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Controlled Retro-*i*-Steroid Rearrangement: Catalytic Regioselective Steroidation of Biomolecules with Steroidal Trichloroacetimidates

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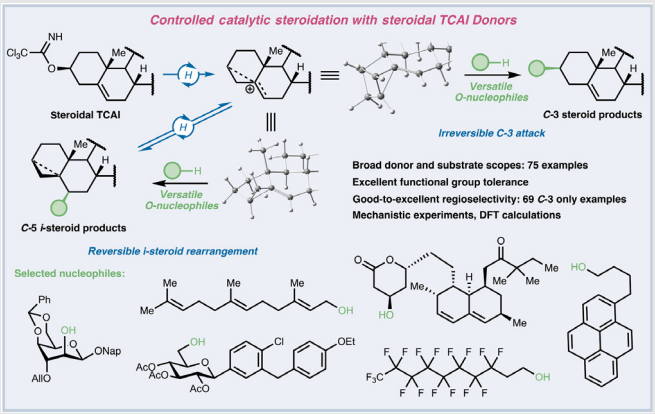
***C*-3-Functionalized steroids represent a pivotal class of molecules with diverse and significant biological functions. However, the reliable chemical synthesis of these compounds is frequently impeded by substrate sensitivity and the propensity for *i*-steroid rearrangement of steroidal cations. Herein, we disclose an efficient $Sc(OTf)_3$-catalyzed steroidation reaction that utilizes readily available steroidal trichloroacetimidates as donors. We have explored a broad spectrum of steroidal donors and acceptor substrates, including biomolecules such as sugars, steroids, amino acids, terpenoids, dye molecules, and small-molecule drugs, all of which possess multiple intricate functionalities. This reaction has been demonstrated to generate novel steroid chimeras with excellent regio- and diastereocontrol within 1 h under mild conditions. We have integrated a series of experimental investigations with density functional theory calculations to elucidate the reaction mechanism. Our findings reveal a controlled retro-*i*-steroid rearrangement of the kinetically favored and acid-activable *C*-6 *i*-steroid intermediates catalyzed by an in-situ generated protonic acid catalyst.**



Keywords: steroids, steroidal glycosides, substitution reaction, carbocations, DFT calculations

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Introduction

Steroid-containing compounds feature vital components of cell membranes and signaling molecules in animals and plants. They mediate diverse physiological processes, including growth, development, energy metabolism, homeostasis, and reproduction.[1,2] Steroid adducts, with their multifaceted biological roles, hence find extensive applications in clinical settings and biological studies, attracting significant academic and industrial interests.[3,4] Consequently, considerable efforts have been directed towards the design and chemical synthesis of novel molecular structures derived from the steroid scaffold, resulting in the discovery of a plethora of chimeric steroids with remarkable bioactivities, particularly those featuring a *C*-3 alkoxy moiety (Figure 1a). Notable examples include pseudo-cholesteryl disaccharide with potent anti-inflammatory activity,[5] CSA-8,[6] and cholesteryl

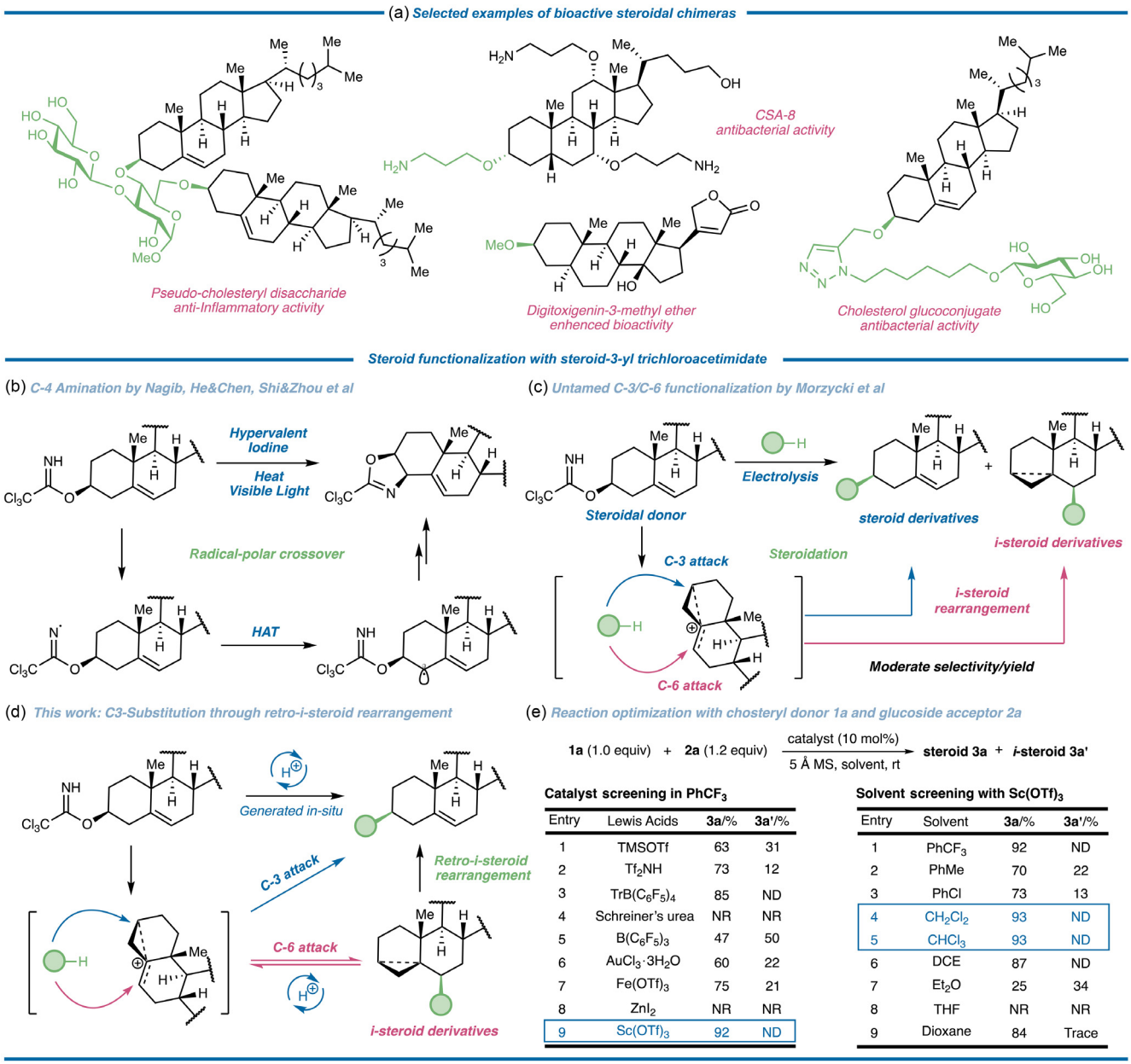

Figure 1 | *Bioactive steroid derivatives and steroid functionalization with steroidal TCAI. (a) Selected steroid chimeras with diverse biological activities. (b) C-4-Amination of steroidal TCAI. (c) C-3-Substitution of steroidal trichloroacetimidate is usually accompanied by the undesired* i*-steroid rearrangement side reactions. (d) Current report on catalytic, highly regioselective steroidation with steroidal trichloroacetimidate donors involving a controlled retro-*i*-steroid rearrangement to acquire steroid derivatives. (e) Reaction optimization of the steroidation with donor* ***1a*** *and acceptor* ***2a****.*

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glucogonjugates,[7] which exhibit broad-spectrum antibacterial properties, and digitoxigenin-3-methyl ether showing potential in improving cardiac function.[8] Despite significant progress in the field, challenges persist. The high demand for discovering new biological activities and deciphering the physiological mechanisms of steroid chimeras thus has created an eager need for steroid derivative synthesis and diversification. However, biochemists and medicinal chemists often encounter challenges in acquiring such substrates mainly due to the lack of reliable access to them. Therefore, there is an urgent need for synthetic chemists to devise and implement robust, convenient and versatile methods for the synthesis of steroidal derivatives, enabling the production of diverse steroidal structures with precise selectivity. This advancement is key to furthering the exploration and identification of innovative lead compounds that incorporate the steroid framework.

Steroidal trichloroacetimidates (TCAIs) offer distinct benefits as precursors for steroid modification, including commercial availability, ease of preparation, cost-effectiveness of the starting materials, and, importantly, the efficient activation. These attributes render steroidal TCAIs as promising agents for the direct chemical modification of steroids. A well-established method involves the radical-polar crossover *C*-4 amination of steroids through single electron transfer from steroidal TCAI using hypervalent iodine reagents. This process generates an oxazoline product, which can subsequently be hydrolyzed under acidic conditions to yield *C*-4 aminated steroids (Figure 1b).[9–11] This protocol offers a direct route to *C*-4 *N*-functionalization of steroids with precise regio- and stereo-control. An alternative approach to steroid functionalization using steroidal TCAI is the steroidation of various nucleophiles with an in-situ generated non-classical steroidal cation, which has seen sporadic success. Morzycki and colleagues demonstrated the feasibility of this approach by electrolyzing steroidal TCAI, enabling the steroidation of several simple acceptors.[12,13] However, the electrochemical reactions have typically resulted in the formation of isomeric products—namely, *C*-3 steroid products and *C*-6 *i*-steroid products—as mixtures with yields ranging from low to moderate. This outcome is particularly unsatisfactory, especially considering the requirement for stoichiometric amounts of electrolyte and a large excess of acceptors (Figure 1c). This moderate yield and selectivity can be attributed to multiple side reactions, including over-oxidation, hydrolysis, aglycon transfer, and notably, the *i*-steroid rearrangement—an often-encountered challenge in controlling the reactivity of steroidal cations under mild conditions. Notably, Peterson and Sun successfully utilized cholesteryl mesylates to synthesize 3β-cholesteryl azide and halides through a stereospecific retro-*i*-steroid rearrangement process involving cyclocholestan-5-yl azide and halides.[14,15] However, the direct rearrangement of *C*-5-biomolecule-substituted cyclocholestanes remains challenging, even at elevated temperatures.[16] To encapsulate, achieving catalytic steroidation of biomolecules with a readily available steroid donor, precise regio- and diastereocontrol is a highly desirable yet daunting task, especially given the diverse biomedical potentials of *C*-3-substituted steroid products.

Recognizing the significance of synthesizing steroidal chimeras with promising bioactivities, we have developed a practical and convenient steroidation reaction, employing easily accessible steroidal TCAI under mild, catalytic acidic conditions (Figure 1d). The steroidal TCAI donors share significant atom economy with a small leaving group (LG). This method applies to the steroidation of a wide range of bioactive molecules, including sugars, amino acids, steroids, terpenoids, fluorescent dye molecules, and drug molecules with various operational and delicate functionalities for downstream steroid elaborations. It offers a reliable and straightforward chemical route for constructing a wide variety of steroidal chimeras, catering to diverse potential needs such as fluorescent labeling, drug development, and biological probe studies, thereby significantly advancing the chemical space of steroid conjugates. We have combined experimental studies with density functional theory (DFT) calculations to delineate a retro-*i*-steroid rearrangement process of an advanced *i*-steroid intermediate, which facilitates the regeneration of reactive steroid cations for nucleophilic attack at the *C*-3 position. The easy access to both commercial donors/acceptors and the simplicity of experimental operations present a straightforward, robust, user-friendly and versatile method. Scientists in diverse fields can utilize this method to access the modified steroid derivatives for relevant studies. We anticipate that the current protocol will be widely adopted by scientists in diverse fields to acquire steroid derivatives, advancing the steroid chemistry, and relating medicinal chemistry and chemical biology.

Experimental Methods

General procedure for the synthesis of steroidal trichloracetimidates 1a-e

An oven-dried 100 mL round-bottom flask containing a dry magnetic stir bar was charged with steroid (3.00 mmol, 1.0 equiv). Anhydrous CH_2Cl_2 (30.0 mL) was added to dissolve the starting material and the solution was cooled by an ice bath. To this solution was added trichloroacetonitrile (1.5 mL, 15.00 mmol, 5.0 equiv), followed by dropwise addition of 1,8-diazabicyclo(5.4.0) undec-7-ene (450.0 μL, 3.00 mmol, 1.0 equiv). The ice bath was removed, and the mixture was allowed to stir at room temperature for 1 h during the time the color changed from colorless to dark purple. Upon completion of the reaction, as identified by thin-layer

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chromatography (TLC), the mixture was directly concentrated under reduced pressure. The residue was dissolved by the minimum amount of CH_2Cl_2 and further purified by triethylamine-deactivated silica gel column chromatography to afford the desired steroidal TCAIs as white or pale-yellow solids.

General procedure for catalytic steroidation with steroidal TCAI donors

To an oven-dried 5 mL vial containing freshly activated 5 Å molecular sieve (MS) (100.0 mg) and a dry magnetic stir bar were added sequentially steroidal TCAI donor (0.10 mmol, 1.0 equiv) and acceptor (if solid or syrup, 0.12 mmol, 1.2 equiv). Anhydrous CH_2Cl_2 (1.0 mL) was added to dissolve the starting materials, and to this solution was added the acceptor (if liquid, 0.12 mmol, 1.2 equiv). The mixture was stirred at room temperature for 15 min before $Sc(OTf)_3$ (4.9 mg, 0.01 mmol, 0.1 equiv) was added to the reaction mixture. The mixture was allowed to stir at room temperature for 1 h. Upon completion of the reaction as identified by TLC, the reaction was quenched with triethylamine, and the mixture was directly loaded onto the silica gel under reduced pressure, which was further purified by silica gel column chromatography to afford the desired steroid derivatives.

Results and Discussion

Reaction development

Our study began with developing the steroidation reaction between cholesteryl TCAI **1a** and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **2a**, aiming to identify the optimal combination of catalyst and solvent to produce immunoregulatory pseudo-steroidal glycoside (Figure 1e). Initially, the reaction was exposed to 10.0 mol % of various nonmetal Lewis acids in $PhCF_3$ (left table, entries 1–4),[16] revealing significant differences in yield and selectivity. Higher acidity generally led to increased selectivity, evident in a comparison between super acid Tf_2NH,[17] the strong cationic catalyst TrB $(C_6F_5)_4$,[18] and Schreiner's urea. Metal-centered Lewis acids were then evaluated, with $B(C_6F_5)_3$,[19–21] $AuCl_3$,[22] and ZnI_2[23,24] showing limited selectivity or no reaction due to their relatively low acidities. Notably, $Sc(OTf)_3$ emerged as the optimal catalyst,[25–27] delivering product **3a** with excellent yield (92%) and exclusive *C*-3 selectivity. Interestingly, catalyst loading also influenced selectivity; a 30.0 mol % loading of TMSOTf achieved complete *C*-3 selectivity, whereas a 5.0 mol % loading of $Sc(OTf)_3$ resulted in unsatisfactory selectivity (see Supporting Information Table S1). Subsequently, the solvent effect was explored (right table), revealing aromatic solvents and halogenated solvents (CH_2Cl_2, $CHCl_3$, 1,2-dichloroethane) as providing good-to-excellent selectivities and yields, with complete *C*-3 selectivity. Conversely, ether-type solvents (Et_2O, THF) yielded poor results presumably due to their relatively stronger basic nature or their tendency to coordinate with the $Sc(OTf)_3$ catalyst. Interestingly, dioxane, a similar basic solvent, can produce the desired product with excellent yield and diastereocontrol, although the exact reason for this result remains unclear. Based on these findings, the optimal conditions entail using 1.0 equiv of donor, 1.2 equiv of acceptor, and 10.0 mol % $Sc(OTf)_3$ in CH_2Cl_2 at room temperature for 1 h.

Scope and limitation of steroidation reaction

With the established protocol, we proceeded to evaluate the versatility of the steroidation reaction using cholesteryl TCAI **1a** by exposing various acceptors to optimal conditions. Given the significant role of pseudo-steroidal glycosides in immune modulation, a diverse range of sugar acceptors were employed for steroid functionalization (Figure 2).[28,29] It is evident that the current steroidation method applies to various types of sugar acceptors with versatile protection strategies. Glucosides, galactosides, mannosides, rhamannosides, 2-deoxy-2-aminosugar derivatives, rare monosaccharides, oligosaccharides, and glycodrugs bearing benzoyl (Bz), benzyl (Bn), acetonide, lactone, thioether, silyl ether (*tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl), benzylidene, phthalimido, azido, *para*-methoxyphenyl (MP), allylic (All), and 2-naphthylmethyl (Nap) groups all served as suitable substrates, consistently yielding the desired immunoregulatory *C*-3 pseudo-steroidal glycosides in good-to-excellent yields, except acceptor **2r**.

To gain further insights into the reaction, acceptors were meticulously categorized into distinct groups, revealing additional beneficial characteristics of the steroidation reaction. Both disarmed glycosyl acceptors **2a** and armed glycosyl acceptors **2b** proved to be viable substrates. Notably, compared to using glycoside as the donor, employing glyconolactone acceptor **2e**[30,31] did not hinder the steroidation process, underscoring the robustness of the reaction (**2d** vs **2e**). The influence of the linkage position was investigated using a series of benzyl-protected secondary glucoside alcohols (**2g–i**), all of which yielded the desired products with complete *C*-3 selectivity. This expands the scope of steroidal glycosides, as natural linkages between sugars and steroids typically occur at the *O*-1 position of the sugar.[32] Despite axially oriented hydroxyl groups typically being less nucleophilic compared to their equatorial counterparts, galactoside 4-OH and mannoside 2-OH (**2j–l**) were found to be suitable for the reaction regardless of the anomeric configurations. Acceptors **2m–o**, featuring acid-labile benzylidene groups, transformed pseudo-steroidal glycosides with good yields while leaving the benzylidene group intact. Notably, in the presence of 2.4 equiv of donor, compound **2o** allowed for the installation of two

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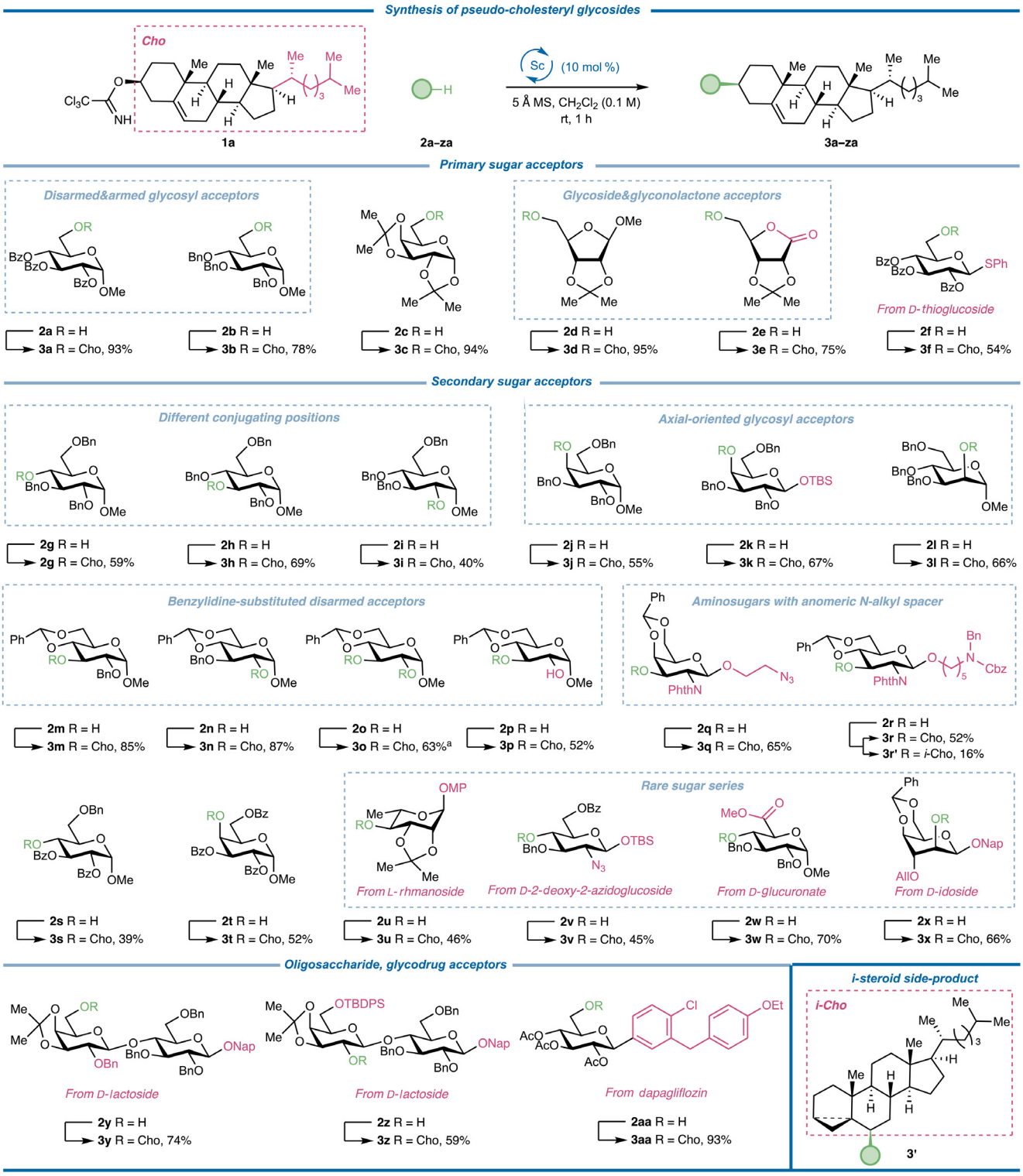

Figure 2 | *Synthesis of pseudo-cholesteryl glycosides. For all steroidation reactions, 1.0 equiv of donor and 1.2 equiv of acceptor were used in the presence of 10.0 mol % of Sc(OTf)$_3$ in CH_2Cl_2 (0.1 M) at room temperature for 1 h.* [a]*The reaction was performed in the presence of 2.4 equiv of the acceptor.*

cholesteryl residues simultaneously while when 1.2 equiv of acceptor was subjected to the reaction with the donor as the limiting agent, the *O*-3 of acceptor could be regioselectively cholesterated to afford **2p**, indicating that the steric hindrance of anomeric methoxy group could pose significant effect on the reaction outcome. Furthermore, 2-deoxy-2-amino-gluco/galactosides **2q–r**, featuring two different types of anomeric amino/

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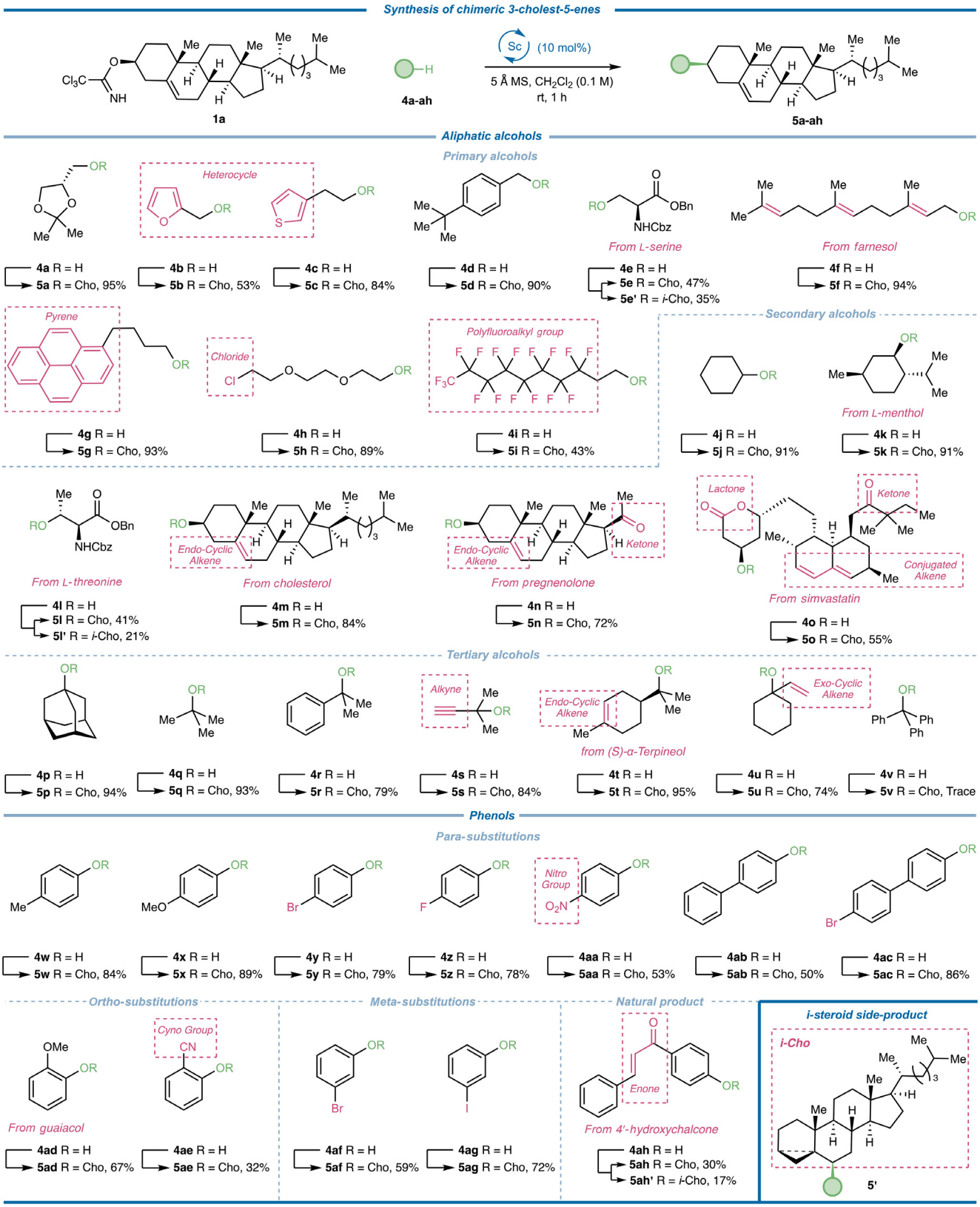

Figure 3 | *Synthesis of cholesteryl chimeras. For all steroidation reactions, 1.0 equiv of donor and 1.2 equiv of acceptor were used in the presence of 10.0 mol % of $Sc(OTf)_3$ in CH_2Cl_2 (0.1 M) at room temperature for 1 h.*

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azidoalkyl spacers, were successfully cholesterated, presenting a possibility to conjugate these molecules to carrier proteins for further investigation of their immunoactivity.[33,34] Compound **2t**, characterized by the electro-withdrawing effects of an axial-oriented C–O bond and disarming 2,3,6-tri-*O*-benzoyl groups, exhibited weak nucleophilicity; however, the reaction regiospecifically proceeded smoothly to afford **3t** in a yield of 52%.

With the promising results obtained thus far, we proceeded to assess the applicability of our protocol in cholesterating rare sugars, oligosaccharides, and glycodrugs. Subsequently, L-sugar **2u**, 2-deoxy-2-azido-sugar **2v**, glucuronate **2w**, and D-idoside **2x** were subjected to the optimized conditions, yielding steroid-decorated rare sugar entities **3u–x** in good yields invariably at *C*-3 of cholestane. This presents an opportunity to investigate the biological and medicinal properties of these rare sugar-doped pseudo-steroidal glycosides. Moreover, primary and secondary acceptors derived from D-lactosides proved to be suitable substrates, highlighting the versatility of our approach beyond monosaccharide acceptors. In addition, the approved sodium-glucose cotransporter-2 (SGLT-2) inhibitor dapagliflozin,[35] a *C*-glycoside-derived acceptor, was successfully employed in the steroidation reaction, yielding cholesteryl dapagliflozin in an excellent yield of 93% with exclusive *C*-3 selectivity, underscoring the efficacy of our protocol for modifying sugar-based drug molecules.

We aimed to broaden the acceptor scope to include common aliphatic alcohols and phenols, which are typically challenging to conjugate with steroids (Figure 3). Primary, secondary, and tertiary aliphatic alcohols, as well as phenols with *ortho*-, *meta*-, and *para*-substitution patterns, all proved to be compatible substrates, yielding valuable steroidal chimeras in good-to-excellent yields. Most reactions occurred at the *C*-3 position of the steroid backbone, indicating that the excellent regioselectivities extend beyond sugar alcohols. It is noteworthy that numerous functional groups were all well-tolerated under mild acidic conditions, including heterocycles (**4b** & **4c**), alkenes (**4f**, **4m–o**, **4t**, **4u**), chloride (**4h**), ketones (**4n-o**), lactone (**4o**), terminal alkyne (**4s**), nitro group (**4aa**), cyano group (**4ae**), and enone moiety (**4ah**). This tolerance offers opportunities for the modification of complex molecules with diverse substitution patterns. This method's applicability extends beyond carbohydrate acceptors to a range of biomolecules, including amino acids (**4e** & **4l**), farnesol **4f**, terpenoids (**4k** & **4t**), steroids (**4m** & **4n**), drug molecules **4o**, and chalcone **4ah**. The successful incorporation of the cholestane backbone into these biomolecules allows for the merging of their properties with those of steroids, altering their biophysical characteristics, such as solubility, permeability, and distribution, which could lead to altered pharmacological properties. Importantly, peptide-steroid conjugates have demonstrated crucial therapeutic effects by accumulating in cartilage and reversing arthritis without systemic corticosteroid exposure.[36] Furthermore, cholesterol-conjugated peptides have exhibited antiviral efficacy against influenza virus and highly fatal Filoviridae family, including the Ebola and Marburg viruses,[37,38] which cause hemorrhage and multiple organ failure. Therefore, our novel conjugation protocol introduces a promising new genre of steroid-peptide conjugates.

Moreover, this steroidation method can be extended to modify functional molecules, such as **4g** with a fluorescent pyrene motif,[39–41] resulting in fluorescent-labeled **5g** with an excellent yield of 93%. Acceptor **4h** could serve as a linker to increase substrate solubility in water. The presence of chloride offers opportunities to connect to other biomolecules, albeit prohibiting the use of strong basic conditions, which might cause decomposition or cross-linking. The mild acidic conditions allow for the synthesis of **5h** in excellent yield, showcasing the unique advantage of the weakly acidic conditions. Furthermore, attachment of poly-fluoroalkyl groups onto steroids can be easily achieved in good yield.[42,43] The steroidation of **4m** and **4n** yields di-steroids with homo- or hybrid-dimers in specific regio- and stereo-selectivities. This reaction is also applicable for hindered tertiary alcohols. Notably, under mild conditions, activation of the exo-alkene of **4u** was not observed.

The coupling reaction between various phenols and steroidal donor **1a** yielded novel types of steroids inaccessible through Williamson etherification, which vividly showcased the potential of steroidation reaction. Phenols with various substitution patterns were found to have a negligible effect on reaction efficiency, while maintaining consistent *C*-3 selectivity. Both electron-rich and electron-poor phenols were viable substrates for steroidation. The presence of bromide, iodide, and nitro groups[44] further expands the potential for elaborating these functional molecules through transition-metal-catalyzed cross-coupling reactions. Additionally, chalcone could be connected to the steroid with good yield to afford steroidal chalcone derivatives with potential pharmacotherapeutic applications.[45,46] It is noteworthy that, despite the separation of two isomers—*C*-3 steroidal chalcone and *C*-6 *i*-steroidal chalcone—the possible Nazarov cyclization was not observed.[47,48]

However, the current reaction does have certain drawbacks. Four substrates (**2r**, **4e**, **4l**, and **4ah**) have been observed to yield a pair of *C*-3/*C*-6 isomers. These substrates exhibit relatively low solubilities in CH_2Cl_2, which could hinder the retro-*i*-steroid rearrangement process (vide infra). Neither an increase in catalyst loading nor an extension of the reaction duration has led to a significant improvement in selectivity. Furthermore, reducing the reaction concentration has resulted in an increased formation of the trichloroacetamide rearranged side product. In the case of the extremely hindered substrate **4v**, only trace amounts of product were observed.

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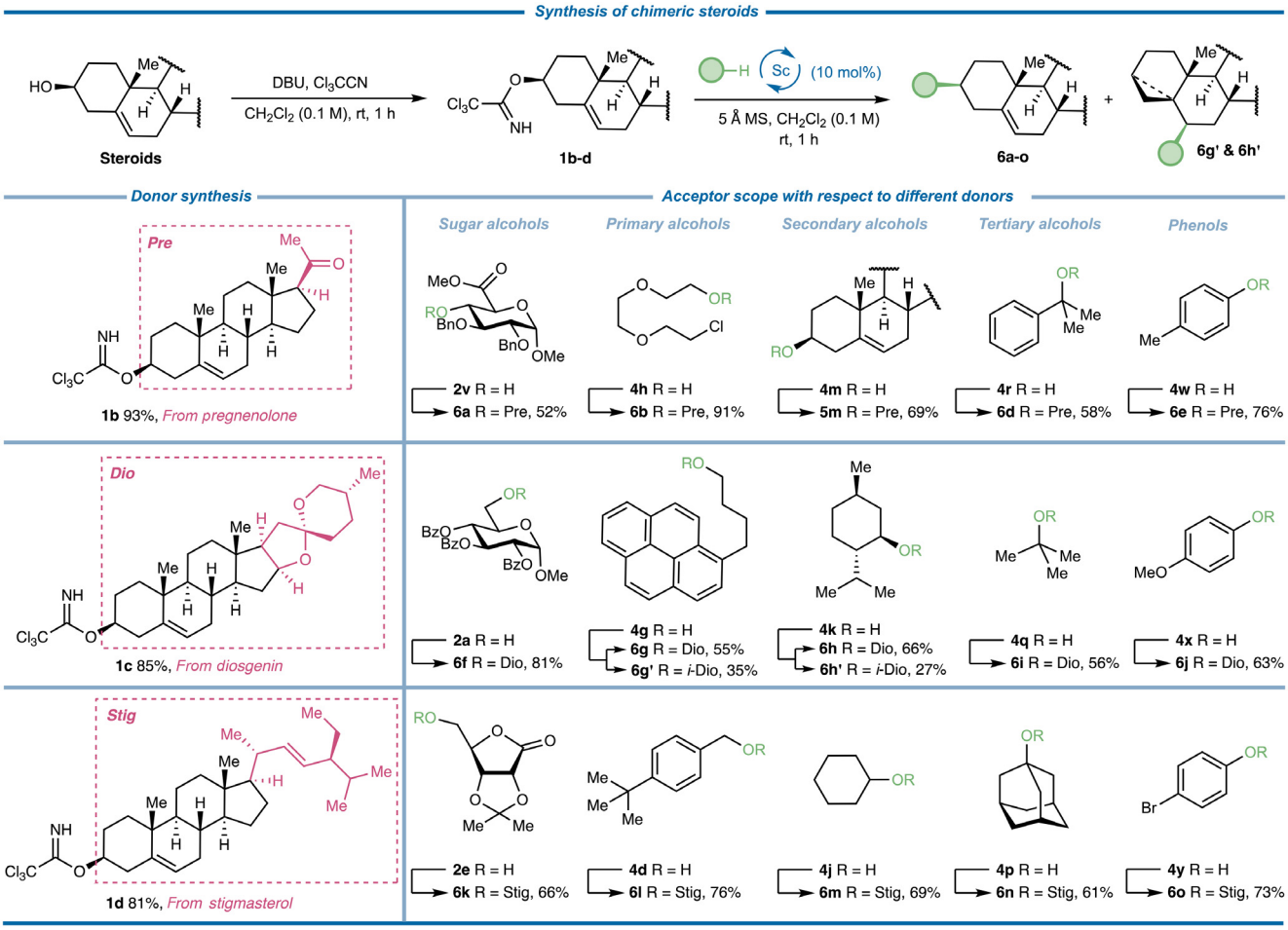

Figure 4 | *Substrate scope with steroidal TCAI derived from different steroids. For all steroidation reactions, 1.0 equiv of donor and 1.2 equiv of acceptor were used in the presence of 10.0 mol % of $Sc(OTf)_3$ in CH_2Cl_2 (0.1 M) at room temperature for 1 h.*

Meanwhile, for the cases with relatively low yields, the unignorable side reaction was identified as the trichloroacetamide rearrangement. These observed drawbacks have accordingly directed our efforts toward further improving our steroidation reaction.

To investigate the feasibility of activating other steroidal TCAI donors under the present mild conditions, we synthesized three steroidal donors derived from pregnenolone, diosgenin, and stigmasterol, achieving yields of 81%–93%. Subsequently, three sets of acceptors, comprising sugar alcohols, primary, secondary, and tertiary alcohols, and phenols, were randomly paired with the three donors for steroidation, and the results are shown in Figure 4. Encouragingly, the efficiency of the steroidation reaction remained consistent when other steroidal donors were used, yielding products **6a–o** in yields of 52%–91%. Special carbohydrate substrates, rare sugar glucuronate **2v**, disarmed glucoside **2a**, and ribonolactone **2e**, could be conveniently converted into the corresponding pseudo-steroidal glycosides. Additionally, hydrophilic linker **4h** and fluorescent molecule **4g** could be attached to the skeletons of pregnenolone and diosgenin, respectively. Natural products such as cholesterol and L-menthol were also amenable to steroidation, allowing for the synthesis of chimeric steroids. Furthermore, phenols with different electronic properties were used as coupling partners, resulting in the synthesis of three unusual phenolated steroids in 63%–76%. These results underscore the generality and power of the steroidation reaction with steroidal TCAI donors in obtaining versatile steroid derivatives.

Mechanistic investigations

To elucidate the root of the regioselectivity, we conducted a series of mechanistic experiments (Figure 5). First, to probe the interaction between the acceptor and $Sc(OTf)_3$ catalyst, we performed an nuclear magnetic resonance (NMR) experiment. Upon stirring a 1:1 molar ratio of acceptor **2a** and $Sc(OTf)_3$ in CD_2Cl_2 for 1 h, it was observed that the initial solid–liquid two-phase mixture transitioned into a translucent suspension, indicating the

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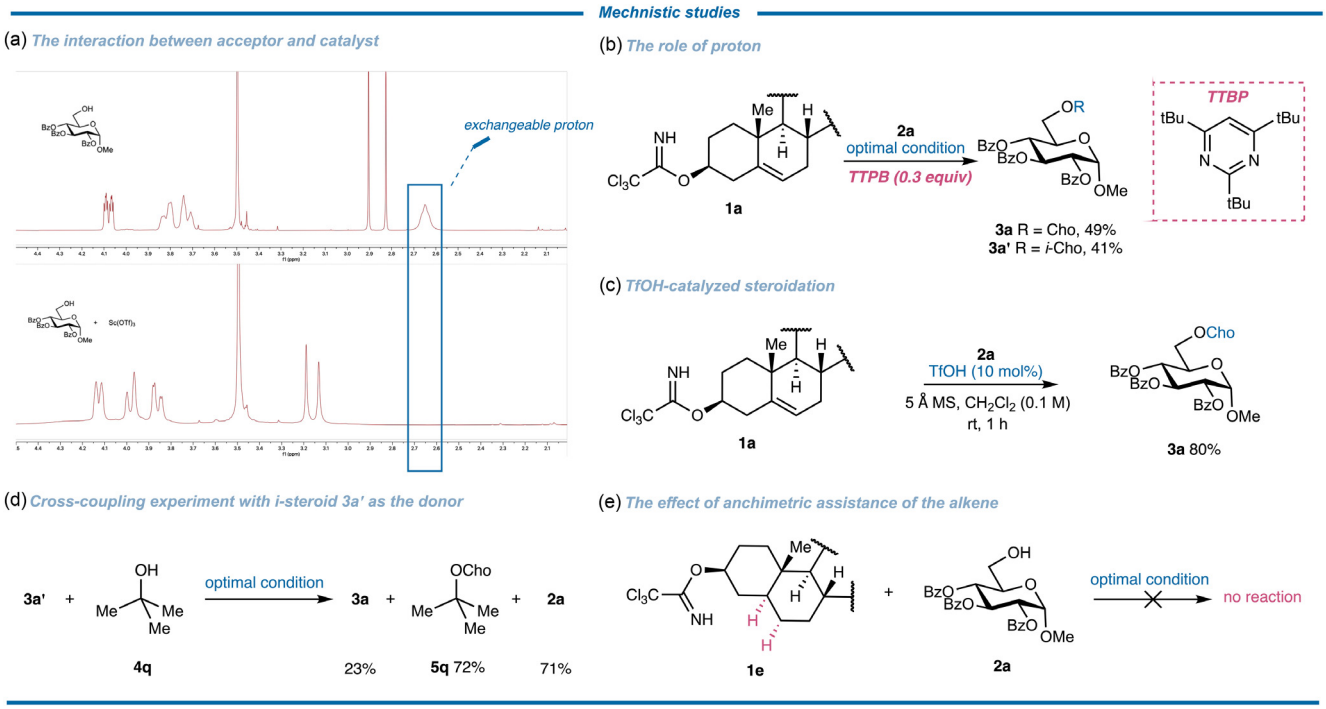

Figure 5 | *Mechanism studies. (a) The NMR observations of the interaction between the acceptor and Sc(OTf)₃. (b) Proton scavenging experiment. (c) TfOH-catalyzed steroidation between **1a** and **2a**. (d) Cross-coupling experiment with* i*-steroid **3a**′ as the donor. (e) Steroidation with dihydrocholesteryl TCAI **1e** as the donor.*

coordination between **2a** and the catalyst. Subsequently, we recorded the ^{1}H NMR spectrum of this sample (Figure 5a). Compared to the spectrum of **2a** alone, we observed the disappearance of the exchangeable proton of **2a**, along with minor changes in chemical shifts of other protons, strongly supporting coordination of the scandium center with the hydroxyl group. This process likely generates one equivalent of TfOH, which we hypothesized to be crucial for activating the steroidal TCAI donor. To demonstrate the importance of the protonic acid, we performed a proton scavenging experiment by adding 30.0 mol % of 2,4,6-tri-*tert*-butylpyrimidine (TTPB), a sterically hindered base that selectively scavenges protons from the reaction without coordinating with the metal. Surprisingly, although the donor could be fully consumed, the selectivity of the reaction dramatically decreased (Figure 5b). To gain direct evidence that TfOH could catalyze the reaction, we performed the reaction between **1a** and **2a** in the presence of 10.0 mol % TfOH. Under this condition, the desired **3a** could be obtained in good 80% yield without *i*-steroid product detected (Figure 5c). These results underscore the pivotal role of the protonic acid in dictating the regioselectivity of the steroidation reaction. Subsequently, we separated the *i*-steroid **3a**′ and subjected it to steroidation with acceptor **4q**, yielding three major products: pseudo-steroidal glucoside **3a** (23%), steroid derivative **5q** (72%), and recovered acceptor **2a** (71%), respectively (Figure 5d). This observation suggests that the *i*-steroid might serve as an intermediate during the reaction and can be activated under optimal conditions to undergo a retro-*i*-steroid rearrangement. Furthermore, the formation of **3a** demonstrates that the departing acceptor **2a** can be re-engaged in the steroidation to form the desired *C*-3 steroid product. Additionally, we synthesized donor **1e** from dihydrocholesterol and exposed it to the steroidation reaction, but no reaction occurred under optimal conditions, highlighting that the steroidation is driven by the push-and-pull effect of the anchimerically participatory homoallylic system (Figure 5e).[49] These mechanistic insights not only shed light on the reaction mechanism but also offer explanations for moderate selectivities observed with acceptors of low solubilities; low acceptor concentrations may hinder retro-*i*-steroid rearrangement. It is noteworthy that acid-catalyzed retro-*i*-steroid rearrangement with simple LGs such as chloride, methoxy, tosylate, and trichloroacetate and in the presence of largely excess amounts of solvent-based nucleophiles are documented.[50,51] However, the rare observation of retro-*i*-steroid rearrangement with complex *O*-nucleophiles provides further insight into the distinctive reactivities of unclassical homoallylic carbocations. This observation offers an opportunity to uncover valuable steroid feedstocks of biological and medicinal interests.

The reaction paths along two different steroidal trichloroacetimidate activation modes and the following

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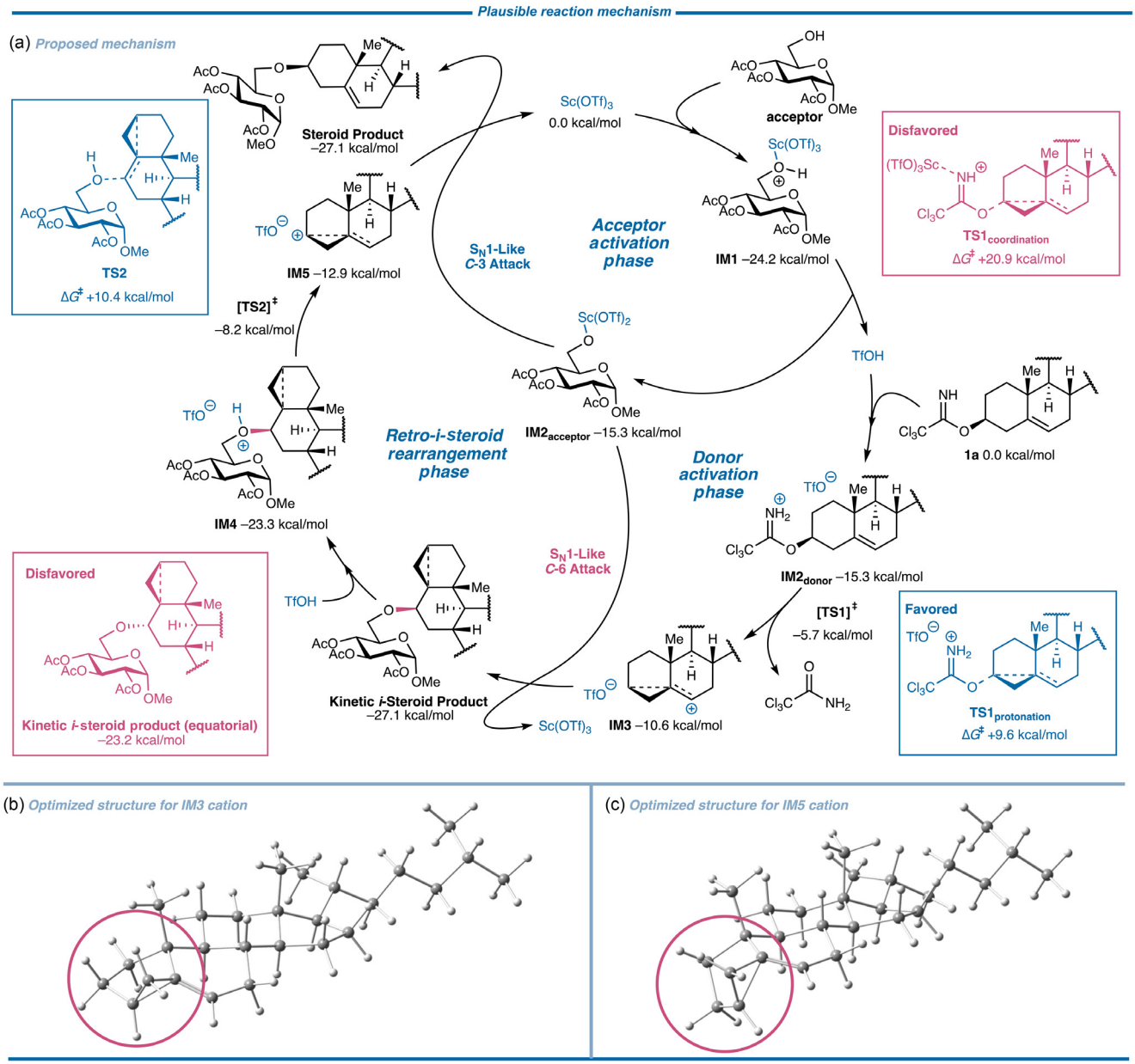

Figure 6 | *Possible mechanism. (a) Proposed mechanism based on experimental and DFT calculation studies. (b) Optimized structure for **IM3** cation. (c) Optimized structure for **IM5** cation.*

nucleophilic attack were further simulated with DFT computations at the MN15-L/def2-ma-TZVPP/SMD (solvent=CH_2Cl_2) level of theory using Gaussian 16 software,[52,53] employing model structures starting from the steroidal trichloroacetimidate **1a**, a simplified glucose acceptor with benzoyl protecting groups replaced with smaller acetyl groups, and the $Sc(OTf)_3$ catalyst. We identified the intermediates (**IMs**) and transition state structures (**TSs**) involved in the reaction routes and calculated Gibb's free energies of the optimized structures (see Supporting Information for details), which are reported in the unit of kcal/mol, taking the Gibbs free energy level of starting materials as reference. Results indicate that for the dissociation of the trichloroacetimidate LG from the donor steroidal ring, the reaction path with the LG activated by direct coordination of the nitrogen atom to the $Sc(OTf)_3$ catalyst acting as a Lewis acid involves a free energy barrier of +20.9, while the reaction path with the LG activated by the protonation of the nitrogen atom is associated with a significantly lower energy barrier of +9.6 (see Supporting Information for the optimized IM and TS structures), and therefore the activation through protonation is favored; this is also supported by our coordination experiment study.

Based on the DFT results and experimental mechanistic investigations, we proposed the catalytic cycle, in

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which three phases exist (Figure 6a). In the first phase of acceptor activation, the $Sc(OTf)_3$ catalyst coordinates to the 6-OH of the glucose acceptor to form **IM1** (ΔG = –24.2), and then the triflic acid dissociates from the metal center, leaving $\mathbf{IM2_{acceptor}}$ Glc-6O-$Sc(OTf)_2$ (ΔG = –15.3). The triflic acid then is involved in the second stage of donor activation to protonate and activate the steroid donor into $\mathbf{IM2_{donor}}$ comprising the donor with the protonated LG with an accompanying triflate anion. Following dissociation of the protonated LG passing through $\mathbf{TS1_{protonation}}$ ($\Delta G^{\ddagger}$ = +9.6) gives rise to the ion pair **IM3** (ΔG = –10.6) with steroidal cation structure **I** (Figure 6b). Calculated natural bond orbital (NBO) and Hirschfeld atomic charges and Fukui function (see Supporting Information for details) indicated that the *C*-6 is a more positively charged and electrophilic site (NBO charge of atoms: *C*-6: +0.194; *C*-3: –0.104, Fukui function: *C*-6: +0.298; *C*-3: +0.012), and nucleophilic attack of the *C*-6 site on the steroidal cation in **IM3** by the Glc-6O-Sc$(OTf)_2$ in an S_N1 manner is favored over nucleophilic attack of the acceptor on the steroidal *C*-3, giving rise to the *C*-6 *i*-steroid intermediate product (ΔG = –27.1). Comparison of the Gibbs energies of the isomeric *C*-6 *i*-steroid **IMs** arising from nucleophilic attack from different faces of the steroidal cation ring indicates that the isomer with *C*-6 axial glucose acceptor above the steroid ring is more stable than the isomer with *C*-6 equatorial glucose acceptor approximately on the steroidal ring, aligning with the experimentally observed stereochemical outcome. Moreover, the calculated free energy of the optimized regioisomer, that is, the *C*-3 glucosylated steroid product **3** (ΔG = –29.4) indicates that product **3** is the stabler regio-isomer. And further simulations demonstrated the *i*-steroid rearrangement phase, in which the ether bond of product **6** can be protonated by triflic acid to form **IM4** (ΔG = –23.3), and following breakage of the bond passing through **TS2** ($\Delta G^{\ddagger}$ = +15.1) gives rise to the ion pair **IM5** (ΔG = –12.9) with steroidal cation structure **II** (Figure 6c), in which the steroidal ring A becomes distorted with *C*-3 below the plane of the rest of the steroid planes and positively charged. The steroidal cation ring of **IM5**, adopting a more distorted conformation compared to **IM3**, has a distinct distribution of positive charges on the atoms, with *C*-3 more positively charged than *C*-6 and becoming the electrophilic site (NBO charge of atoms: *C*-6: +0.037; *C*-3: +0.175, Fukui function: *C*-6: +0.003; *C*-3: +0.142), promoting the nucleophilic attack on *C*-3. Following nucleophilic attack of the *C*-6 site on the steroidal cation in **IM5** by the Glc-6O-$Sc(OTf)_2$ in an S_N1 manner ensues and produces the thermodynamically favored product **3**.

Conclusion

In conclusion, we have established a robust steroidation method utilizing steroidal TCAI donors, facilitating the facile synthesis of chimeric steroid derivatives with exceptional regioselectivity. This methodology allows for the attachment of key steroid motifs onto a variety of complex bioactive molecules, including sugars, amino acids, steroids, terpenoids, and drug molecules, under mild acidic conditions. Such conditions are crucial for maintaining the integrity of labile functionalities on the biomolecular acceptors. Mechanistic experiments confirmed the coordination of $Sc(OTf)_3$ catalyst to the acceptor, leading to the in-situ generation of TfOH. DFT calculation provided further insights into the plausible reaction pathway, suggesting that the protonic acid activates the kinetically favored but reactive *C*-6 *i*-steroid **IMs**, promoting retro-*i*-steroid rearrangement to yield thermodynamically stable *C*-3 steroid products. Given the accessibility of steroidal TCAI donors, mild activation conditions, and excellent regioselectivity of the reaction, coupled with the pivotal functions and promising bioactivities of chimeric steroids, we anticipate widespread adoption of this approach by synthetic chemists, chemical biologists, and medicinal chemists. This method not only advances the field of steroid chemistry but also paves the way for new directions in drug development and the synthesis of complex biomolecules.

Supporting Information

Supporting Information is available and includes the experimental procedures, characterization, including the spectra of the new compounds, and details of the theoretical studies are available in the Supporting Information.

Author Contributions

X.-W.L. and H.D. conceived the idea. H.D. developed the reaction and performed the substrate scope and experimental mechanism studies. X.-L.Z., Y.L., X.S., and K.Z. performed the substrate scope studies. C.C., M.L., and H.C. discussed the results. A.G. performed the DFT calculation. X.-W.L., H.D., A.G., C.C., M.L., H.C. cowrote the paper with the input from all other authors.

Conflict of Interest

The authors declare no competing interests.

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