Stereocontrolled Coupling between Aldehydes and Conjugated Alkenals Mediated by TiIII/H2O

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ABSTRACT

In the presence of water, titanocene(III) complexes promote a stereoselective C−C bond-forming reaction that provides γ-lactols by radical coupling between aldehydes and conjugated alkenals. The method is useful for both intermolecular reactions and cyclizations. The relative stereochemistry of the products can be predicted with confidence with the aid of model Ti-coordinated intermediates. The procedure can be carried out enantioselectively using chiral titanocene catalysts.

The Michael-type addition of nucleophilic reagents to α,β-unsaturated carbonyl systems is one of the most powerful C–C bond-forming reactions in organic synthesis.1 Although aldehydes have electrophilic properties and their addition to Michael-acceptor groups might seem counterintuitive, ketyl radical anions can behave as nucleophilic radicals, thus encouraging the umpolung of aldehydes and facilitating their 1,4-addition to α,β-unsaturated carbonyl derivatives. In fact, SmI2-induced ketyl radicals have been demonstrated to mediate radical additions of aldehydes and ketones to α,β-unsaturated esters and nitriles.2 Nevertheless, radical coupling between aldehydes and conjugated alkenals has remained virtually unexplored to date.3 Here, we report that this novel, selective C−C bond-forming reaction can be promoted by bis(cyclopenta-
water, on the other hand, gives a mixture of reduction and pinacol coupling products. When we treated α,β-unsaturated geranial (1) with Cp₂TiCl (1 equiv) in the presence of water (100 equiv), however, instead of the expected reduction and pinacol coupling products we obtained an 86% yield of 4R*,5S* γ-lactol 2 (5:1 mixture of C-2 epimers) (Scheme 1). The structure and stereochemistry of 2 were established on the basis of spectroscopic techniques, including NOE experiments, and confirmed by oxidation to γ-lactone 3.

This Ti(III)/H₂O-promoted reaction was much more regioselective than the electrochemical reduction of geranial, in which stereoisomeric mixtures of 2 (head-to-tail) and pinacol (head-to-head) coupling products were obtained. Moreover, the Ti(III)/H₂O-promoted process proceeded not only regioselectively but also stereoselectively. Thus, the reaction of the geranial isomer neral (4) under the same conditions resulted in the formation of 4R*,5R* γ-lactol 5 (5:1 mixture of C-2 epimers) (Scheme 2).

The selectivity observed for the homocouplings of geranial and neral prompted us to explore Ti(III)/H₂O-induced cross-couplings between aldehydes (6, 7) and the conjugated alkenals (1, 4, 8, 9). The results (Table 1) confirm the viability of this method for the straightforward, selective synthesis of substituted γ-lactols and, consequently, γ-lactones. Both classes of compounds constitute very widespread motifs among natural terpenoids with biological activity.

In fact the cross-coupling processes proceeded with ratios of about 9:1 in favor of 4R*,5S* isomers (products 10, 13, 15, and 18) when utilizing E-conjugated alkenals 1 or 8. Similar ratios in favor of the 4R*,5R* isomers 14 and 19 were obtained with (Z)-alkenal 4. Gratifyingly, the combined γ-lactol yields ranged from an acceptable 62% for products 14 + 13, obtained from the coupling between 6 and 4, to an excellent 97% yield for products 18 + 19, obtained from the coupling between 7 and 1.13

In contrast to the lack of stereoselection shown by the electrohydrodimerization,3c,d the TiIII/H2O-induced couplings proved to be both stereoselective and stereospecific processes. This stereochemistry highlights the crucial role played by titanium during the coupling process, probably via substrate coordination. Bearing this idea in mind, the mechanism depicted in Scheme 3 may well account for the homocoupling of benzaldehyde.7b In the presence of water, however, titanium presumably coordinates with H2O to give aqua-complex 21 (Scheme 3a).14 After coordination (by ligand exchange) between 21 and a conjugated alkene such as 1 or 4, the inner-sphere single-electron transfer from TiIII would give a titanooxy-allyl-type radical such as 22 (Scheme 3b). In this titanooxy derivative the TiIV atom has only 16 e− in the valence shell and therefore could coordinate again with the oxygen atom of an aldehyde, such as 6, to give an intermediate such as 23. This intermediate shows the suitable spatial arrangement to facilitate the required overlap between the π-orbitals of the carbonyl group and the delocalized allylic radical (Scheme 3c). Thus the crucial coupling step from 23 to 24 might be viewed as a 7-endo-dig cyclization favored by Baldwin’s rules.15 Moreover, the stereoselective formation of 13 from the (E)-alkenal 1 and 14 from the (Z)-alkenal 4 strongly suggests a notable retention of the original alkene configuration in the delocalized allyl-type radicals 22 and 23. Subsequently, a second reduction of TiIV to TiIII by the excess of Zn used would facilitate the formation of 25, which would finally hydrolyze to 26 (presumably with the formation of a stable oxygenated titanium species), thus accounting for the formation of the corresponding γ-lactol 13 or 14.

From a mechanistic point of view, the Ti-mediated coupling between a delocalized allyl-type radical and a carbonyl group such as that depicted in Scheme 3 would be conceptually different from the SmI2-promoted coupling between ketyl radicals and conjugated carbonyl derivatives.2 Nevertheless, there has been a recent report suggesting an allyl-type radical addition to carbonyl compounds for the SmI2-promoted coupling of α,β-ununsaturated esters and amides to N-acyl oxazolidinones,10 which lends support to our mechanistic proposal.

Among naturally occurring bioactive terpenoids there are numerous substances containing a fused γ-lactol or γ-lactone ring with a stereodefined interanular junction in their molecule.12 Within this context we deemed that the intramolecular version of the TiIII/H2O-based reaction could provide a novel cyclization procedure that might considerably facilitate the synthesis of these often scarce natural products. To confirm this hypothesis we chose as target molecules the C-3 epimeric, trans-fused menthane lactones 27, which are components of Italo Mitcham black peppermint oil (Mentha piperita) and have interesting olfactory properties.17 On the basis of the anticipated cyclic intermediate 28 (adapted from

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**Scheme 3.** Proposed Mechanism for the Cp2TiCl/H2O-Promoted Cross-Coupling between 6 and 1 or 4

**a)** 21

**b)** 21 + R'CHO → R'CHO → OTiIV(Cl)Cp2 + H2O

**c)** 22 + 6 → 23

**d)** 23 + Zn → 24

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main regio- and stereochemical features observed for the cross-coupling between an aldehyde (represented by 6) and each of the two stereoisomeric conjugated alkenals (1 and 4).

It has been suggested that under anhydrous conditions dimer 20 is mainly responsible for the stereoselective pinacol

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(9) Lactol 2 was accompanied by a trace of its 4R*,5R* stereoisomer.

(10) Lactol 5 was accompanied by a minor amount (9%) of the pinacol coupling product (dilmesa, 3/2) and a trace of its 4R*,5S* stereoisomer.

(11) We utilized NOE studies as well as oxidation to the corresponding γ-lactones to confirm the stereochemistry of γ-lactols described in Table 1. For experimental details see Supporting Information.


(13) γ-Lactols 10–19 were accompanied by minor quantities (roughly 10%) of decanol or 3-phenylpropanol, presumably derived from the slow TiIII/H2O-promoted reduction of the excess (1 equiv) of 6 or 7 employed for these syntheses.

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We anticipated that \( \text{27} \) might easily be synthesized from the \((E)\)-alkenal \( \text{29} \) (Scheme 4).

Therefore, we prepared dialdehyde \( \text{29} \) from commercial citronellal and treated it with \( \text{Cp}_2\text{TiCl} \) (1 equiv) and water (100 equiv) for 6 h (Scheme 5).

As predicted by the analysis of model \( \text{28} \), we obtained a mixture of \( \text{trans} \)-fused \( \gamma \)-lactols (58% yield),\(^{19}\) the PCC oxidation of which provided menthane lactones \( \text{27a} \) and \( \text{27b} \) at a ratio of about 3/1.\(^{20}\) These lactones showed \( ^1\text{H} \) and \( ^13\text{C} \) NMR spectra matching those of the corresponding natural products.\(^{17}\)

Asymmetric catalysis plays a leading role in organic synthesis. Therefore we decided to attempt a catalytic and enantioselective version of our method. In this way we treated a mixture of \( \text{7} \) and \( \text{9} \) with a substoichiometric quantity of \( \text{Cp}_2\text{TiCl}_2 \) (0.2 equiv), Zn (8 equiv), \( \text{H}_2\text{O} \) (10 equiv), and 2,4,6-collidine hydrochloride (3 equiv), a titanocene-regenerating agent that can be recovered after the reaction by simple acid–base extraction.\(^{21}\) In this way we obtained an excellent 95% yield of \( \text{17} \), thus confirming the viability of the catalytic procedure. Moreover, when we employed commercial dichloro\((R,R)\)-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)\)-titanium(IV) (0.2 equiv) as precatalyst\(^5\) we obtained a 49% yield of \((\pm)\)-\( \text{17} \) ([\(\alpha\)]\text{D}\(^{25}\) = + 8.47) with roughly 33% ee.\(^{22}\) This ee is similar to that observed for Barbier-type reactions catalyzed by this chiral complex\(^{23}\) and despite its moderate value demonstrates that the method can be adapted for asymmetric catalysis.

In summary, we describe here a novel, stereoselective, C–C bond-forming method that provides \( \gamma \)-lactols by radical coupling between aldehydes and conjugated alkenals mediated by Ti\text{III} complexes in the presence of water. The reaction occurs at room temperature under mild conditions, fits the principle of atom economy, and is useful for both intermolecular reactions and cyclizations, and the relative stereochemistry of the products can be predicted with confidence with the aid of model intermediates such as \( \text{23} \) and \( \text{28} \).

Moreover, the procedure can be carried out enantioselectively using chiral titanocene catalysts. At the moment we are searching for new chiral titanocene catalysts to improve the ee values of this reaction.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Twenty-five percent dialdehyde \( \text{29} \) was recovered unchanged.
(20) Besides \( \text{27a} \) and \( \text{27b} \), a trace of a third \( \text{trans} \)-fused menthane lactone, the \( 3R^*,3aR^*,6aR^*,7aS^* \) diastereomer, was detected. GC–MS analysis indicated that these three lactones constituted more than a 96% of the mixture.
(22) Enantiomeric excess (ee) was determined on the acetyl derivative of \((\pm)\)-\( \text{17} \) with the aid of chiral lanthanide NMR shift reagents; see: Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. J. Org. Chem. 1987, 52, 2273–2276.