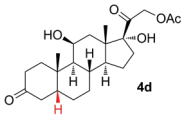
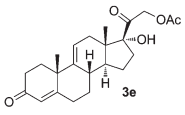
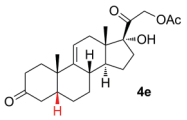
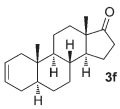
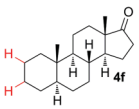
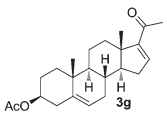
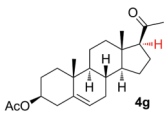
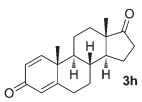
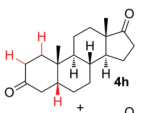
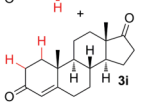
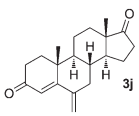
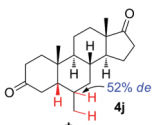
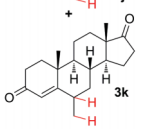
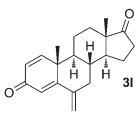
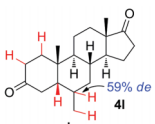
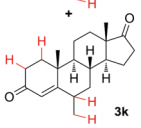
The steroid pregnadienolone-3-acetate **3g** under Pd/C mediated transfer hydrogenation with **2a** (Condition-9) yielded the product pregnenolone-3-acetate **4g** with >99% *de* as an inseparable mixture with pyridine byproduct (Table 3, entry 5). Later, the mixture was deacetylated and the *de*/relative stereochemistry of the reaction was unambiguously determined through comparing with pregnenolone.[13] Interestingly, Pd/C–Hantzsch ester mediated transfer hydrogenation of dienone containing steroids **3h**, **3j** and trienone-containing steroid **3l** resulted in a mixture of totally hydrogenated products **4h**, **4j**, and **4l** as major products and also partially hydrogenated enones **3i** and **3k** as minor products. The use of lower equiv. of **2a** on the above reactions also could not perform the stereoselective product generation (Table 3, entries 6–8). Resulting 5β-3-ketosteroids **4** are synthetically and medicinally useful precursors as shown in Chart 1, especially the product pregnenolone-3-acetate **4g** which has been used as an important precursor in the synthesis of vitamin D_3, inhibitors of ecdysone and potent anti-tumor reagents.[13]

Synthesis of chiral 5β-dihydrosteroids through organocatalysis

After demonstrating the transfer hydrogenation of highly functionalized steroids **3c–l** by using Hantzsch ester **2a** as a hydrogen source over Pd/C as catalyst, the next focus was turned towards testing the simple less functionalized steroids **3** as substrates under the emerging amine catalysis (Table 4).[9,10] The need for novel bio-inspired synthetic routes to 5β-steroids and their biological importance gave inspiration to develop a diastereoselective synthesis (Table 4).[14] Once again we have chosen achiral amine pyrrolidine **1a**·$HClO_4$ as the catalyst to study the transfer hydrogenation of the less functionalized steroid 4-cholesten-3-one **3m** in both Conditions 1 and 2. Surprisingly, 5β-cholestan-3-one **4m** was furnished in only 28% yield with 90% *de* and <10% yield with 90% *de*, respectively (eqn (S1), see ESI†). As a further investigation to improve the yield and *de*, relatively less functionalized 4-ene-3-ketosteroids **3** were reacted with catalyst **1b**·D-CSA and **2a** as the hydrogen source (Condition-3) in refluxing CH_3CN for 72 h.

Table 3 Synthesis of 5β-dihydrosteroids **4c–l** through Pd/C-catalysis[a]



Entry	Starting material	Product(s)	Time (h)	Yield (%)[b]	*de* (%)[c,d]
1	 **3c**	 **4c**	6	73	87
2	 **3d**	 **4d**	5	80	51
3	 **3e**	 **4e**	16	79	65
4	 **3f**	 **4f**	6	87	—
5[e]	 **3g**	 **4g**	6	64	>99
6	 **3h**	 **4h** +  **3i**	22	58 27	78 —
7[f]	 **3j**	 52% *de* **4j** +  **3k**	18	56 14	52 23
8	 **3l**	 59% *de* **4l** +  **3k**	18	62 19	59 18

[a] Unless otherwise mentioned, all reactions were carried out in 0.2 mmol of enone **3a–l** applying modified Condition-9, using 3 equiv. of Hantzsch ester **2a** in refluxing ethanol. [b] Yield refers to the column-purified product. [c] *de* was determined based on the NMR analysis. [d] Unless otherwise mentioned, *cis*-**4a–l** were obtained as the major diastereomers. [e] **4g** was isolated as an inseparable mixture with pyridine, *de* was determined after deacetylation of the resulting mixture. [f] **3k** was isolated with other inseparable regioisomers.

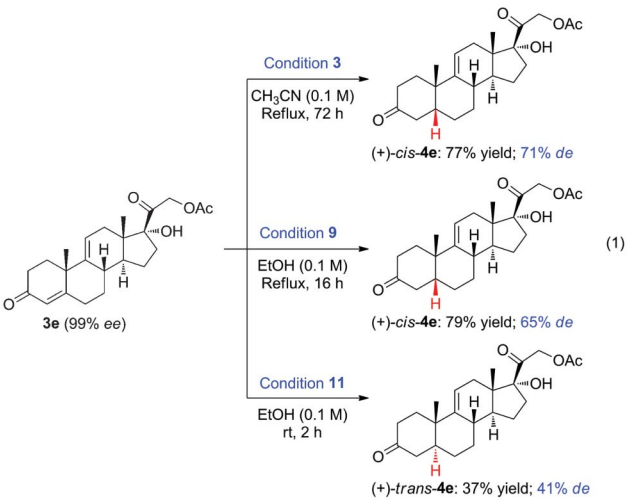
The organocatalytic transfer hydrogenation (Condition-3) was observed as an inefficient tool for the reduction of steroids **3a** and **3b**, but it was found to be suitable for steroids **3c** and **3d** to furnish the products **4c–d** in moderate yields and *de*'s. The hydrogenated products **4c** and **4d** were obtained in 33% yield with 8% *de* and 52% yield with 66% *de* after 72 h, respectively (Table 4, entries 1 and 2). However, **3b** and **3c** were poor and non-reacting substrates under Condition-3, but their corresponding acetates were found to be good reactive substrates. For example, steroid **3e** (acetylated steroid **3c**) was found to provide the hydrogenated product **4e** in 77% yield with 71% *de* (Table 4, entry 3). This observation clearly explains that the reactivity and selectivity of 4-ene-3-ketosteroids **3** under Condition-3 is also controlled by the polar functional groups. Pregnadienolone-3-acetate **3g** was stereoselectively reduced only in the D-ring during the transfer hydrogenation under Condition-3 and furnished the medicinally important pregnenolone-3-acetate **4g** in 64% yield with >99% *de* (Table 4, entry 4). Unfortunately, the organocatalytic transfer hydrogenation (Condition-3) was observed as an inefficient tool for the reduction of steroids **3f** and **3h** as compared to Pd-mediated transfer hydrogenation (results not shown in Table 4).

Surprisingly, reaction of less functionalized steroids 4-androstene-3,17-dione **3i**, 4-cholesten-3-one **3m**, testosterone **3n** and 16-dehydroprogesterone **3o** with transfer hydrogenation Condition-3 furnished the respective 5β-dihydro-3-ketosteroids **4i–o** in excellent yields and *de*'s (Table 4, entries 5–8). Interestingly, a metabolite of the neuroactive steroid progesterone [5β-dihydro progesterone **4o**] was furnished through selective double transfer hydrogenation of **3o** with 4 equiv. of Hantzsch ester **2a** under organocatalysis as shown in Table 4, entry 8. Without much steric influence, angular hydroxymethyl substituted 19-hydroxy-4-androstene-3,17-dione **3p** provided the hydrogenated product **4p** with 72% yield and 79% *de* through organocatalysis (Table 4, entry 9). 19-Nortestosterone **3q** was found to be less selective under the transfer hydrogenation Condition-3 by providing the **4q** in 82% yield with only 82% *de*, compared to its acetate **3r** which furnished the expected product **4r** in 90% yield with 96% *de* (Table 4, entries 10–11). Interestingly, the 6-dehydro-19-nortestosterone acetate **3s** was found to furnish the double hydrogenated product **4s** or **4r** in 64% yield with 92% *de* through organocatalytic transfer hydrogenation as shown in Table 4, entry 12. The structure and relative stereochemistry of the hydrogenated products **4** were confirmed by NMR analysis and also finally confirmed by the X-ray structure analysis of (+)-**4i** and (+)-**4r** as shown in Fig. S1 and S2 respectively (see ESI†).[15]

Mechanistic insights

The organocatalytic **1b**·D-CSA catalyzed transfer hydrogenation reaction was found to be substrate and catalyst controlled as demonstrated in Tables 1–4. With controlled experimental results in hand, the mechanism for the organocatalytic transfer hydrogenation of steroids **3** has been proposed as shown in Scheme 2.[16] The approach of the hydride source **2a** to the iminium ion (**I**) generated *in situ* is the main controlling factor apart from the thermodynamic stability of the resulting hydrogenated products *cis*-**4**/*trans*-**4**. Approach of the Hantzsch ester **2a** from the *exo*-face (same side to the alkyl group) of the iminium ion (**I**) **TS-3** is more favorable than through the *endo*-face (opposite to the alkyl group) **TS-4**. This may be due to the existence of more steric hindrance in an *endo*-face approach because of the formation of *Z*-iminium ion (**I**) as major isomer.

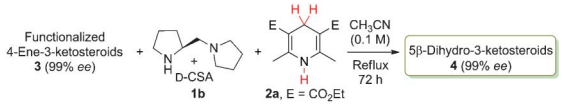
As shown in Scheme 2, steric strain control is the main controlling factor rather than product stability control, because the thermodynamically stable isomers *trans*-**4** are formed as the minor products. The selective *in situ* formation of the proposed active iminium species was confirmed by carrying out the NMR experiment between **3i** and **1b** as shown in Scheme 3.[17] Surprisingly, the iminium ion (**I**) was obtained in >99% stereoselectivity within 5 min at 25 °C. The observation of two non-equivalent *N*-CH_2 carbons of pyrrolidine ring (C9 and C12) in the *in situ* formed iminium ion (**I**) strongly supports the *Z*-imine formation. Further, the formation of iminium ion (**I**) was confirmed by ESI-HRMS analysis through online monitoring (Fig. S3, ESI†). The ESI-HRMS spectrum of an on-going reaction of **3i** and **1b** in CD_3CN at 25 °C revealed the presence of iminium ion $[\mathbf{I}]^+$ (*m*/*z* 423.3375) as shown in Fig. S3 (see ESI†).



Even though activation modes are different in an enzyme- and amine/acid-catalysis, the stereoselective synthesis of *cis*-isomers as the major product during organocatalytic transfer hydrogenation makes it possible to compare the transition state **TS-3** in Scheme 2 with transition state **TS-1** in Fig. 1. In both the transition states, *endo*-face has been selectively shielded by the chiral components which are present to activate the enone towards conjugate reduction. This in turn, allows the hydride delivery only through *exo*-face of the steroid and results in the stereoselective *cis*-isomer formation. Comparison of both the transition states (**TS-1** and **TS-3**) undoubtedly states that **1b**·D-CSA-catalysis is nothing but the enzyme-inspired mild catalysis.

In a similar manner, the mechanism for Pd-catalyzed Hantzsch ester **2a** mediated transfer hydrogenations can be proposed based on the controlled experiments and also recent Pd-mediated transfer hydrogenations reported by Liu *et al.*[11a] The generation of hydrogen gas from Hantzsch ester **2a** over Pd/C surface under refluxing condition and also transfer hydrogenation of the non-activated double bond in steroid **3f**

Table 4 Synthesis of 5β-dihydrosteroids **4** through organocatalysis[a]



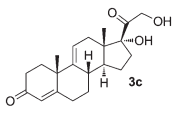
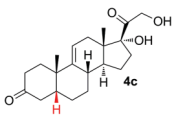
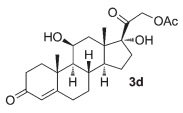
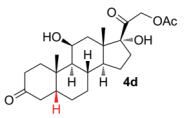
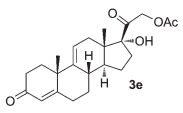
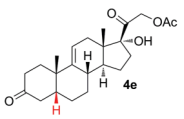
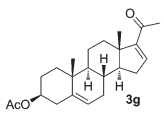
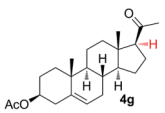
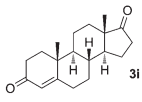
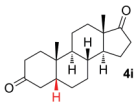
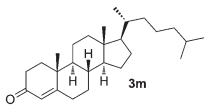
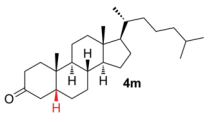
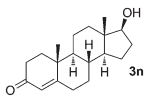
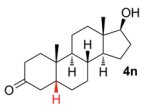
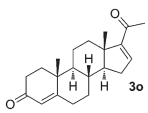
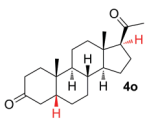
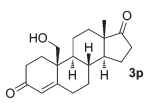
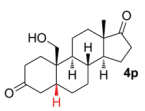
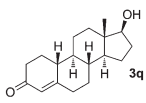
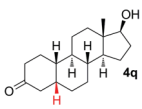
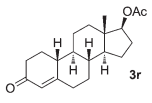
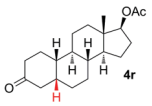
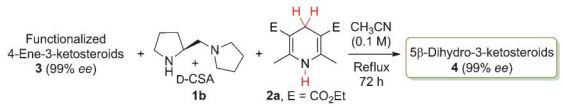
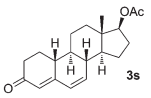
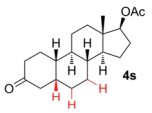
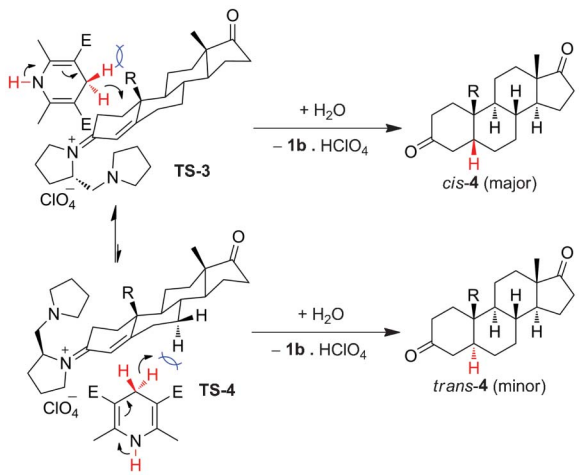
Entry	Starting material	Products	Yield (%)[b]	*de* (%)[c,d]
1	 **3c**	 **4c**	33	8
2	 **3d**	 **4d**	52	66
3	 **3e**	 **4e**	77	71
4[e]	 **3g**	 **4g**	64	>99
5	 **3i**	 **4i**	86	86
6	 **3m**	 **4m**	84	86
7	 **3n**	 **4n**	82	94
8[f]	 **3o**	 **4o**	78	86
9	 **3p**	 **4p**	72	79
10	 **3q**	 **4q**	82	82
11	 **3r**	 **4r**	90	96

Table 4 (*Continued*)



Entry	Starting material	Products	Yield (%)[b]	*de* (%)[c,d]
12	 **3s**	 **4s**	64	92

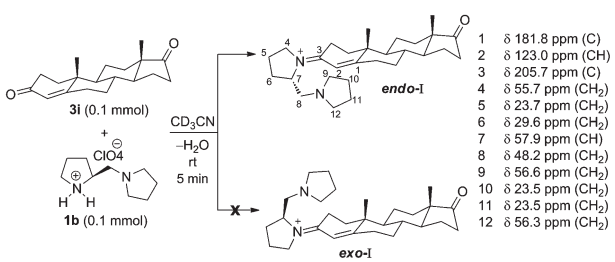
[a] All reactions were carried out in 0.2 mmol of **3** through Condition-3 in refluxing CH_3CN (0.1 M) for 48–72 h. [b] Yield refers to the column-purified product. [c] *de* was determined based on the NMR analysis. [d] Unless otherwise mentioned, *cis*-**4** was obtained as major diastereomers. [e] **4g** was isolated as an inseparable mixture with pyridine, *de* was determined after deacetylation of resulting mixture and the reaction time was 48 h. [f] 4 equiv. of **2a** was used.



Scheme 2 Proposed mechanism for the diamine **1b**-catalyzed *syn*-selective transfer hydrogenation of **3** with **2a**.

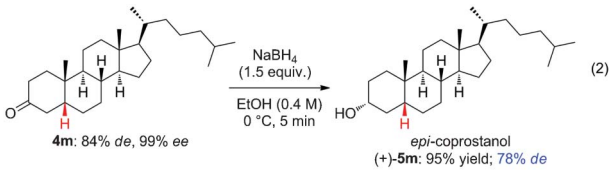
(Table 3, entry 6) reveal that the reaction goes through hydrogen addition rather than hydride addition.

Finally, a comparative study was carried out to understand the selectivity and reactivity of various catalyses on the



Scheme 3 NMR experiment to detect the pre-transition state intermediate (**I**).

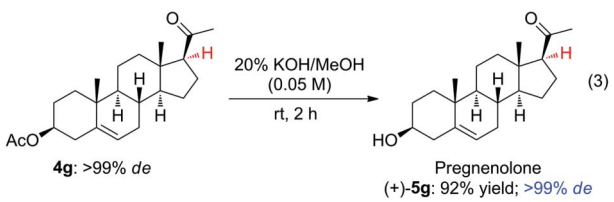
reduction of medicinally important steroid, anecortave acetate **3e** (eq. 1). The transfer hydrogenation of **3e** catalyzed by **1b**·D-CSA with **2a** (Condition-3) in refluxing CH_3CN for 72 h yielded *cis*-(+)-**4e** in 77% yield with 71% *de*. The same steroid **3e** under Pd/C with **2a** (Condition-9) in refluxing ethanol for 16 h furnished the *cis*-(+)-**4e** in 79% yield with reduced (65%) *de*. When hydrogen gas was used directly with Pd/C (Condition-11) for the hydrogenation of **3e**, the opposite isomer *trans*-(+)-**4e** was obtained as the major product in 37% yield with 41% *de*. Thus pure organocatalytic transfer hydrogenation (Condition-3) and Pd-mediated transfer hydrogenation with **2a** (Condition-9) are better conditions compared to the Pd-mediated hydrogenation with hydrogen gas (Condition-11), which highlights the importance of NADPH-mimicking organic hydrides in transfer hydrogenations.



(2)

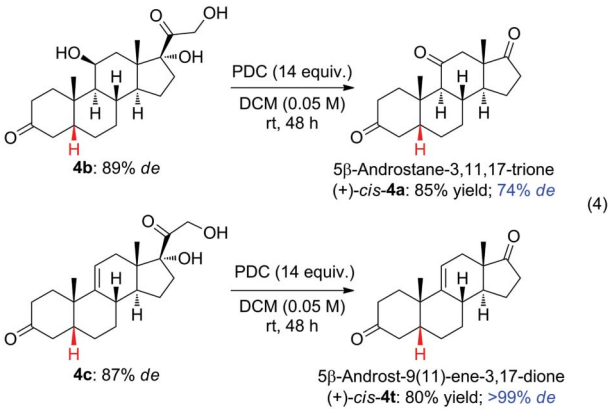
Synthetic applications

With many pharmaceutical applications of the 5β-dihydro-3-ketosteroids in mind, a few synthetic transformations were carried out on the hydrogenated products **4** to provide important intermediates of natural and designed products. 5β-Cholestan-3-one **4m** was successfully transformed to *epi*-coprostanol (+)-**5m**[14] with 1.5 equiv. of $NaBH_4$ in EtOH at 0 °C for 5 min. The product (+)-**5m** was obtained in 95% yield with 78% *de* (eq. 2). With the scope of obtaining synthetically useful precursor (+)-**5g**,[13] the hydrogenated product **4g** was deacetylated using 20% methanolic KOH at 25 °C for 2 h to yield (+)-**5g** in 92% yield with >99% *de* (eq. 3).



(3)

For the demonstration of better synthetic strategies for the preparation of key intermediate (+)-*cis*-**4a**, hydrogenated product *cis*-**4b** was oxidized using 14 equiv. of PDC in DCM for 48 h at 25 °C. The product *cis*-**4a** was isolated in 85% yield with 74% *de* (eq. 4). The same oxidation methodology was applied for the selective synthesis of (+)-**4t** from **4c** in 80% yield with >99% *de* (eq. 4). The product (+)-**4t** has been found to be the key intermediate in the total synthesis of deoxycholic acid (DCA) and thus emphasizes the synthetic importance of the organocatalytic transfer hydrogenations.[8]



(4)

Conclusions

In conclusion, an organocatalytic transfer hydrogenation methodology has been successfully demonstrated for the *syn*-selective reduction of various steroids. Diastereoselective synthesis of many 5β-steroids have been reported through organocatalysis, which have broad medicinal and pharmaceutical applications. The mechanistic studies clearly indicated that the catalyst **1b**·D-CSA is mild enough to activate the various functionalized chiral cyclic enones through iminium ion formation during the transfer hydrogenation with Hantzsch ester **2a** as hydrogen source.[17] In a further support, the selective formation of *in situ* iminium species $[\mathbf{I}]^+$ have been investigated through on-line monitoring of controlled reactions by NMR and ESI-HRMS analyses.

Experimental

Experimental procedures, compound characterization data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) and X-ray crystallographic data (CIF) for (+)-**4i** and (+)-**4r**. This material is available free of charge in the ESI.†

Materials

All solvents and commercially available chemicals were used as received.

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