

# Stereocontrolled Coupling between Aldehydes and Conjugated Alkenals Mediated by $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$

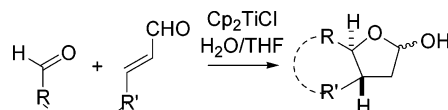
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## ABSTRACT



In the presence of water, titanocene(III) complexes promote a stereoselective C–C bond-forming reaction that provides  $\gamma$ -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  $\alpha,\beta$ -unsaturated carbonyl systems is one of the most powerful C–C bond-forming reactions in organic synthesis.<sup>1</sup> 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  $\alpha,\beta$ -unsaturated carbonyl derivatives. In fact,  $\text{SmI}_2$ -induced ketyl radicals have been demonstrated to mediate radical additions of aldehydes and ketones to  $\alpha,\beta$ -unsaturated esters and nitriles.<sup>2</sup> Nevertheless, radical coupling between aldehydes and conjugated alkenals has remained virtually unexplored to date.<sup>3</sup> Here, we report that this novel, selective C–C bond-forming reaction can be promoted by bis(cyclopenta-

dienyl)titanium(III) chloride<sup>4</sup> in the presence of water. Moreover, the commercially available enantiomerically pure Brintzinger complex<sup>5</sup> can catalyze the process enantioselectively.

In recent years,  $\text{Cp}_2\text{TiCl}$  has become a useful reagent in organic synthesis.<sup>6</sup> Thus, it is known that under anhydrous conditions  $\text{Cp}_2\text{TiCl}$  promotes and catalyzes the pinacol coupling of aromatic and  $\alpha,\beta$ -unsaturated aldehydes.<sup>7</sup> Treating an aromatic aldehyde with  $\text{Cp}_2\text{TiCl}$  in the presence of

(3) There are a few examples of the  $\text{SmI}_2$ -mediated intramolecular addition of aldehydes to conjugated alkenones: (a) Sato, A.; Masuda, T.; Arimoto, H.; Uemura, D. *Org. Biomol. Chem.* **2005**, *3*, 2231–2233. (b) Nguyen, T. C.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033–4036. We have also found two reports dealing with the electrohydrodimerization of  $\alpha,\beta$ -unsaturated aldehydes: (c) Barba, F.; de la Fuente, J. L.; Galakhov, M. *Tetrahedron*, **1997**, *53*, 5831–5838. (d) Johnston, J. C.; Faulkner, J. D.; Mandell, L.; Day, R. A., Jr. *J. Org. Chem.* **1976**, *41*, 2611–2614.

(4) Bis(cyclopentadienyl)titanium(III) chloride generated in situ by stirring commercial  $\text{Cp}_2\text{TiCl}_2$  with Zn dust in anhydrous THF exists as an equilibrium mixture of the monomer  $\text{Cp}_2\text{TiCl}$  and the dinuclear species  $(\text{Cp}_2\text{TiCl})_2$ ; see: Enemark, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864. For the sake of clarity, we represent this complex herein as  $\text{Cp}_2\text{TiCl}$ .

(5) Brintzinger's complexes dichloro[(*R,R*)-ethylenebis-(4,5,6,7-tetrahydro-1-indenyl)]-titanium(IV) and its enantiomer can be bought from commercial sources or prepared by the resolution of (*rac*)-ethylenebis-(tetrahydroindenyl)-titanium derivatives; see: Chin, B.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 5650–5651.

<sup>†</sup> University of Granada.

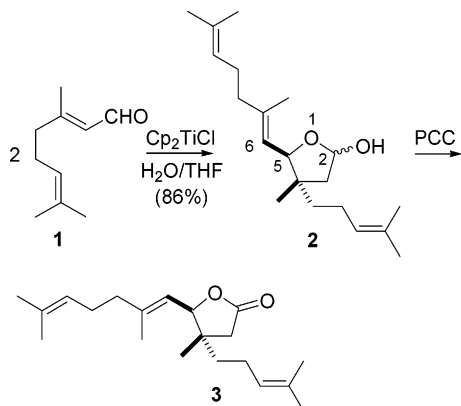
<sup>‡</sup> Kekulé Institut für Organische Chemie und Biochemie der Universität Bonn.

(1) (a) Carruthers, W.; Coldham, I. *Modern Methods of Organic Synthesis*, 4th ed.; Cambridge University Press: Cambridge, 2004; pp 19–27. (b) Smith, M. B. *Organic Synthesis*, 2nd ed.; McGraw-Hill: Boston, 2002; pp 794–798.

(2) For a review, see: Molander, G. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim: 2001; Vol. 1, pp 165–174.

water, on the other hand, gives a mixture of reduction and pinacol coupling products.<sup>8</sup> When we treated  $\alpha,\beta$ -unsaturated geranial (**1**) with  $\text{Cp}_2\text{TiCl}$  (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  $4R^*,5S^*$   $\gamma$ -lactol **2** (5:1 mixture of C-2 epimers) (Scheme 1).<sup>9</sup> The structure and stereochemistry of **2** were established

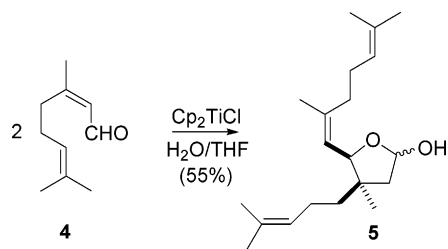
**Scheme 1.**  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -Promoted Homocoupling of Geranial



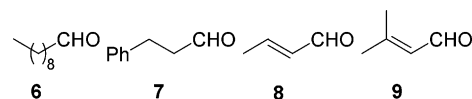
on the basis of spectroscopic techniques, including NOE experiments, and confirmed by oxidation to  $\gamma$ -lactone **3**.

This  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -promoted reaction was much more regioselective than the electrochemical reduction of geranial,<sup>3d</sup> in which stereoisomeric mixtures of **2** (head-to-tail) and pinacol (head-to-head) coupling products were obtained. Moreover, the  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -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  $4R^*,5R^*$   $\gamma$ -lactol **5** (5:1 mixture of C-2 epimers) (Scheme 2).<sup>10</sup>

**Scheme 2.**  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -Promoted Homocoupling of Neral



The selectivity observed for the homocouplings of geranial and neral prompted us to explore  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -induced cross-couplings between aldehydes **6** and **7** and the conjugated alkenals **1**, **4**, **8**, and **9**. The results (Table 1) confirm the



**Figure 1.**

viability of this method for the straightforward, selective synthesis of substituted  $\gamma$ -lactols and, consequently,  $\gamma$ -lac-

**Table 1.**  $\text{Cp}_2\text{TiCl}/\text{H}_2\text{O}$ -Promoted Cross-Couplings between Aldehydes (**6**, **7**) and Conjugated Alkenals (**1**, **4**, **8**, **9**)<sup>11</sup>

s.m. <sup>a</sup>	products (yields)
<b>6 + 8</b>	<b>10</b> (56%) <sup>b</sup> + <b>11</b> (7%)
<b>6 + 9</b>	<b>12</b> (72%) <sup>c</sup>
<b>6 + 1</b>	<b>13</b> (62%) <sup>c</sup> + <b>14</b> (5%)
<b>6 + 4</b>	<b>14</b> (55%) <sup>c</sup> + <b>13</b> (7%)
<b>7 + 8</b>	<b>15</b> (60%) <sup>b</sup> + <b>16</b> (7%)
<b>7 + 9</b>	<b>17</b> (63%) <sup>c</sup>
<b>7 + 1</b>	<b>18</b> (93%) <sup>c</sup> + <b>19</b> (4%)
<b>7 + 4</b>	<b>19</b> (72%) <sup>c</sup> + <b>18</b> (11%)

<sup>a</sup> s.m. = starting material. <sup>b</sup> Roughly 1:1 mixture of C-2 epimers. <sup>c</sup> Roughly 5:1 mixture of C-2 epimers.

tones.<sup>11</sup> Both classes of compounds constitute very widespread motifs among natural terpenoids with biological activity.<sup>12</sup>

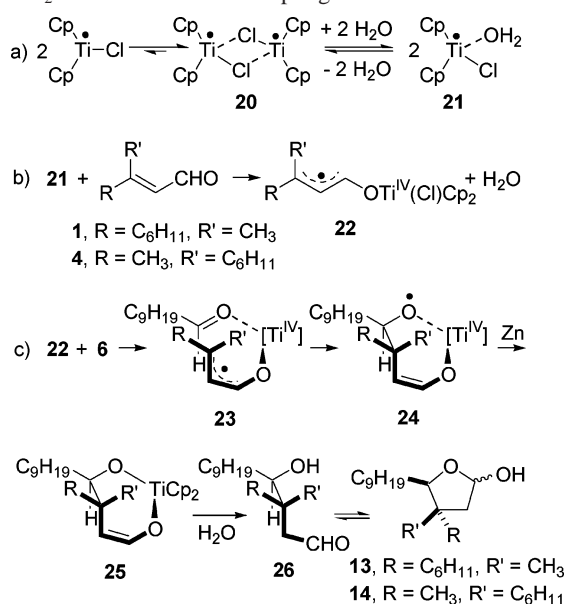
(6) For pioneering work, see: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997. For recent reviews, see: (b) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63–91. (c) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556–5573.

(7) (a) Enemærke, R. J.; Larsen, J.; Hjöllund, G. T.; Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2005**, *24*, 1252–1262. (b) Dunlap, M. S.; Nicholas, K. M. *J. Organomet. Chem.* **2001**, *630*, 125–131. (c) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070–2071. (d) Gansäuer, A. *Chem. Commun.* **1997**, 457–458. (e) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717–5718.

In fact the cross-coupling processes proceeded with ratios of about 9:1 in favor of 4*R*\*,5*S*\* isomers (products **10**, **13**, **15**, and **18**) when utilizing *E*-conjugated alkenals **1** or **8**. Similar ratios in favor of the 4*R*\*,5*R*\* isomers **14** and **19** were obtained with (*Z*)-alkenal **4**. Gratifyingly, the combined  $\gamma$ -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**.<sup>13</sup>

In contrast to the lack of stereoselection shown by the electrohydridimerization,<sup>3,c,d</sup> the Ti<sup>III</sup>/H<sub>2</sub>O-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

**Scheme 3.** Proposed Mechanism for the Cp<sub>2</sub>TiCl/H<sub>2</sub>O-Promoted Cross-Coupling between **6** and **1** or **4**



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

homocoupling of benzaldehyde.<sup>7b</sup> In the presence of water, however, titanium presumably coordinates with H<sub>2</sub>O to give aqua-complex **21** (Scheme 3a).<sup>14</sup> After coordination (by ligand exchange) between **21** and a conjugated alkenal such as **1** or **4**, the inner-sphere single-electron transfer from Ti<sup>III</sup> would give a titanoxo-allyl-type radical such as **22** (Scheme 3b). In this titanoxo derivative the Ti<sup>IV</sup> atom has only 16 e<sup>−</sup> 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  $\pi$ -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.<sup>15</sup> 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 Ti<sup>IV</sup> to Ti<sup>III</sup> 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  $\gamma$ -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 SmI<sub>2</sub>-promoted coupling between ketyl radicals and conjugated carbonyl derivatives.<sup>2</sup> Nevertheless, there has been a recent report suggesting an allyl-type radical addition to carbonyl compounds for the SmI<sub>2</sub>-promoted coupling of  $\alpha,\beta$ -unsaturated esters and amides to *N*-acyl oxazolidinones,<sup>16</sup> which lends support to our mechanistic proposal.

Among naturally occurring bioactive terpenoids there are numerous substances containing a fused  $\gamma$ -lactol or  $\gamma$ -lactone ring with a stereodefined interannular junction in their molecule.<sup>12</sup> Within this context we deemed that the intramolecular version of the Ti<sup>III</sup>/H<sub>2</sub>O-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.<sup>17</sup> On the basis of the anticipated cyclic intermediate **28** (adapted from

(8) Oller-López, J. L.; Campaña, A. G.; Cuerva, J. M.; Oltra, J. E. *Synthesis* **2005**, 2619–2622.

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

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

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

(12) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991.

(13)  $\gamma$ -Lactols **10**–**19** were accompanied by minor quantities (roughly 10%) of decanol or 3-phenylpropanol, presumably derived from the slow Ti<sup>III</sup>/H<sub>2</sub>O-promoted reduction of the excess (1 equiv) of **6** or **7** employed for these syntheses.

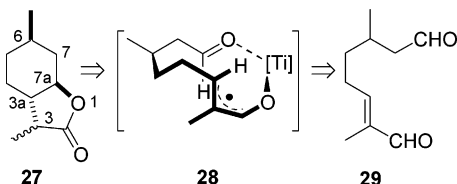
(14) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, 45, 5522–5526.

(15) In contrast, the pinacol-type coupling (head-to-head) would correspond to a 5-*endo-dig* cyclization disfavored by Baldwin's rules, thus explaining the regioselectivity toward head-to-tail coupling products observed. For Baldwin's rules, see: (a) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001; pp 1140–1144. (b) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, 38, 2939–2947. (c) Baldwin, J. E. *Chem. Commun.* **1976**, 734–736. (d) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Chem. Commun.* **1976**, 736–738.

(16) Hansen, A. M.; Lindsay, K. B.; Antharjanam, P. K. S.; Karaffa, J.; Daasbjerg, K.; Flowers, R. A., II; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, 128, 9616–9617.

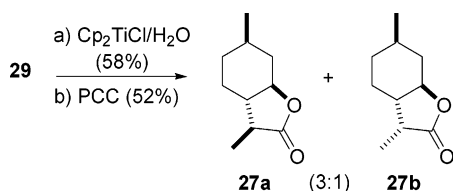
23), we anticipated that **27** might easily be synthesized from the (*E*)-alkenal **29** (Scheme 4).

**Scheme 4.** Retrosynthesis of **27** Based on the Anticipated Intermediate **28**



Therefore, we prepared dialdehyde **29**<sup>18</sup> from commercial citronellal and treated it with  $\text{Cp}_2\text{TiCl}$  (1 equiv) and water (100 equiv) for 6 h (Scheme 5).

**Scheme 5.**  $\text{Ti}^{\text{III}}/\text{H}_2\text{O}$ -Promoted Synthesis of *trans*-Fused Menthane Lactones **27**



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

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 **7** and **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.<sup>21</sup> In this way we obtained an excellent 95% yield of **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<sup>5</sup> we obtained a 49% yield of (+)-**17** ( $[\alpha]_{\text{D}}^{25} = +8.47$ ) with roughly 33% ee.<sup>22</sup> This ee is similar to that observed for Barbier-type reactions catalyzed by this chiral complex<sup>23</sup> 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  $\text{Ti}^{\text{III}}$  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 **23** and **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.

**Acknowledgment.** We thank the Spanish Ministerio de Educación y Ciencia for financial support (project CTQ2005-08402/BQU) and our English colleague Dr. J. Trout for revising our English text.

**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>.

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(17) Gaudin, J. M. *Tetrahedron* **2000**, *56*, 4769–4776 and references therein.

(18) Dawson, G. W.; Pickett, J. A.; Smiley, D. W. M. *Bioorg. Med. Chem.* **1996**, *4*, 351–361.

(19) Twenty-five percent dialdehyde **29** was recovered unchanged.

(20) Besides **27a** and **27b**, a trace of a third *trans*-fused menthane lactone, the  $3R^*, 3aR^*, 6R^*, 7aS^*$  diastereomer, was detected. GC–MS analysis indicated that these three lactones constituted more than a 96% of the mixture.

(21) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

(22) Enantiomeric excess (ee) was determined on the acetyl derivative of (+)-**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.

(23) Rosales, A.; Oller-López, J. L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628–2629.