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Catalyst-Directed Diastereoselective Isomerization of Allylic Alcohols for the Stereoselective Construction of C(20) in Steroid Side Chains: Scope and Topological Diversification

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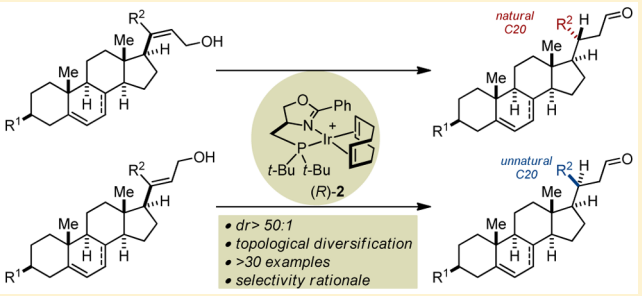
Supporting Information

ABSTRACT: The stereoselective construction of C20 in steroidal derivatives by a highly diastereoselective Ir-catalyzed isomerization of primary allylic alcohols is reported. A key aspect of this strategy is a straightforward access to geometrically pure steroidal enol tosylate and enol triflate intermediates for subsequent high yielding stereoretentive Negishi cross-coupling reactions to allow structural diversity to be introduced. A range of allylic alcohols participates in the diastereoselective isomerization under the optimized reaction conditions. Electron-rich and electron-poor aryl or heteroaryl substituents are particularly well-tolerated, and the stereospecific nature of the reaction provides indifferently access to the natural C20-(*R*) and unnatural C20-(*S*) configurations. Alkyl containing substrates are more challenging as they affect regioselectivity of iridium-hydride insertion. A rationale for the high diastereoselectivities observed is proposed for aryl containing precursors. The scope of our method is further highlighted through topological diversification in the side chain and within the polycyclic domain of advanced and complex steroidal architectures. These findings have the potential to greatly simplify access to epimeric structural analogues of important steroid scaffolds for applications in biological, pharmaceutical, and medical sciences.



INTRODUCTION

Steroids are ubiquitous molecular architectures which constitute a privileged bridge across a variety of scientific disciplines.[1] Since the Nobel prizes of H. O. Wieland and A. O. R. Windhaus in 1927 and 1928, the challenges associated with their synthesis have raised fundamental questions and have repeatedly served as a fertile ground to advance knowledge in synthetic chemistry.[2] Beyond the boundaries of chemistry, the concomitant applications of steroids in biological, pharmaceutical, and medical sciences have led to essential discoveries which have profoundly impacted our society.[1,3] Decades of investigations have revealed that if every single position in the common cyclopentanophenanthrene ring system certainly plays a key role in biological applications, stereogenic centers are particularly sensitive points of mutation.[4] Specifically, C20—the first exocyclic stereocenter of the side chain directly adjacent to the polycyclic framework—is of particular interest (Figure 1A,B).[5,6] A majority of the biologically active steroids possesses the so-called natural C20 configuration (usually C20-(*R*) such as in **A**, **B**, **E**, **H** or C13-(*R*) in **C**). These naturally occurring molecules or their synthetic analogues display an immense spectrum of biological activities ranging from anti-inflammatory properties to various antitumor activities, while some derivatives have been found to act as reversing substances for multidrug resistance in human carcinogenic cell lines. Steroids with the epimeric non-natural C20 configuration (usually C20-(*S*)) are much rarer but distinguish themselves by significantly superior biological activities. Representatively, the *seco*-steroid 20-*epi*-calcitriol (**F**) is not only more potent than its natural epimer in regulating cell growth and cell differentiation, but it also possesses immunosuppressive properties.[7] Although several methods have been introduced for the stereoselective installation of C20, they all come with deleterious impediments.[6,8] With rare exceptions,[8f] two distinct synthetic routes are often needed to individually access each C20 epimer of a specific target. A majority of approaches follows long linear sequences employing stoichiometric rather than catalytic procedures and require repeated functional group manipulations. Noticeably, ablation of the vicinal C17 stereocenter has been regularly practiced to facilitate stereocontrolled construction of C20.[6,8e,f] Finally, nominal modularity has been disclosed and almost invariably the steroidal derivatives possess a methyl substituent at C21.[6,8d] Consequently, these synthetic constrains have precluded exploration of a topological diversification that would match the contemporary standards for wide therapeutic investigations.[9]

The development of catalytic enantioselective reactions from prochiral substrates is a fundamental task in synthetic chemistry.[10] *Substantially more difficult is the development of diastereoselective methods from advanced intermediates possessing multiple stereogenic centers where a chiral catalyst must control the absolute configuration of a given stereocenter independently of a*

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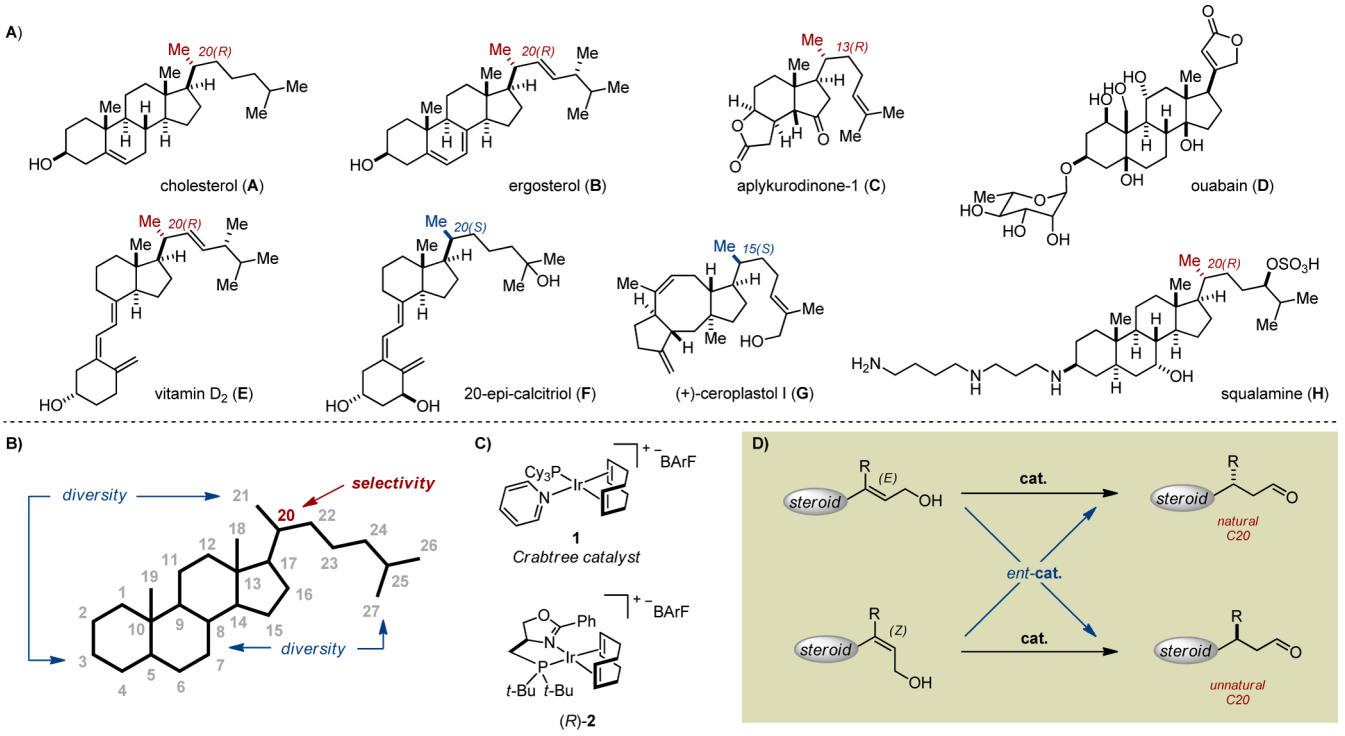

Figure 1. (A) Representative steroids. (B) General nomenclature of the common cyclopentanophenanthrene ring system of steroids with highlights on the potential points of synthetic diversity. (C) Cationic iridium complexes for the isomerization of primary allylic alcohols (BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). (D) Selectivity principle for prochiral olefinic substrates in stereospecific transformations.

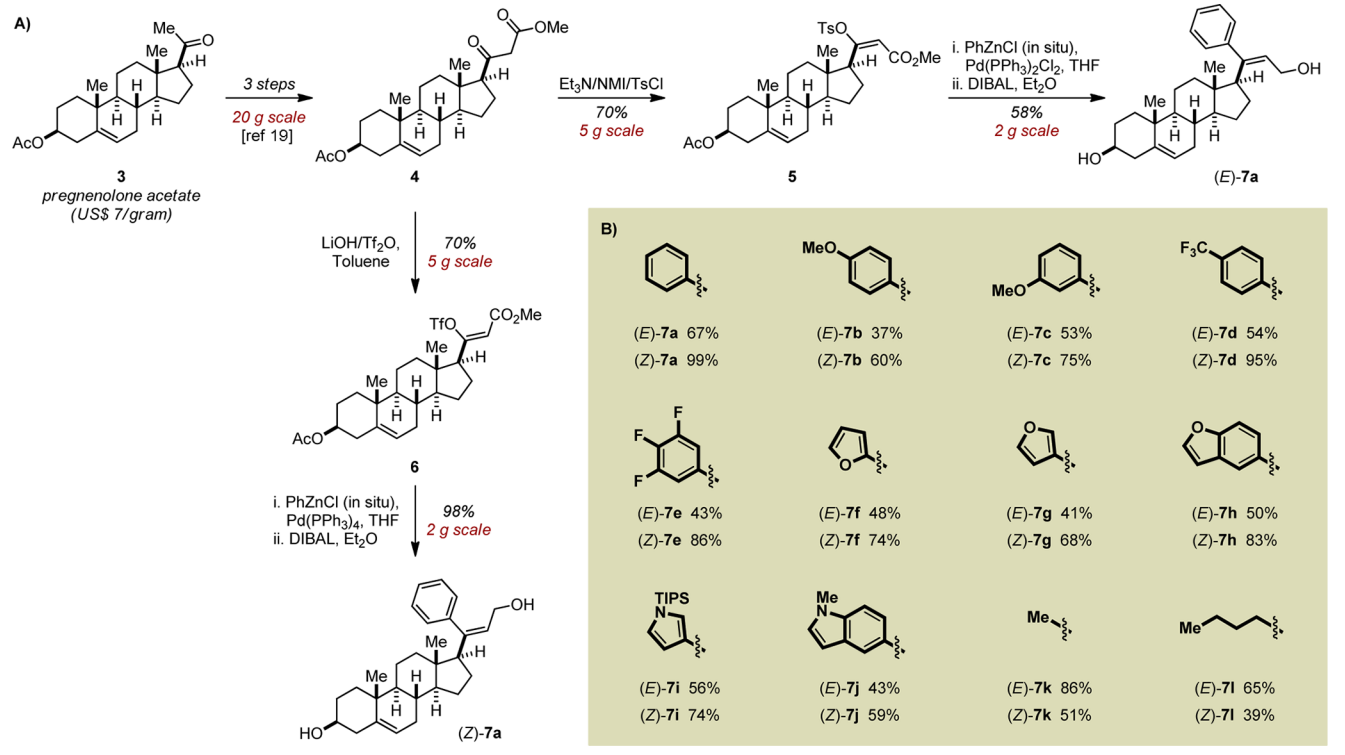

Figure 2. Scalable synthesis of steroid-based allylic alcohols. (A) Synthetic route to both geometrical isomers of steroidal primary allylic alcohols **7a–l**. (B) Scope of (*E*) and (*Z*) allylic alcohols (24 examples). Yields are over two steps from intermediates **5** or **6**. See Supporting Information for experimental details.

highly complex environment. Acyclic substrates are notoriously more challenging than cyclic substrates in such contexts.[10,11]

Thus, stereoselective installation of C20 in the acyclic domain of steroids is especially demanding due to the proximity of the C13 and C17 stereocenters, which adds up to the inherent bulk and complexity of the rigid polycyclic framework.[8g] To devise a general method for the stereoselective construction of C20, we focused on the Ir-catalyzed isomerization of primary allylic

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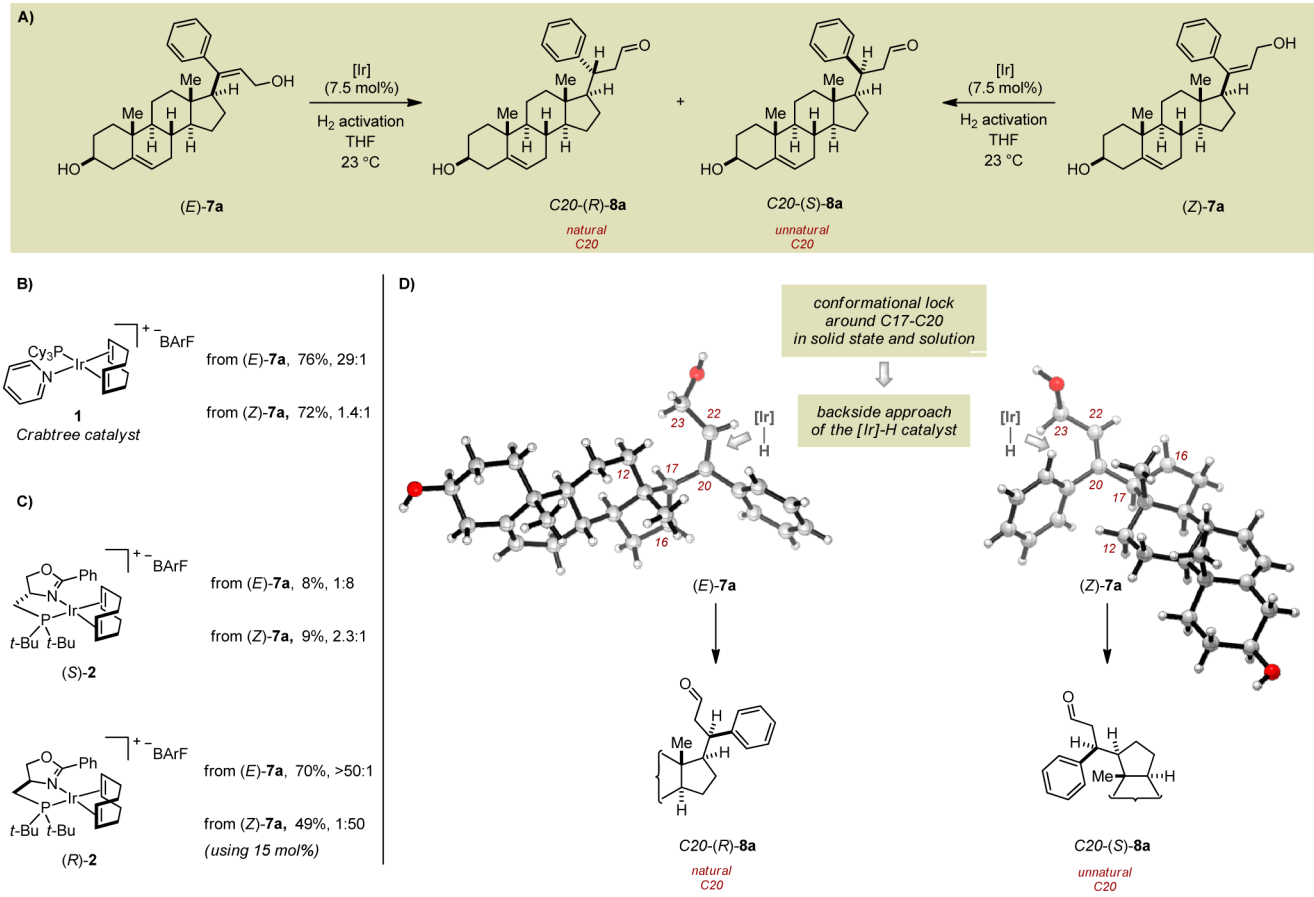

Figure 3. (A) Stereospecific isomerization of the model allylic alcohols (*E*)-**7a** and (*Z*)-**7b** into aldehyde **8a**. Conditions: 0.05 mmol scale, 7.5 mol % of **1** or **2**, THF (1.5 mL). Activation time is 1 min with **1** and 5 min with **2**. Yields and selectivity are average of at least two experiments. The selectivity was determined by ^{1}H NMR analysis. (B) Determination of the innate selectivity imposed by the chiral steroidal scaffold using the achiral catalyst **1** and the model substrates. All ratios are indicated as C20-(*R*):C20-(*S*). (C) Assessment of the ability of each enantiomer of catalyst **2** to potentially override the innate substrate selectivity. (D) Proposed origin of the high diastereoselectivity with catalyst (*R*)-**2**.

alcohols developed in our research laboratories.[12−14] This transformation operates under mild conditions both with achiral and chiral catalysts such as **1** and **2**, respectively (Figure 1C).[13a,c,15] Excellent enantioselectivities have been obtained with the latter and a working selectivity model based on Knowles quadrant diagrams has been proposed for simple prochiral substrates.[13c,d,16,17] More recently, we also explored diastereoselective isomerization of chiral racemic allylic alcohols with the achiral catalyst **1** and found that diastereoselectivity can be quantified using steric descriptors for both the substrate substituents and the catalyst substituents.[13g]

On the basis of the observation that the stereoselective outcome in the Ir-catalyzed isomerization of allylic alcohols depends on olefin geometry, our initial strategy relied on the well-established selectivity principle for prochiral olefinic substrates in stereospecific transformations (Figure 1D).[10] Despite its apparent simplicity, this approach has not been practiced for elaborated structures possessing a dense array of stereocenters at close proximity of the reactive olefin. Aside from potential reactivity issues, we were concerned whether enantiomeric chiral catalysts (*R*)-**2** and (*S*)-**2** would be able to overcome the inherent stereochemical bias imposed by the steroid scaffold and impart high level of selectivity at C20 in both matched and mismatched situations. The lower reactivity and selectivity typically observed in the enantioselective isomerization of (*Z*) configured allylic alcohols in our previous studies were additional source of uncertainty.[13b,d]

RESULTS AND DISCUSSION

Strategy for Substrate Synthesis. At the outset of our investigations, we focused on the devise of a short synthetic route that would give access to geometrically pure (*E*) and (*Z*) allylic alcohols. To facilitate structural diversification, we envisioned that it should be articulated around a common synthetic precursor and rely on the orthogonality provided by transition metal-catalyzed cross-coupling methods.[18] Commercially available pregnenolone acetate **3** was considered as an ideal departing point because it possesses many of the representative attributes of a typical steroid skeleton (i.e., a cyclopentanophenanthrene ring system with multiple stereocenters, a Δ^5-unsaturation, an anchoring point at C3, a keto functionality at C20) (Figure 2). The corresponding 1,3-keto ester **4** was prepared according to a literature procedure in up to 20 g.[19] Treatment of this pivotal intermediate with Et_3N, *N*-methylimidazole, and TsCl (3.0 equiv each) afforded enol tosylate **5** in 70% yield with perfect (*E*) selectivity. Geometrically pure (*Z*)-enol triflate **6** was obtained in a similar yield after reaction of **4** with aqueous LiOH and triflic anhydride. In contrast to the original protocols independently developed by Tanabe and Frantz,[20,21] the stereocomplementary (*Z*)-enol tosylate and (*E*)-enol triflate derived from **4** were not accessible by changing the nature of the base. Subsequently, (*E*)-

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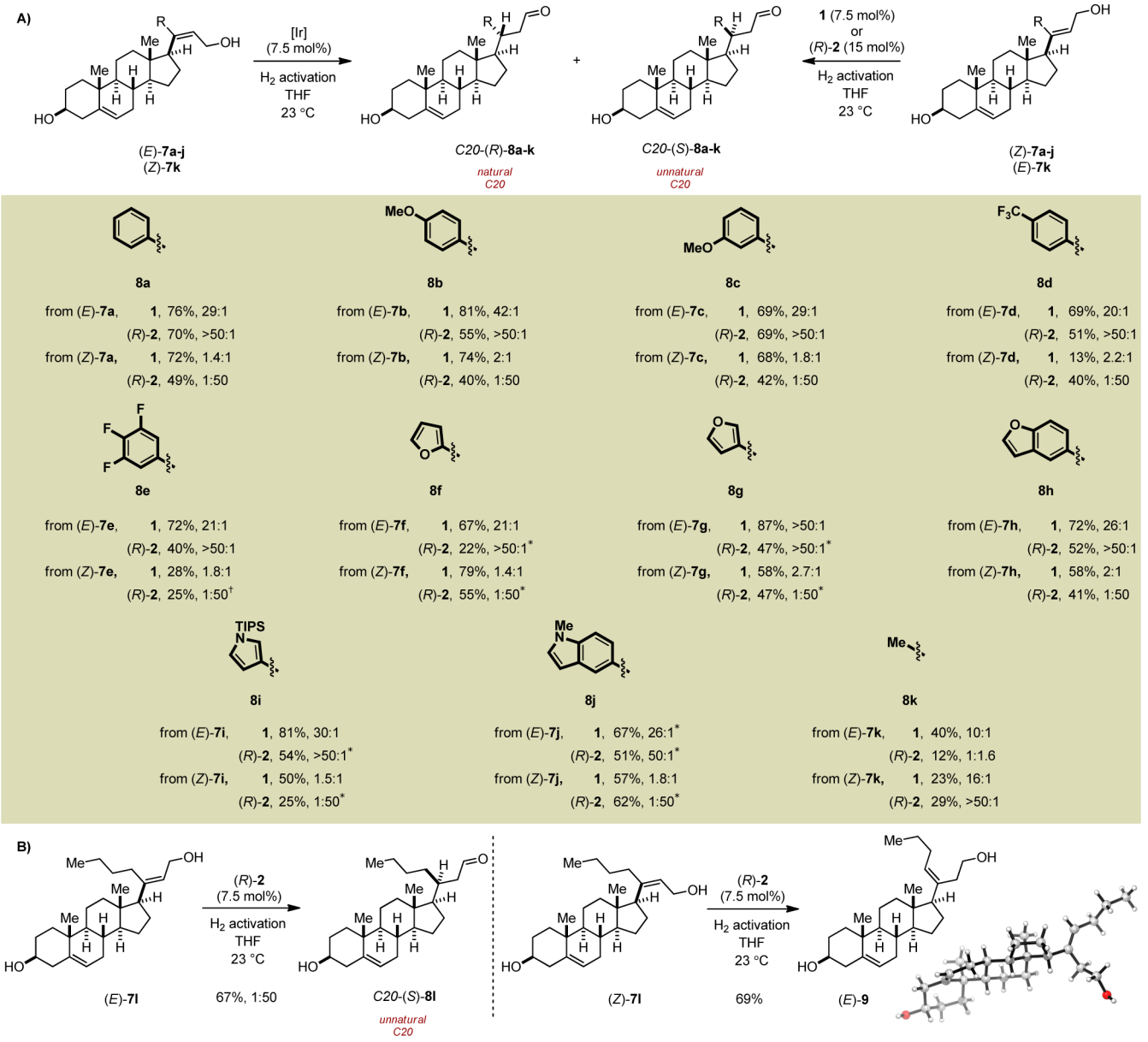

Figure 4. (A) Scope in the isomerization of steroid-based allylic alcohols. All ratios are indicated as C20-(*R*):C20-(*S*). †Contains traces of the corresponding *α*,*β*-unsaturated aldehyde. *A catalytic amount of 2,6-di-*t*-Bu-4-methylpyridine is required (see SI for details). (B) Isomerizations of the purely alkyl containing derivatives **7l**.

5 and (*Z*)-**6** were engaged in stereoretentive Pd-catalyzed Negishi cross-coupling reactions using PhZnCl as transmetalating agent to afford the corresponding *β*,*β*′-disubstituted enoates in excellent yields and perfect control of the olefin geometry.[20,22] Reduction of the enoates and simultaneous deprotection of the 3-hydroxyl moiety with an excess of di-isobutyl aluminum hydride delivered quasi-quantitatively the primary allylic alcohols (*E*)-**7** and (*Z*)-**7** as white crystalline materials. The robustness of our approach was demonstrated by conducting all steps of the synthesis of (*E*)-**7** and (*Z*)-**7** on multigram quantity (2−5 g). Following this uniform synthetic route, a collection of 24 derivatives was prepared ((*E*)-**7a**−**l** and (*Z*)-**7a**−**l**). The mild reactivity associated with the organozinc reagent in the Negishi cross-coupling reactions enabled to introduce a variety of aryl, perfluorinated aryl, heteroaryl and alkyl groups with systematically perfect control of the olefin geometry. The yields obtained were usually very high for the (*Z*) primary allylic alcohols (59−99% over 2 steps), and moderate for the (*E*) isomers (37−67% over 2 steps). This might be due in part to the heterogeneous nature of these reactions.

Catalyst-Directed Diastereoselective Isomerization. To evaluate the feasibility of our approach and to probe the innate selectivity imposed by the chiral allylic alcohols, we tested the achiral catalyst **1** in exploratory experiments with our two model substrates (Figure 3A). Isomerization of (*E*)-**7a** delivered aldehyde **8a** in 76% yield and 29:1 diastereoselectivity in favor of the natural C20-(*R*) epimer as established on the basis of multidimensional NMR experiments (Supporting Information). Isomerization of (*Z*)-**7a** afforded **8a** in 72% but in only 1.4:1 dr, indicating that the steroid domain imparts a very strong bias on the reaction outcome. Aside from the successful application of our method in the isomerization of a complex molecule, the compatibility of the iridium catalyst with the endocyclic homoallylic alcohol is noticeable as this is a common motif for

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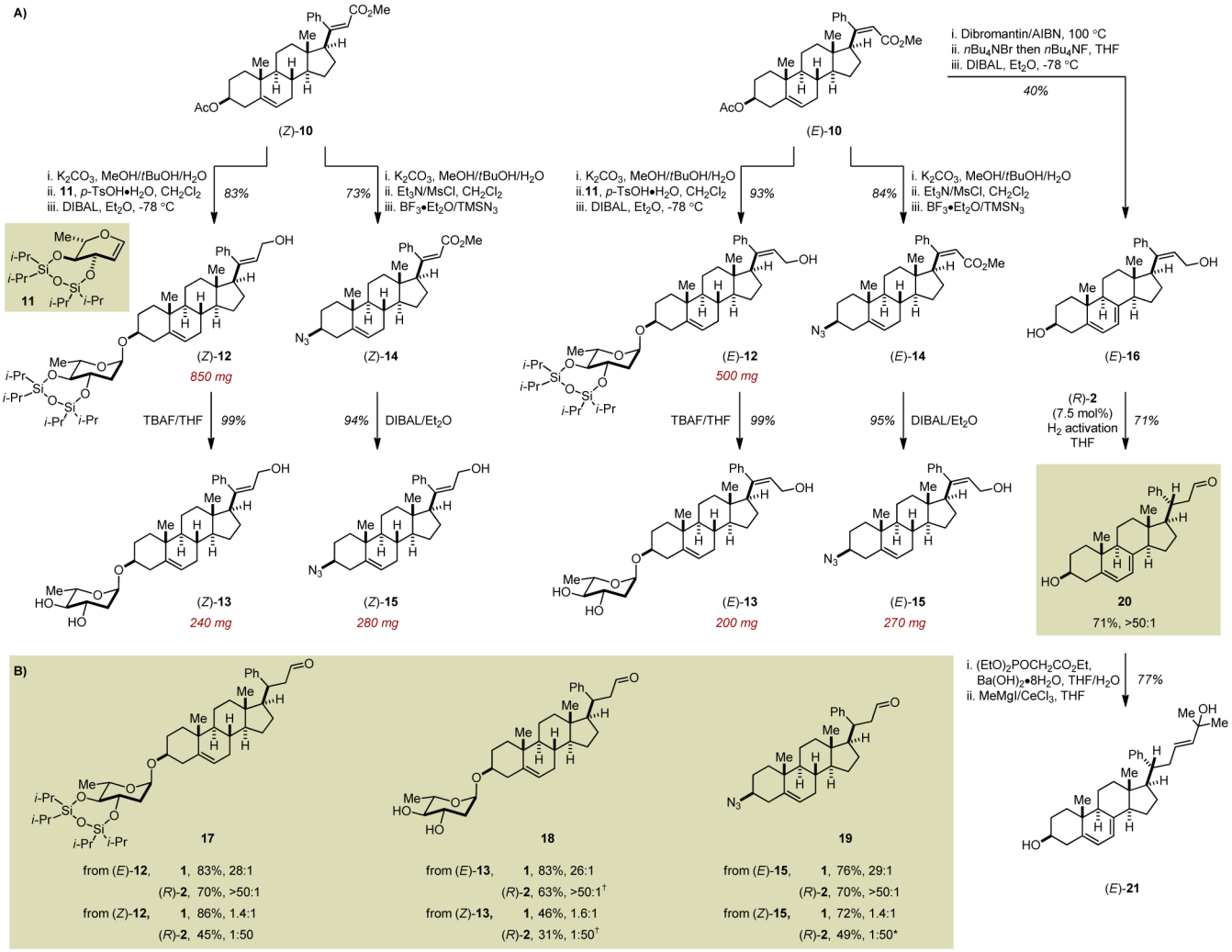

Figure 5. Isomerization of synthetically advanced steroidal allylic alcohols. (A) Synthetic variations around the pregnenolone scaffold to install representative structural motifs. (B) Stereospecific isomerization of these allylic alcohols with (*R*)-**2** provides access to the natural C20-(*R*) and unnatural C20-(*S*) epimers of the corresponding aldehydes. All ratios are indicated as C20-(*R*):C20-(*S*). †Partial deglycosylation was observed. *Isolated as the corresponding saturated alcohol.

directed hydrogenations using **1**.[23] Catalyst-directed diastereoselective isomerization reactions were next conducted with both enantiomers of the chiral iridium catalyst. Although only nominal amounts of aldehyde **8a** were detected when (*S*)-**2** was used for the isomerization of (*E*)-**7a** and (*Z*)-**7a**, catalyst permutation restored satisfactory reactivity. Due to match effects between the chiral catalyst and the chiral substrate, isomerization of (*E*)-**7a** with (*R*)-**2** delivered **8a** in 70% yield, essentially as a single diastereoisomer (C20-(*R*), >50:1 dr). More remarkably, isomerization of (*Z*)-**7a** gave **8a** in 28% yield and 1:50 dr in favor of the unnatural C20-(*S*) epimer, as confirmed by X-ray analysis of a benzoylated derivative (Supporting Information). Despite the low yield, the ability of the chiral catalyst to overcome the natural bias imposed by the substrate to such an extent is simply exceptional. Increasing the catalyst loading for the isomerization of (*Z*)-**7a** led to **8a** in 49% yield with a similarly high diastereoselectivity. Of important note, the remainder of these reactions consisted essentially of unreacted starting material.

Origin of Diastereoselectivity. Comparative analyses of the crystal structures of (*E*)-**7a** and (*Z*)-**7a** revealed informative to rationalize the stereoselective outcome of the isomerization reactions. Specifically, the orientation of the C═C bond of the allylic alcohols constitutes a determining parameter for substrate binding. Whereas the phenyl substituent points to the C12 region of the steroid scaffold in (*Z*)-**7a**, it is directed toward C16 in (*E*)-**7a**. Bidimensional NMR analyses of these two substrates are consistent with the solid state analyses and indicate that these orientations persist in solution. Strong NOE contacts were detected between the diastereotopic protons H23/H23′ and H12 and H17 in (*E*)-**7a**. A characteristic NOE interaction between H22 and H16 was clearly visible for (*Z*)-**7a**. No cross-peaks of chemical exchange were discernible (Supporting Information). Collectively, these observations support the existence of a locked conformation around C17−C20 for both olefin geometries (Figure 3B). Regarding the high steric prominence of the steroid scaffold, it seems reasonable to assume that the catalyst can only approach the allylic alcohol from the back side. Finally, the results obtained in the isomerizations with (*R*)-**2** suggest that the binding orientation of the olefin to the active iridium−hydride intermediate is identical for both substrates and that the C20 substituents are simply permuted. The much reduced reactivity of (*S*)-**2** is presumably due to the lack of efficient coordination of the catalyst to the substrate, likely because of a detrimental steric

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clash between the ligand substituents and the allylic alcohols substituents during back-side approach.[24]

Reaction Scope. The synthetic versatility of the present catalyst-directed diastereoselective isomerization was investigated next. All the aromatic and heteroaromatic steroid derivatives of our collection of (*E*) and (*Z*)-allylic alcohols were found to be suitable candidates (Figure 4). For (*E*)-configured substrates **7a**−**j**, catalyst **1** already provided the corresponding aldehydes in excellent yield and high diastereoselectivity (typically 20:1). The match effect obtained with the chiral catalyst (*R*)-**2** enabled to reach selectivity >50:1 in all cases. For (*Z*)-configured substrates **7a**−**j**, innate selectivities ranging from 1.4:1 to 2.7:1 were measured. As expected, when the chiral catalyst (*R*)-**2** was employed the yields in aldehyde were lower than for the (*E*)-isomers. Nevertheless, diastereoselectivities remained exceptionally high and the C20-(*S*) epimer was formally obtained as a single isomer in all cases. For the most sensitive derivatives, we found that the use of catalytic amounts of the noncoordinating base 2,6-di-*t*-Bu-4-methylpyridine (DTBMP) was beneficial to the reaction, supposedly because of its aptitude to quench traces of acid that may be generated upon iridium hydride decomposition.[25] Overall, the results obtained on 20 different aryl- or heteroaryl-containing substrates clearly demonstrate the remarkable ability of the chiral catalyst to overcome the innate bias imposed by the chiral steroidal scaffold. The compatibility of the method with electron-rich, electron-neutral, perfluorinated electron-deficient aryls, as well as nitrogen or oxygen containing heterocycles, must be particularly emphasized in view of potential applications in biological studies.[9c,d,26,27] Isomerization of (*E*)-**7k** and (*Z*)-**7k** with catalyst **1** proved more difficult as the resulting aldehydes were isolated in 40% and 23% yield. In both cases, the natural C20-(*R*) isomer was obtained preferentially (in 10:1 and 16:1 selectivity, respectively). Gratifyingly, isomerization of (*Z*)-**7k** with (*R*)-**2** allowed to reach an excellent selectivity level (>50:1). In the isomerization of (*E*)-**7k**, both the yield and selectivity dropped significantly. The (*S*)-**2** catalyst did not display any marked reactivity for these substrates. To probe the effect of the length of the alkyl substituent, allylic alcohols (*E*)-**7l** and (*Z*)-**7l** (R = *n*-Bu) were evaluated next. Unexpectedly, no aldehyde was obtained in their isomerization using the achiral catalyst **1**. Nonetheless, whereas isomerization of (*E*)-**7l** by (*R*)-**2** provided C20-(*S*)-**8l** in 67% yield and >50:1 selectivity, isomerization of (*Z*)-**7l** led to the exclusive formation of homoallylic alcohol (*E*)-**9**. Collectively, these results indicate that the electronic nature of the alkene substituent (aryl or heteroaryl vs alkyl) certainly influences site selectivity for migratory insertion of the iridium hydride. This may lead to unproductive isomerization or competing *E*/*Z* isomerization of the substrate and significantly obscure analysis of the stereoselective outcome of the reactions.[13b,g] In the case of small alkyl substituents, the absence of a fixed orientation of the alkene around C17−C20 cannot be excluded. Therefore, it seems premature to elaborate a solid selectivity model for purely alkyl substituted allylic alcohols at this stage of investigations.

Topological Diversification. Although our primary goal was to enable diversification in the closest vicinity of C20 (i.e., C21), the strategic use of the pregnenolone scaffold permits additional variations at crucial positions of the polycyclic domain and extension of the exocyclic side chain. This synthetic flexibility is particularly important for potential applications in pharmaceutical and medical sciences. For instance, steroid glycosides bearing a sugar moiety at C3 have been regularly employed in the treatment of congestive heart failure or as antitumor agents (i.e., ouagabin **D**, Figure 1A).[3,28] Moreover, steroidal alkaloids with an amino group at C3 often display significant antiangiogenic properties (i.e., squalamine **H**, Figure 1A).[3,29] Importantly, steroids with a $\Delta^{5,7}$-unsaturation (such as ergoserol **B** on Figure 1A) not only constitute pivotal biosynthetic precursors of cholesterol derivatives and vitamin D analogues,[1d] but they are also targets for the treatment of fungal infections.[30,31]

Starting from enoate (*Z*)-**10**, a sequential acetate deprotection/acid-catalyzed glycosylation using glucal **11** followed by DIBAL reduction furnished allylic alcohol (*Z*)-**12** bearing a disiloxane-protected glycosyl moiety at C3 with preferential α-selectivity (α/β: 5/1) in 83% overall yield (Figure 5).[32] Subsequent TBAF desilylation quantitatively delivered the corresponding polyhydroxylated allylic alcohol (*Z*)-**13**. Stereoretentive C3 azidation was performed by in situ treatment of the C3-mesylate derived from (*Z*)-**10** with $TMSN_3$ (1.5 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv).[33] Allylic alcohol (*Z*)-**15** was obtained quasi-quantitatively by reduction with di-isobutyl aluminum hydride. Derivatization of enoate (*E*)-**10** following identical synthetic routes afforded the complementary geometrical isomers of these allylic alcohols in uniformly high overall yields ((*E*)-**12** (α/β: 5/1), (*E*)-**13** and (*E*)-**15**). All these reactions were conducted on scales ranging from 200 to 850 mg, exemplifying the synthetic potential of the overall approach.[34] Finally, installation of the $\Delta^{5,7}$-unsaturation was accomplished by C7 radical bromination of enoate (*E*)-**10** followed by dehydrobromination using *n*-Bu_4NBr and *n*-Bu_4NF in THF. Simultaneous C3 deprotection and enoate reduction with excess DIBAL afforded the allylic alcohol (*E*)-**16**.[35] Both geometrical isomers of these synthetically advanced steroidal allylic alcohols were found to readily participate in the iridium-catalyzed isomerization with (*R*)-**2** to deliver the targeted aldehydes with excellent levels of C(20) stereocontrol (>50:1 C20-(*R*), 63−70% yield from (*E*)-configured substrates; 50:1 C20-(*S*), 31−49% yield from (*Z*)-configured substrates). Even though the suitability of the silyl-protected glycosyl fragment in (*E*)-**12** and (*Z*)-**12** was expected, the tolerance of the iridium catalyst vis-à-vis their polyhydroxylated analogues (*E*)-**13** and (*Z*)-**13** was more surprising as catalyst inhibition by the vicinal diols may have occurred. Similarly, the azide-containing substrates (*E*)-**15** and (*Z*)-**15** underwent highly selective isomerization affording the C20-(*S*) and C20-(*R*) epimers in acceptable and good yields, respectively. This clearly opens the possibility to access a variety of *N*-containing functional groups as well as to perform bioconjugation reactions by Staudinger ligations or Huisgen-type cycloadditions.[36] Isomerization of the $\Delta^{5,7}$-unstaturated derivative (*E*)-**16** with (*R*)-**2** proceeded very well (>50:1 C20-(*R*), 71% yield), despite our initial concerns regarding the compatibility of the *cis*−*cis*-1,3-diene moiety with the active iridium hydride intermediates.[37,38] Indeed, when (*E*)-**16** was tentatively isomerized with **1**, a 1:1 mixture of the $\Delta^{5,7}$- and $\Delta^{5,8}$-unstaturated aldehydes was obtained (Supporting Information). From this point, postisomerization diversification was demonstrated by exploiting the orthogonality offered by the different oxidation levels at C3 and C23. A two-step sequence (Horner−Wadsworth−Emmons olefination/double addition to the carbonyl) finally enabled to install the complete skeleton of the steroid side chain and gave access to a C20-(*R*) ergosterol analogue (*E*)-**21** (77% yield).[39,40]

CONCLUSION

In summary, we have developed a stereospecific catalytic strategy for the perfectly stereocontrolled installation of C20, the first

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tertiary stereocenter of the acyclic domain in steroid derivatives. Compared to other approaches, the catalytic isomerization reaction is remarkable for its mildness and high level of stereochemical predictability. The design of a uniform yet modular synthetic route to access a variety of steroidal primary allylic alcohols is another notable feature of our study. A range of allylic alcohols participates in the diastereoselective isomerization. Electron-rich and electron-poor aryl or heteroaryl substituents are particularly well-tolerated and the stereospecific nature of the reaction provides indifferently access to the natural C20-(*R*) and unnatural C20-(*S*) configurations, despite the strong innate bias imposed by the steroid scaffold. Alkyl containing substrates are more challenging as they affect regioselectivity of iridium−hydride insertion. Opportunity for postisomerization topological diversification was also demonstrated. Given the central role played by steroids in biological, pharmaceutical, and medical sciences, we expect our approach to become broadly applicable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06281.

Experimental procedures, spectroscopic data, spectrometric data and crystallographic details for compounds (*E*)-**7a**; (*Z*)-**7a**; (*Z*)-**7k**, (*Z*)-**25**; (*E*)-**9** and **27** (CCDC 1063427−1063432) (PDF)

Crystallographic data for all compounds (CIF)

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Notes

The authors declare no competing financial interest.

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