

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

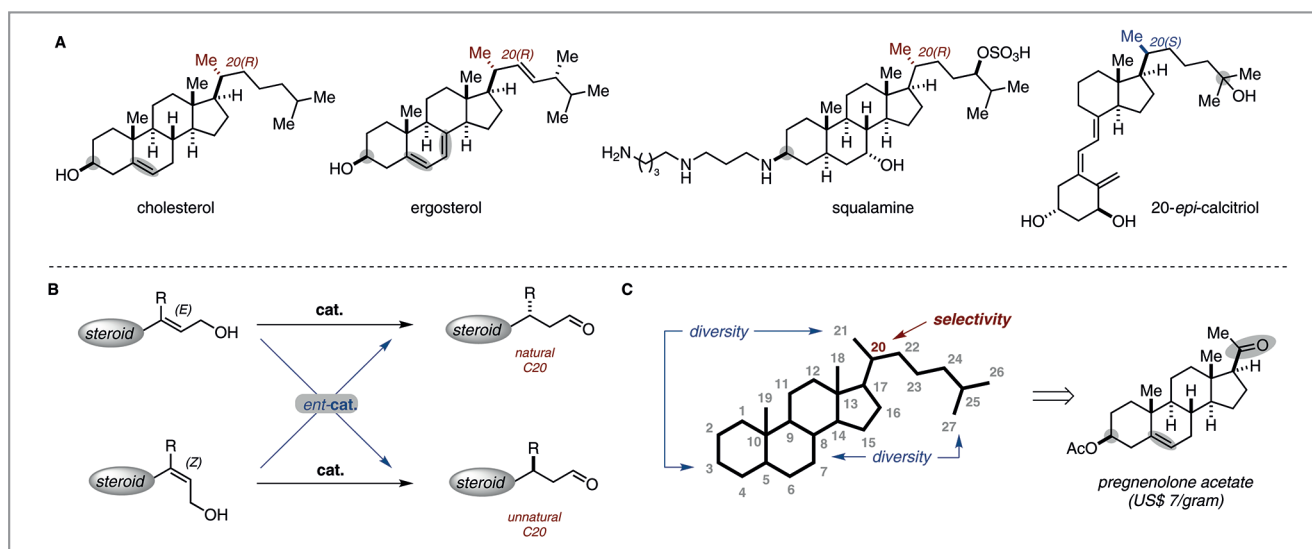
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Steroids are characterized by a prototypical cyclopentenophenanthrene ring system and a side chain attached to this polycyclic framework at C17. Driven by the distinguished biological activity differences between C20-(*R*) and C20-(*S*) isomers, the specific stereocontrolled construction of this exocyclic stereocenter is recognized as one of the most difficult challenges in the field (Review: *Chem. Rev.* **2014**, *114*, 6349). In 2010, Prof. S. Danishefsky pointed out that ‘One of the vexing problems in steroid total synthesis is that of exercising control of the configuration at C-20. The challenge is that of correlating the configuration of the presumably “freely rotating” C-20 with the resident stereochemistry of the polycyclic domain’ (*J. Am. Chem. Soc.* **2010**, *132*, 9567). The group of Professor Clément Mazet at the University of Geneva (Switzerland) has recently reported a stereospecific catalytic strategy for the perfectly stereocontrolled installation of C20, using a catalyst-directed diastereoselective isomerization of allylic alcohols.

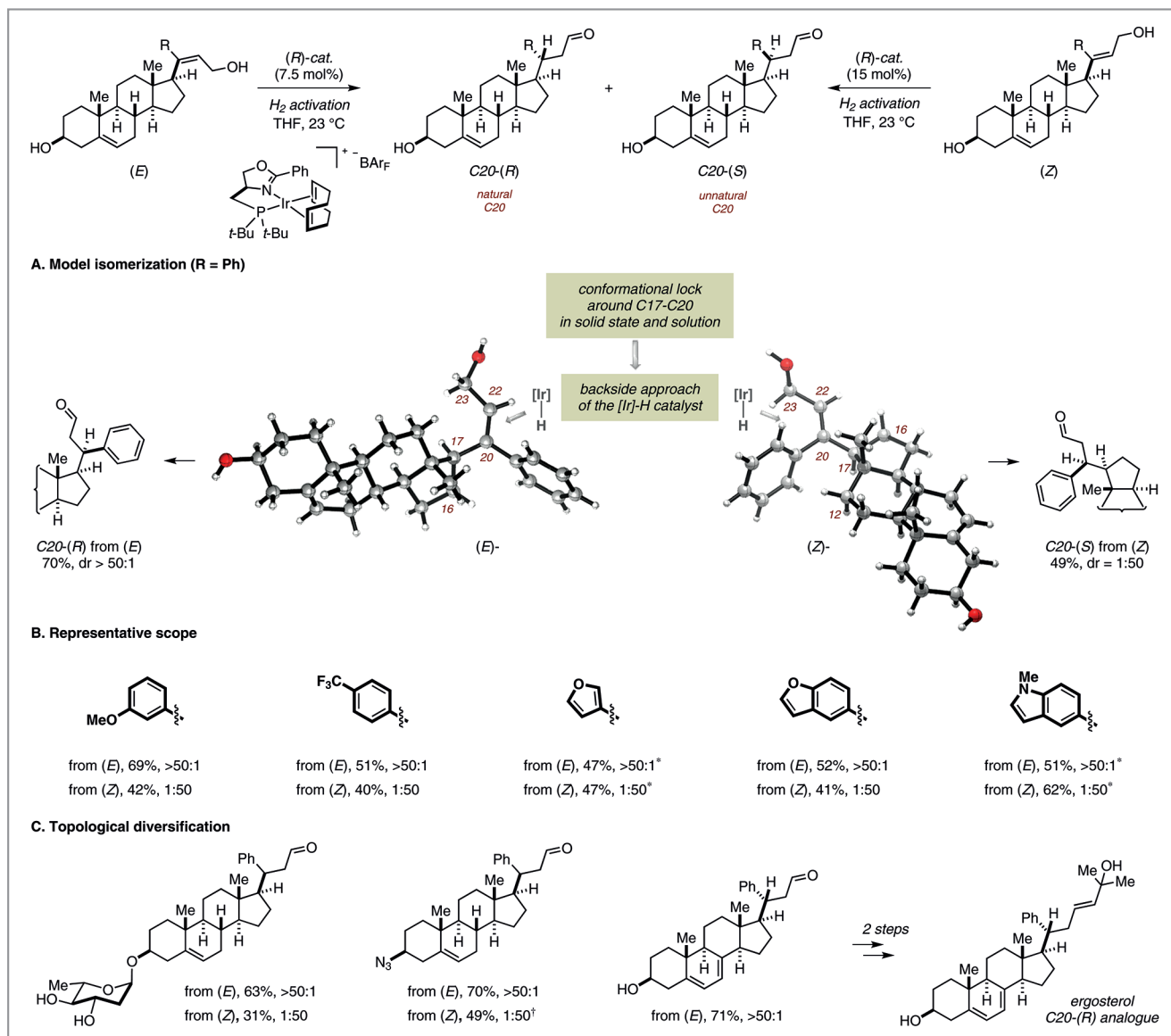
Professor Mazet said: “The portfolio of current methods to stereoselectively construct C20 is rather limited and these strategies all come with severe limitations. In most cases, two

distinct synthetic routes are needed to individually access each C20 epimer and a majority of these approaches follows long linear sequences employing stoichiometric rather than catalytic procedures.” He continued: “Repeated functional group manipulations often render these sequences lengthy and preclude rapid scale-up. Perhaps more importantly, ablation of the vicinal C17 stereocenter has been regularly practiced to facilitate stereocontrolled construction of C20 – indicating that installation of molecular complexity at one point of the molecule requires simplification on another part.”

Nominal modularity has been disclosed and almost invariably the steroidal derivatives possess a methyl substituent at C21. “As often in steroid chemistry, synthetic constraints preclude exploration of a chemical space that would match the contemporary standards for wide therapeutic investigations,” said Professor Mazet, continuing: “In order to facilitate structural diversification, at the outset of our investigations, we envisioned that an ideal strategy should be based on a common synthetic precursor and rely on the orthogonality provided by transition-metal-catalyzed cross-coupling methods.”



Scheme 1 Representative steroids and Mazet's strategy



Scheme 2 Stereocontrolled installation of C20 in steroids; all ratios are indicated as C20-(R):C20-(S). * A catalytic amount of 2,6-di-*tert*-butyl-4-methylpyridine is required. † Isolated as the corresponding saturated alcohol.

In essence, the authors in this work developed a uniform yet modular synthetic route to access a variety of steroidal primary allylic alcohols with aryl, perfluorinated aryl, heteroaryl and alkyl substituents with perfect control of the olefin geometry. Professor Mazet said: “The development of catalytic enantioselective reactions from prochiral substrates is a recurrent challenge in modern organic synthetic chemistry. Nevertheless, the development of diastereoselective methods from advanced intermediates possessing multiple stereogenic centers where a chiral catalyst must control the absolute con-

figuration of a given stereocenter independently of a highly complex environment certainly constitutes an even more demanding challenge.” Professor Mazet remarked: “We were pleased to achieve such high levels of diastereoselectivity in the catalyst-directed diastereoselective isomerization of steroidal allylic alcohols in both the match and mismatch situations (dr > 50:1).”

Compared to other approaches, the catalytic isomerization reaction is remarkable for its mildness and high level of stereochemical predictability. “A rationale based on the con-

formational lock of allylic alcohols around C17–C20 both in solid state and in solution has been proposed to account for the high diastereoselectivities observed,” explained Professor Mazet. A range of allylic alcohols containing electron-rich and electron-poor aryl or heteroaryl substituents are well tolerated and the stereospecific nature of the reaction provides access to the natural C20-(R) and unnatural C20-(S) configurations. Professor Mazet commented: “The scope of our method is further highlighted through structural diversification in the side chain and within the polycyclic domain of advanced and complex steroidal architectures.”

A number of challenges were encountered in this work. Professor Mazet revealed that the first challenge he and his co-worker met was the development of a short and modular synthetic route that would give access to geometrically pure (*E*)- and (*Z*)-allylic alcohols and simultaneously facilitate structural diversification. He said: “We spent half a year on this and were finally able to get straightforward access to geometrically pure steroidal (*E*)-enol tosylate and (*Z*)-enol triflate intermediates.” Professor Mazet acknowledged that the procedures independently reported by Tanabe (*Org. Lett.* **2008**, *10*, 2131) and Frantz (*Org. Lett.* **2008**, *10*, 2901) were instrumental in the successful development of this approach. High-yielding stereo-retentive Negishi cross-coupling reactions were performed from these key intermediates to enable structural diversification at C21. Professor Mazet said: “During this exercise, we were able to capitalize on some recent advances in Negishi cross-coupling reactions reported by the Buchwald group (*Angew. Chem. Int. Ed.* **2013**, *52*, 615). Once optimized, we also demonstrated that these reactions were amenable to multi-gram scales.”

Comparative analyses of the crystal structures of the model substrates chosen for establishing the method, as well as bidimensional NMR analyses, revealed the existence of a conformational lock around C17–C20 both in solid state and in solution for aryl-substituted allylic alcohols and enabled the authors to propose a rationale for the high levels of diastereoselectivity observed. Another challenge faced by the authors was that the heterocyclic-containing substrates proved particularly sensitive to traces of acid generated during the isomerization reaction – presumably upon decomposition of the active iridium hydride. Professor Mazet remarked: “To circumvent this issue, we found that the use of catalytic amounts of the non-coordinating base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was beneficial to the reaction.”

Professor Mazet recalled: “We have been working on the iridium-catalyzed isomerization of allylic alcohols for about seven years. After initially identifying conditions where a hydrogenation catalyst (i.e., Crabtree catalyst; *Tetrahedron Lett.*

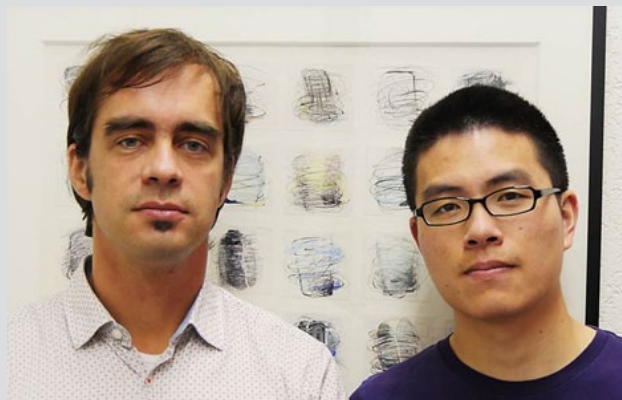
2009, *50*, 4141) could be turned exclusively into an isomerization catalyst, we subsequently developed several generations of chiral iridium complexes for the enantioselective variant of this transformation (*Angew. Chem. Int. Ed.* **2009**, *48*, 5143; *Chem. Commun.* **2010**, *46*, 445; *Chem. – Eur. J.* **2010**, *16*, 12736).” He continued: “Interestingly, it is only when exploring the catalyst-directed isomerization that we have been really delineating the functional group tolerance of our method. Specifically, the compatibility with unprotected sugar moieties, 1,3-diene motifs and azides was particularly unexpected.”

Concerning the future prospects of this work, because steroids with the epimeric non-natural C20 configuration [usually C20-(*S*)] are much rarer but distinguish themselves by significantly superior biological activities, the group believes that their findings have the potential to greatly simplify access to epimeric structural analogues of important steroid scaffolds for applications in biological, pharmaceutical and medical sciences.

Professor Mazet concluded: “Alkyl-containing substrates are more challenging at this stage as they affect regioselectivity of iridium–hydride insertion. More efforts are still needed in order to stereoselectively install C20 stereochemistry with alkyl substituents.”



About the authors



From left: Prof. C. Mazet, H. Li

Clément Mazet received his Ph.D. from the University of Strasbourg (France) under the supervision of Professor L. H. Gade (2002). After postdoctoral stays with Professor A. Pfaltz (University of Basel, Switzerland, 2003–2005) and Professor E. N. Jacobsen (Harvard University, USA, 2006–2007) he joined the University of Geneva (Switzerland) to establish his independent research program. His interests include mechanistic and synthetic chemistry with particular emphasis on all aspects of selective catalysis. He recently received the Zasshikai Lectureship Award from the University of Tokyo (2012) and the Werner Prize from the Swiss Chemical Society (2013).

Houhua Li studied carbohydrate chemistry under the supervision of Professor Xinshan Ye during his B.Sc. and M.Sc. degrees at Peking University (P. R. of China). In 2009 he moved to the National Institute of Biological Sciences (NIBS) and worked with Professor Xiaoguang Lei on Lycopodium alkaloid synthesis. He joined the University of Geneva (Switzerland) in 2011 to start his graduate studies in the group of Professor Clément Mazet. His research project focuses on Ir-catalyzed selective isomerizations of allylic alcohol.