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Hydrometallation-asymmetric conjugate addition: application to complex molecule synthesis†‡

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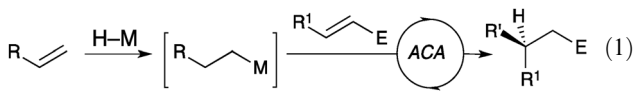
Copper catalysis allows alkyl zirconium species, generated *in situ* from alkenes, to undergo conjugate addition reactions. A hydrometallation-catalytic asymmetric 1,4-addition was used to synthesize either enantiomer of a natural product in one step from commercially available materials. Hydrometallation-addition sequences applied to steroids containing a cross-conjugated dienone or 1,6-acceptor give highly functionalized products.

The copper-catalyzed asymmetric 1,4-addition of unstabilized alkyl nucleophiles such as Grignard reagents, dialkylzincs and alkyl aluminiums has emerged as a powerful method for forming C–C bonds.[1–4] We recently reported that alkenes can be used as equivalents of premade alkylmetal species in catalytic asymmetric reactions *via* a process where an alkene undergoes hydrometallation, and the resulting organometallic species is used as a nucleophile in conjugate additions (eqn (1)).[5] Using the



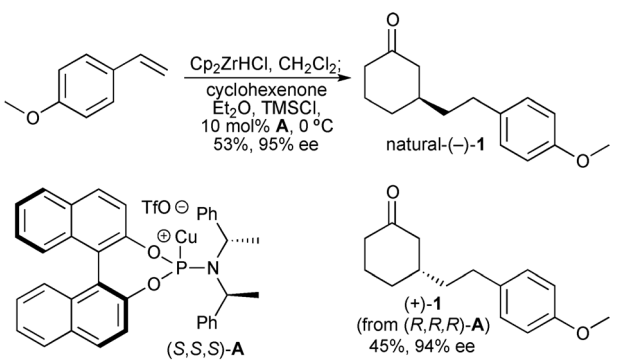
(1)

Schwartz reagent[6] as the hydrometallating agent, the resulting alkyl zirconium species[7] undergo copper-catalyzed enantioselective 1,4-addition at room temperature.[5] Here, we explore the application of this approach in the context of complex molecule synthesis.

We selected **1** as a simple target, for proof of concept that natural products could be synthesized using hydrometallation-asymmetric conjugate addition (HM-ACA). **1** is an aromatic compound isolated from the New Zealand liverwort *Balantiopsis rosea*.[8] Using the conditions shown in Scheme 1, natural (−)-**1** was synthesized in one step (53% yield, 95% ee) using catalyst (*S*,*S*,*S*)-**A** at 0 °C. These conditions gave slightly better results than experiments carried out at room temperature (37%, 90% ee). The unnatural enantiomer of the natural product ((+)-**1**) was synthesized (one step, 45% yield, 94% ee) using the other enantiomer (*R*,*R*,*R*, not shown) of the catalyst complex.‡ The CD spectrum of (−)-**1**,‡ is consistent with the natural material[8] and the absolute configuration shown.[9]

We decided to examine the method on more challenging substrates – commercially available steroids that contain additional functional groups, which could potentially interfere with conjugate addition processes (Fig. 1). 1,4-Androstadiene-3,17-dione (**2**) is a cross-conjugated dienone capable of 1,4-addition reactions, 1,2-additions to the dienone and ketone moieties, as well as other possibilities, such as rearrangement. Canrenone **3**, contains a lactone, and is capable of 1,2-, 1,4-, and 1,6-addition reactions. The products of hydrometallation-addition to **2** and **3** would be functionalized steroids, which are valuable compounds, for example cholesteryl benzoate was the first compound found to form chiral nematic liquid crystals,[10] and fulvestrant (Faslodex)[11] is an established breast cancer drug.[11–14]

Hydrometallation-addition of 1-hexene to **2**, catalyzed by copper complex (*S*,*S*,*S*)-**A** at room temperature, was found to



Scheme 1 One step synthesis of natural (−)-**1** and its enantiomer (+)-**1**.

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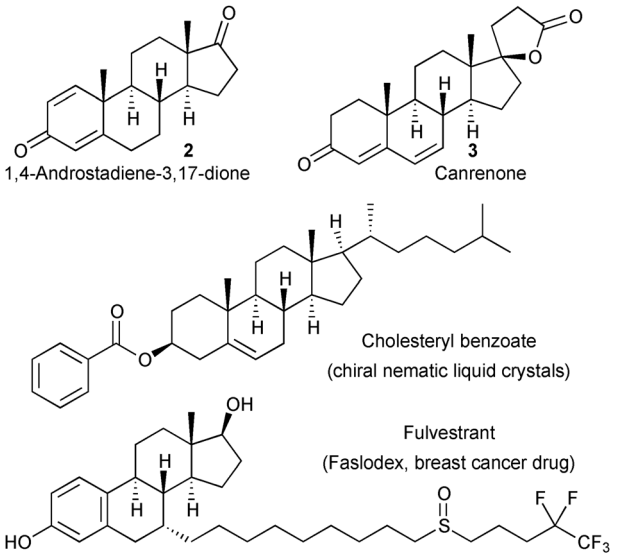


Fig. 1 Selected steroid derivatives.

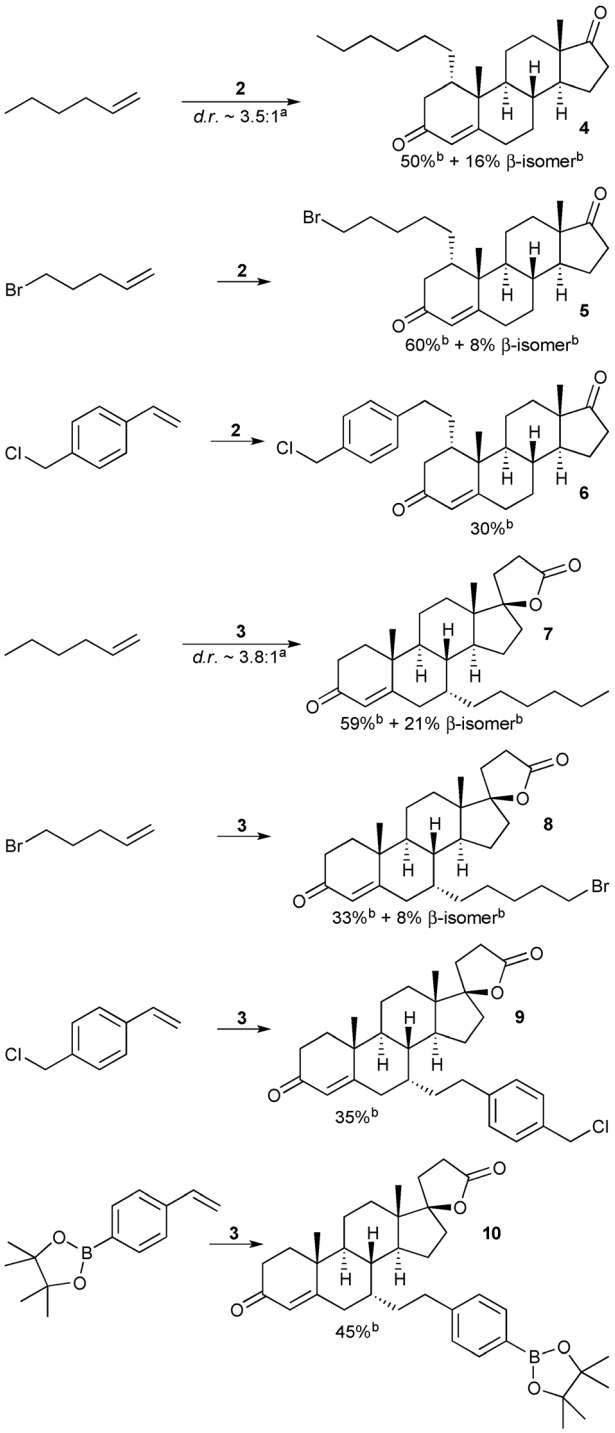
proceed in a 1,4-fashion to give a crude ~3.5 : 1 ratio¶ of diastereoisomers in favour of the 1-α-isomer **4**, which was isolated in 50% yield by flash column chromatography (Scheme 2). The 1-β-isomer could also be isolated in 16% yield. Hydrometallation-addition of functionalized alkenes to **2** illustrates that reactive functional groups such as bromides and benzyl chlorides are tolerated (see compounds **5** and **6**).

In the case of canrenone **3**, hydrozirconation of 1-hexene, followed by (*S*,*S*,*S*)-**A** catalyzed addition, favoured‖ the α-1,6-addition product **7**, which was isolated in 59% yield. A minor, β-isomer, 1,6-addition product could also be isolated in 21% yield.

We examined the possibility of adding functionalized alkenes to canrenone, and found that, while the yields are lower, alkenes and styrenes bearing reactive groups are surprisingly well tolerated. These reactions give steroids containing groups that should be useful handles for further derivatization – primary alkyl bromides (**8**), benzyl chlorides (**9**), and boronic esters (**10**). In the case of benzyl chloride **9** single crystal X-ray diffraction studies** confirmed the stereochemistry of the product (Fig. 2).

The addition of hard organometallic nucleophiles to steroids in 1,4-additions to cross conjugated enones[15–18] and 1,6-addition processes,[19–23] has previously been reported, but as far as we are aware, the functional group compatibility of reported procedures is much more limited than demonstrated here.[11,12,15–23] In comparison to relevant procedures, the hydrometallation – addition approach is operationally simple, convenient, and tolerates important functional groups – factors that may make these procedures useful[24,25] in the synthesis of medically important derivatives. We are also unaware of any reported procedures that use alkenes as the equivalents to sp^3 hybridized nucleophiles in conjugate addition reactions to steroids.

In conclusion, we have used alkenes as equivalents to premade alkyl-metal species in conjugate addition reactions.



Scheme 2 1,4- and 1,6-addition reactions to steroids. Conditions: alkene (2.5 eq.), Cp_2ZrHCl (2 eq.), CH_2Cl_2;(*S*,*S*,*S*)-**A** (10 mol%), steroid (1 eq.), Et_2O, room temperature. [a] Crude diastereomeric ratio determined by ^1H NMR spectroscopy. [b] Isolated yields.

We applied a hydrometallation-asymmetric conjugate addition sequence in the highly enantioselective one-step synthesis of a natural product. In the case of unsaturated steroids we examined a hydrometallation-addition sequence and found that copper catalyzed conjugate addition reactions readily occur, and functional groups are tolerated.

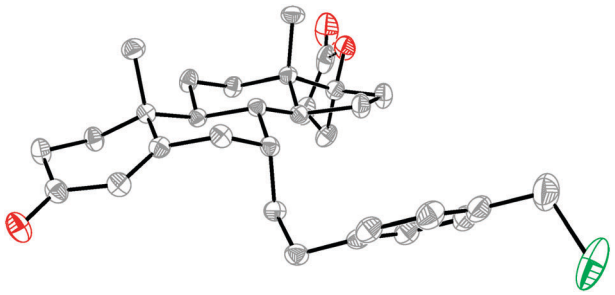


Fig. 2 X-ray crystal structure of **9**; atomic displacement parameters are drawn at 50% probability and hydrogen atoms are omitted for clarity.

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Notes and references

¶ Use of the (*R*,*R*,*R*)-enantiomer of complex **A** in the addition of 1-hexene to **2** showed a matched/mismatched effect. Here, the crude ratio of isomers was ~5 : 1 in favour of the α-isomer **4**. We also very briefly examined the hydrometallation-addition of 1-hexene to **2** promoted by the achiral copper sources $(CuOTf)_2$·PhH and CuBr·Me_2S,[26,27] – each gave α : β ratios >8 : 1, but in the case of $(CuOTf)_2$·PhH numberous minor byproducts were observed, and in the case of CuBr·Me_2S the reaction stopped after <25% conversion.

‖ Use of (*R*,*R*,*R*)-**A** in the addition of 1-hexene to canrenone altered the diastereoselectivity to favour the β-isomer, so that the α : β ratio was about ~1 : 2, as determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

** Single crystal X-ray diffraction data were collected at 150 K with an Oxford Diffraction SuperNova diffractometer and processed with CrysAlisPro as per the ESI.‡ The structure was solved with SuperFlip[28] and refined with CRYSTALS[29,30] including the Flack x parameter[31,32] which refined to −0.011(11) (unrestrained). CCDC 904095.

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