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Sequential enolboration/hydroformylation/aldol addition: a new one-pot cascade reaction for the regio- and diastereoselective formation of carbocyclic quaternary centres from acyclic olefins †

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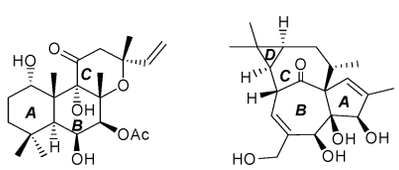
Starting from unsaturated carbonyl compounds a mild new cascade reaction involving enolboration, rhodium-catalysed hydroformylation and intramolecular aldol addition in a regio- and diastereoselective fashion leads to cyclic compounds containing highly-functionalised quaternary carbon centres.

The construction of quaternary carbon centres that retain a high amount of neighboring functionality is a persistent goal in natural product synthesis, since a good number of highly oxygenated, biologically active molecules like forskolin (**1**) (*AB*-fusion) and ingenol (**2**) (*ABC*-fusion) possess these particular structural characteristics. Methods resulting in the formation of quaternary carbon centres are numerous, but if desiring to perform this transformation in a diastereoselective[1] or enantioselective[2] fashion the number of available strategies drastically decreases. Therefore, in the realm of total synthesis, new methods resulting in the stereoselective formation of quaternary carbon centres are always in demand.



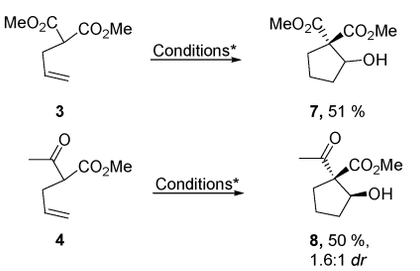
1 **2**

In our continuing investigations of C–C bond forming reactions in tandem with Rh-catalysed hydroformylation,[3] we extended our efforts to approach the issue of obtaining carbocycles of various ring sizes bearing such functionality *via* intramolecular regio- and diastereoselective aldol processes following a regioselective *n*-hydroformylation in a one-pot cascade reaction.

In order to accomplish this feat, alternatives to the known acid-catalysed and Mukaiyama variants[4] of activation towards aldol addition under hydroformylation conditions were necessary because of selectivity problems present when using compounds bearing more than one enolisable site. With this problem in mind, we explored the use of dialkylboron enolates, as they are known to affect high degrees of selectivity in intermolecular aldol additions.[5]

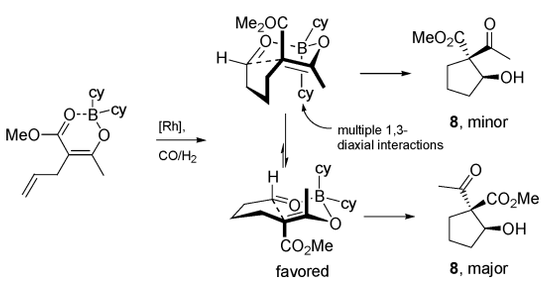
Malonate **3**[6] and the ketoesters **4**[7] and **6**[8] used in this study were prepared through the use of proven literature methods starting from dimethyl malonate or methyl acetoacetate.[9] Ketoester **5**[10] was prepared *via* Barbier-type addition of prenyl bromide to ethyl cyano-acetate followed by methylation.

An initial experiment was performed with dimethyl allylmalonate **3**, which was exposed to standard conditions for stereoselective *E*(O)-enolboration[11] prior to a regioselective *n*-hydroformylation in the presence of XANTPHOS[12] ligand to afford after oxidative workup dimethyl 2-hydroxy-cyclopentane-1,1-dicarboxylate (**7**) in 51%, a result which further extends the scope of the (*cy*-hex)$_2$BCl/Et$_3$N reagent combination to include activated esters such as malonates.[13] Now that the conditions required for enolboration were determined to be compatible with those required for regioselective hydroformylation, we proceeded to test whether the same protocol was successful with ketoester **4** (Scheme 1). After oxidative workup, the fragrant and volatile methyl 1-acetyl-2-hydroxy-cyclopentane-carboxylate (**8**) was isolated as the sole product in 50% yield as a 1.6 : 1 mixture of diastereoisomers as detected by NMR (see Scheme 1). ‡



Scheme 1 *Conditions* 1.05 eq (*cy*-hex)$_2$BCl, 1.05 eq. Et$_3$N, 0 °C, 0.9 mol% Rh(CO)$_2$(acac), 1.8 mol% XANTPHOS, 16 h, 60 bar CO/H$_2$, 80 °C.

The absence of a 7-membered ring adduct showed that under the conditions chosen, the enolboration does indeed proceed with complete regioselectivity to form the α,α-disubstituted boron enolate.[14] Additionally, this cascade reaction is accompanied by a small but significant degree of diastereoselectivity in the aldol addition. As depicted in Scheme 2, the amount of 1,3-diaxial interactions leading to the minor diastereoisomer is reduced in the ring-flipped chair transition state affording the major diastereoisomer.



Scheme 2 Transition states responsible for the observed diastereoselectivity in 5-membered ring formation.

† Electronic supplementary information (ESI) available: Full analytical data for all new compounds and NOE experiments conducted with **10**. See http://www.rsc.org/suppdata/ob/b4/b405120c/

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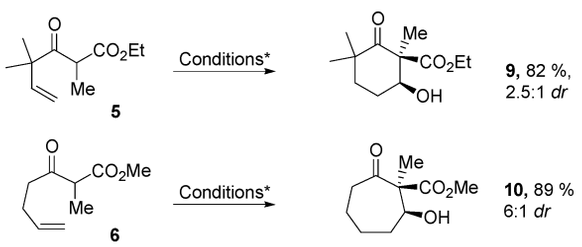
Next, the generation of 6- and 7-membered ring carbocycles was attempted by applying the same conditions to ketoesters **5** and **6**. In the case of **5**, the desired cyclization product ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexanecarboxylate (**9**) was obtained in 82% isolated yield as a 2.5 : 1 mixture of diastereoisomers. This product is potentially useful as a stereodefined building block, offering direct access to the *A*-ring system of forskolin (**1**) in one step.

Another encouraging result was obtained when ketoester **6** was subjected to the same conditions, resulting in the formation of the 7-membered ring of methyl 2-hydroxy-1-methyl-7-oxo-cycloheptane-carboxylate (**10**) as the sole product in 89% yield as a 6 : 1 mixture of diastereoisomers (Scheme 3). The suitability of this method to form functionalized β-hydroxycycloheptanones bearing α-quaternary centres in high yields and good diastereoselectivities is particularly attractive, since stereoselective methods leading to substituted 7-membered rings—such as the central *B*-ring of ingenol (**2**)[15]—are much less commonplace.



Scheme 3 *Conditions* 1.05 eq (*cy*-hex)$_2$BCl, 1.05 eq. Et$_3$N, 0 °C, 0.9 mol% Rh(CO)$_2$(acac), 1.8 mol% XANTPHOS, 16 h, 60 bar CO/H$_2$, 80 °C.

The relative configuration of the two stereogenic centres of compounds **9** and **10** was established by 1D gradient NOE experiments. A summary of the characteristic NOE interactions observed are shown for **10**—the compound obtained in the highest diastereoselectivity—in Fig. 1.

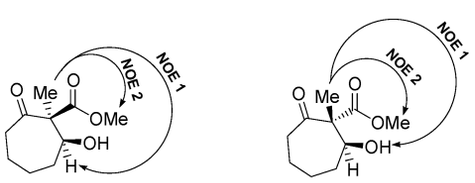
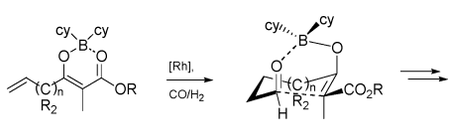


Fig. 1 Characteristic NOE interactions present in **10**.

The aldol addition in the latter cases proceeds with a considerably higher degree of diastereoselectivity when compared to the conversion of **4**. A potential transition state assembly that accounts for this can be seen in Scheme 4. The enolate geometry here again is determined by chelation during the enolboration prior to hydroformylation. After hydroformylation, chelation switches from the ester group to the aldehyde, resulting in a rigid bicyclic transition state for the aldol addition.



Scheme 4 Transition state responsible for the diastereoselectivity observed in 6- and 7-membered ring formation.

In summary, we herein report a new one-pot enolboration/hydroformylation/aldol addition cascade reaction, and demonstrate its utility in the regio- and diastereoselective synthesis of 5-, 6-, and 7-membered carbocycles bearing functionalised quaternary carbon centres starting from easily available unsaturated carbonyl compounds. The generation of the aldehyde from its olefin precursor allows for the initial enolboration of the preexisting carbonyl group to proceed selectively, which circumvents the more laborious construction of protected aldehyde substrates necessary to accomplish this transformation *via* intramolecular Lewis acid-mediated acetal cyclisation techniques.[16] Notably, the boron enolate tolerates the hydroformylation conditions and reacts immediately with the aldehyde group, thus preventing unwanted side reactions.

Acknowledgements

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Notes and references

‡ **Procedure for sequential enolboration/hydroformylation/aldol addition reactions.** Et$_3$N (1.05 eq. to carbonyl compound) was pre-complexed under an argon atmosphere with (*cy*-hex)$_2$BCl (1.05 eq.) in dry CH$_2$Cl$_2$ (5 mL) at 0 °C for 15 min. The unsaturated carbonyl compound in approx. 1 mL of solvent was then added slowly *via* syringe and the enolboration was allowed to stir for an additional 30 min before being transferred into the autoclave containing 0.9 mol% Rh(CO)$_2$(acac), 10–15 mL of solvent and 1.8 mol% XANTPHOS. The autoclave was then pressurised to 60 bar with equal pressures of CO and H$_2$ ***CAUTION!*** and heated overnight to 80 °C. Upon cooling the autoclave to RT, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue (~25 mL) along with 2 mL of conc. pH 7 phosphate buffer and 1 mL of 30% H$_2$O$_2$, and the reaction was allowed to stir overnight before being extracted with ether (100 mL), washed with sat. aq. NaHCO$_3$ (1 × 75 mL), dried and concentrated prior to further purification when necessary *via* flash chromatography or Kugelrohr distillation.

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