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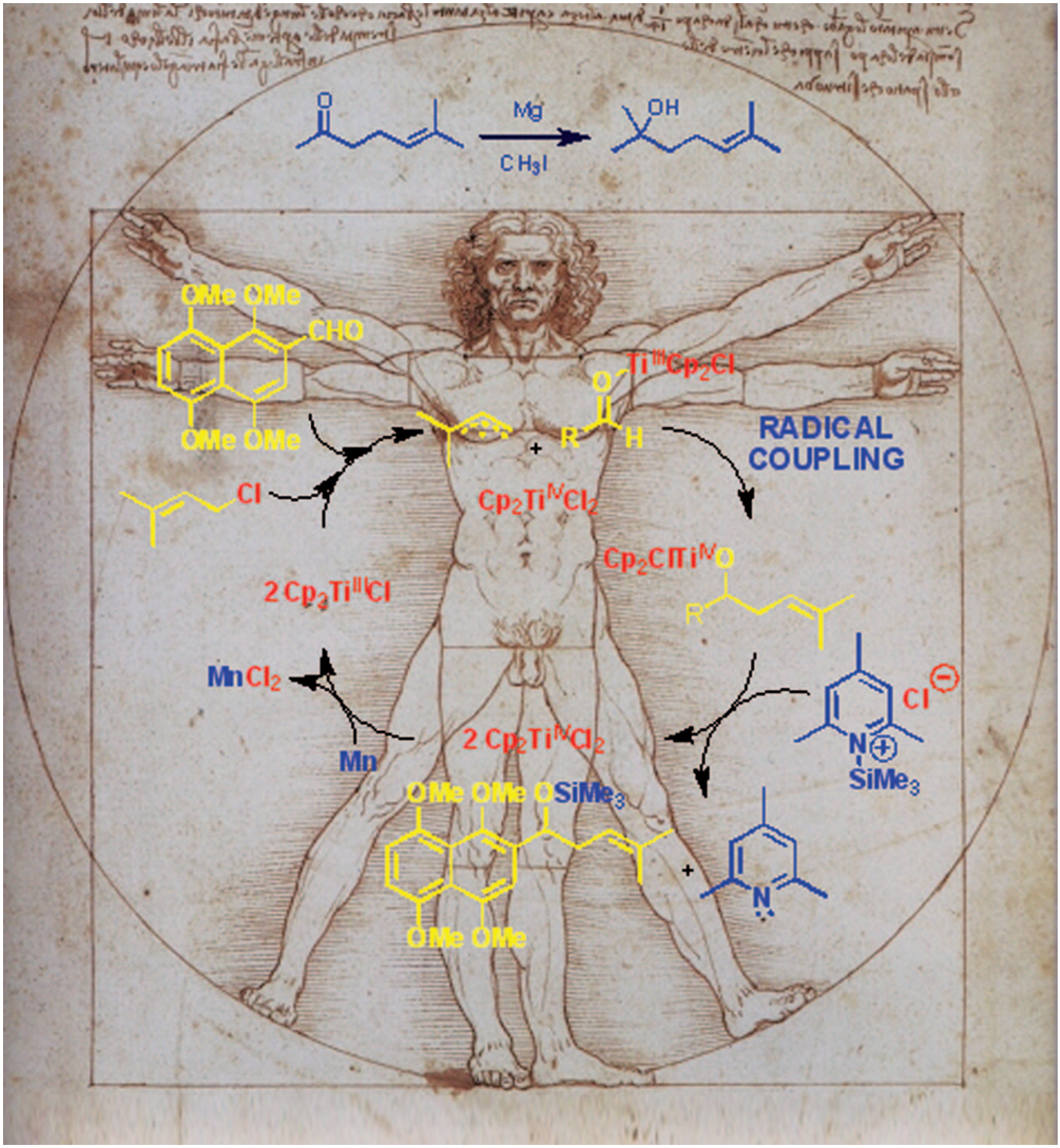
Ti-Catalyzed Barbier-Type Allylations and Related Reactions

Rosa E. Estévez,[a] José Justicia,[a] Btissam Bazdi,[a] Noelia Fuentes,[a] Miguel Paradas,[a] Duane Choquesillo-Lazarte,[b] Juan M. García-Ruiz,[b] Rafael Robles,[a] Andreas Gansäuer,[c] Juan M. Cuerva,*[a] and J. Enrique Oltra*[a]



Abstract: Titanocene(III) complexes, easily generated in situ from commercial Ti^{IV} precursors, catalyze Barbier-type allylations, intramolecular crotylations (cyclizations), and prenylations of a wide range of aldehydes and ketones. The reaction displays surprising and unprecedented mechanistic subtleties. In cyclizations a fast and irreversible addition of an allyl radical to a Ti^{III}-coordinated carbonyl group seems to occur. Intermolecular additions to conjugated aldehydes proceed through a coupling of a Ti^{IV}-bound ketyl radical with an allyl radical. Reactions of ketones with allylic halides take place by the classical addition of an allylic organometallic reagent. The radical coupling processes enable transformations such as the highly regioselective α-prenylation that are otherwise difficult to achieve. The mild reaction conditions and the possibility to employ titanocene complexes in only catalytic quantities are highly attractive features of our protocol. These unusual properties have been taken advantage of for the straightforward synthesis of the natural products rosiridol, shikalkin, and 12-hydroxysqualene.

Keywords: allylation · homogeneous catalysis · natural products · synthetic methods · titanium

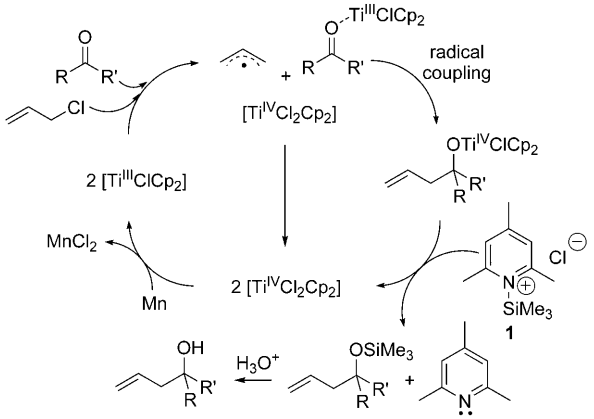
As long ago as 1899 Phillipe Barbier reported a coupling reaction between a ketone (6-methyl-5-hepten-2-one) and an alkyl halide (CH_3I) in the presence of a stoichiometric quantity of magnesium metal,[1] thus establishing the basis for the one step C–C bond-forming process currently known as the Barbier reaction.[2] The one-step strategy of this reaction is often more convenient than the two-step one (involving the preparation of the organometallic reagent and subsequent coupling with the carbonyl derivative) characteristic of Grignard-type processes. This is especially so in two cases. First, with allylic halides the Grignard reagent can be difficult to prepare in high yields.[3] Second, cyclization reactions can in principle be carried out efficiently only under the Barbier-type conditions.

Due to the considerable synthetic relevance of allylation reactions,[4] different transition metals have been assayed in Barbier-type allylations,[2,5] including Sn, Pb, In, Zn, Cr (the Nozaki–Hiyama–Kishi allylation),[6] and SmI_2 (the samarium Barbier reaction).[7] Nevertheless, the use of stoichiometric proportions of many of these metals has serious limitations due to their toxicity, low solubility causing problems in the reproducibility of results and/or high costs. Therefore, the development of novel, safer, and more sustainable reactions for the realization of Barbier-type allylations and related reactions remains an attractive and important goal.

Titanium, the seventh most abundant metal on earth, is one of the cheapest transition metals and a lot of titanium compounds are nontoxic and environmentally friendly.[8] Moreover, allyltitanium complexes have proven to be capable of reacting with carbonyl compounds with considerable chemo-, regio-, diastereo-, and even enantioselectivity.[8,9] These reactions, however, require stoichiometric quantities of the titanium complex, which is disadvantageous in the case of enantioselective additions. Moreover, due to the closed transition state of allylation reactions with organotitanium complexes, α-prenylations, which are important in natural product synthesis, cannot be realized.

In this context we deemed that titanocene(III) complexes (such as $[TiClCp_2]$ and others)[10] might be used in a Barbier-type strategy to transform allyl halides into allyl radicals, which would subsequently react with a carbonyl compound present in the medium. In this manner, new reactivity manifolds for addressing these regioselectivity issues might become available.

Additionally, with the aid of titanocene-regenerating agents such as **1** (generated by mixing Me_3SiCl and 2,4,6-collidine),[11] the process should become catalytic in titanium (Scheme 1).[12] Such a procedure is highly attractive for the



Scheme 1. Anticipated catalytic cycle for Ti-induced Barbier-type allylations.

[a] R. E. Estévez, Dr. J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, Dr. R. Robles, Dr. J. M. Cuerva, Prof. J. E. Oltra
Department of Organic Chemistry
University of Granada, Faculty of Sciences
C. U. Fuentenueva s/n 18071 Granada (Spain)
Fax: (+34) 958-248437
E-mail: joltra@ugr.es

[b] Dr. D. Choquesillo-Lazarte, Prof. J. M. García-Ruiz
Laboratorio de Estudios Cristalográficos
IACT, CSIC-University of Granada
P. T. Ciencias de la Salud, 18100, Granada (Spain)

[c] Prof. A. Gansäuer
Kekulé Institut für Organische Chemie und Biochemie
University of Bonn, Gerhard Domagk Strasse 1
53121 Bonn (Germany)

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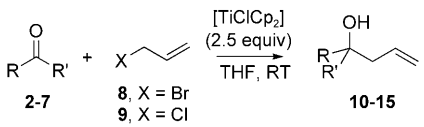
development of enantioselective Barbier-type allylations with enantiomerically pure titanium catalysts.

Here, we disclose a comprehensive study of our novel C–C bond-forming process that features Barbier-type allylation, intramolecular crotylation (cyclization), and prenylation reactions catalyzed by titanocene(III) reagents. We also describe the straightforward synthesis of the natural products rosiridol, shikalkin, and 12-hydroxysqualene via α-prenylations that are unprecedented with titanium.

Results and Discussion

Barbier-type allylations promoted and catalyzed by titanocene(III) complexes: For the last twenty years bis(cyclopentadienyl)titanium(III) chloride[10] has proven to be a useful single-electron-transfer agent to promote and catalyze the homolytic ring opening of epoxides,[13] pinacol couplings of conjugated aldehydes,[14] stereoselective couplings between aldehydes and conjugated alkenals,[15] Reformatsky-type processes,[16] divergent C–C bond-forming reactions with modulation by Ni or Pd,[17] and other free-radical-based transformations, thus becoming a formidable tool in organic synthesis.[18] [$TiClCp_2$] can be prepared by reaction between $TiCl_3$ and thallium cyclopentadienide,[13a] or simply generated in situ by stirring commercially available [$TiCl_2Cp_2$] with Zn or Mn dust,[10,13a] which is often the most convenient procedure from a practical point of view. It is known, however, that Zn is capable of promoting not only Reformatsky reactions,[19] but also Barbier-type allylations[5] and consequently might interfere in the titanium-mediated process. So, as it is believed that without an activating agent such as iodine or $ZnCl_2$ Mn does not promote Barbier-type allylations in THF,[20,21] we chose this metal to generate [$TiClCp_2$] in situ for the experiments described in this report.

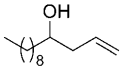
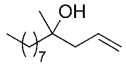
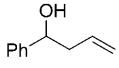
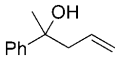
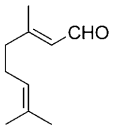
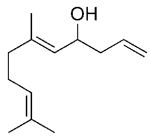
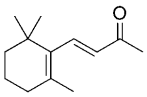
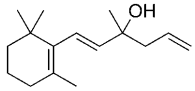
We started by exploring the experimental conditions suitable for optimizing the yields for the allylation of model carbonyl compounds, including aliphatic (**2**, **3**), aromatic (**4**, **5**), and α,β-unsaturated aldehydes and ketones (**6**, **7**), with allyl halides **8** and **9**, promoted by an excess of [$TiClCp_2$] (2.5 equiv) at room temperature (Scheme 2).



Scheme 2. Barbier-type allylation of carbonyl compounds **2**–**7** promoted by [$TiClCp_2$].

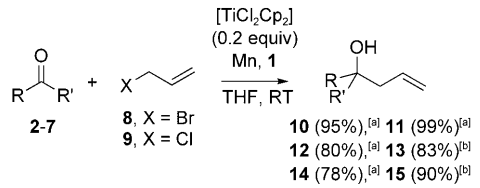
The best yields[22] for alcohols **10** (91%) and **11** (99%) were obtained by adding the allylic halide slowly into a previously prepared solution of [$TiClCp_2$] and the corresponding carbonyl compound (**2** or **3**) in THF (**8** and **9** provided similar yields; the best being set out in Table 1). This is probably because the slow addition of the halide partner minimizes the concentration of allyl radicals and thus reduces the possibility of radical–radical homocoupling side reactions, which would lead to undesirable Wurtz-type byproducts.[23] It is known, however, that aromatic and α,β-unsaturated aldehydes are prone to pinacol coupling in the presence of [$TiClCp_2$];[14] a side reaction that might also occur with conjugated ketones, although presumably at a slower rate due to steric factors. Therefore, we deemed that the experimental procedure should be changed for substrates **4**–**7**. In fact the best yields for alcohols **12** (75%), **13** (99%), **14** (85%), and **15** (92%; Table 1) were obtained by the simultaneous addition of allyl halide and carbonyl compound into a solution of [$TiClCp_2$] in THF. In this way the formation of pinacol-coupling byproducts was minimized. Allyl bromide (**8**) and allyl chloride (**9**) provided similar yields for tertiary alcohols **13** and **15**. In contrast, the use of chloride **9** instead of bromide **8** provided substantially lower yields for secondary alcohols **12** and **14**, possibly because the formation of an allyl radical from chloride **9** (BDE = 71.3 kcal mol^{-1})[24] was slower than from bromide **8** (BDE = 56.7 kcal mol^{-1})[24] and thus the fast pinacol coupling of conjugated aldehydes **4** and **6** predominated.

Table 1. Barbier-type allylation of carbonyl compounds **2**–**7** promoted by stoichiometric proportions of [$TiClCp_2$].

Electrophile	Halide	Product (yield)
 **2**	**8**	 **10** (91%)
 **3**	**8** or **9**	 **11** (99%)
 **4**	**8**	 **12** (75%)
 **5**	**8** or **9**	 **13** (99%)
	**8**	 **14** (85%)
 **7**	**9**	 **15** (92%)

Organometallic catalysis plays an important role in both laboratory and industrial organic synthesis.[25] Therefore we decided to assay a Ti-catalyzed version of our allylation process. To this end we treated carbonyl compounds **2**–**7** with halides **8** or **9** in the presence of a mixture of a substoichiometric proportion of [$TiCl_2Cp_2$] (0.2 equiv),[10] relatively

cheap Mn dust (8 equiv), and a combination of Me_3SiCl (4 equiv) and 2,4,6-collidine (7 equiv) to form the titanocene-regenerating agent **1**.[26] Thus we obtained good-to-excellent yields of homoallylic alcohols **10**–**15** (Scheme 3). A control experiment in the absence of titanium did not provide any coupling product.



Scheme 3. Titanocene-catalyzed allylation of **2**–**7**. [a] Yield obtained employing **8**. [b] Yield obtained employing **9**.

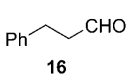
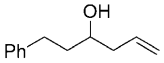
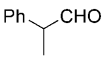
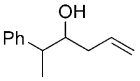
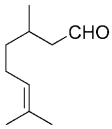
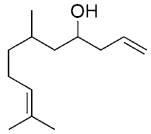
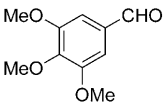
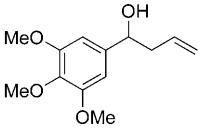
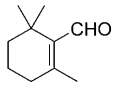
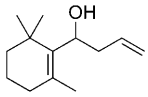
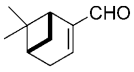
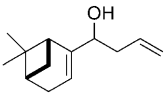
The results summarized in Scheme 3, obtained with titanocene quantities one order of magnitude lower than in the stoichiometric procedure, supported the viability of the catalytic version and pointed to the potential synthetic value of the Ti-catalyzed Barbier-type allylation process. The high yields obtained for allylation of ketones **3**, **5**, and **7** were especially intriguing, because some years ago Roy et al. reported that ketones did not react in Barbier-type allylations promoted by $[TiClCp_2]$ under the reaction conditions they used.[27] Our results demonstrate however that under our conditions $[TiClCp_2]$ can promote and catalyze the Barbier-type allylation of ketones to produce good yields of tertiary homoallylic alcohols.

Once we were confident about the synthetic potential of the Ti-catalyzed method we decided to explore its scope, limitations, and stereochemical behavior in more detail. To this end we assayed the $[TiClCp_2]$-catalyzed reaction of aldehydes **16**–**21** (Table 2), ketones **28**–**34** (Table 3), and functionalized carbonyl derivatives **42**–**46** (Table 4) with allylic halides **8** and **9**.

The results summarized in Table 2 suggested that the Ti-catalyzed procedure might become a general method for the allylation of aldehydes, including the selective 1,2-addition to α,β-unsaturated aldehydes such as **20** and **21**, with good yields. Additionally, a modest stereoselectivity was observed for the allylation of the α-substituted aldehyde **17** (*syn*/*anti*-isomers ratio 3:2). Moreover, the yields we obtained for these reactions employing stoichiometric proportions of $[TiClCp_2]$ were roughly similar to those presented in Table 2, lending weight to the idea that this catalytic cycle is effective.[28]

The results summarized in Table 3 confirmed that the procedure was also useful for the allylation of aliphatic, aromatic, and α,β-unsaturated ketones, including cyclic and acyclic ones. Additionally, the yields obtained from Ti-catalyzed reactions were roughly similar to those obtained employing stoichiometric proportions of $[TiClCp_2]$,[28] highlighting once more the usefulness of the catalytic version. It is known that in the allylation of 4-*tert*-butylcyclohexanone (**30**) by

Table 2. Titanocene(III)-catalyzed Barbier-type allylation of aldehydes **16**–**21**.

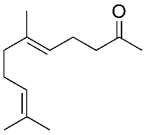
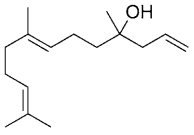
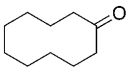
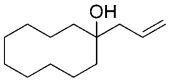
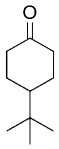
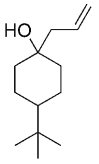
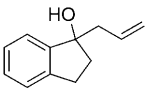
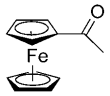
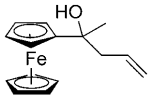
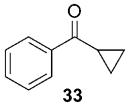
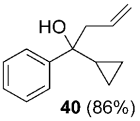
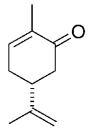
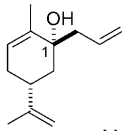
Aldehyde	X[a]	Product (yield)
 **16**	**8**	 **22** (84%)
 **17**	**9**	 **23** (71%)[b]
 **18**	**9**	 **24** (81%)[c]
 **19**	**8**	 **25** (70%)
 **20**	**8**	 **26** (89%)
 **21**	**8**	 **27** (81%)[c]

[a] Alkyl halide that provided the best yield. [b] Mixture *syn*/*anti* 2:3. [c] 1:1 mixture of diastereomers.

Nozaki–Hiyama–Kishi[29] and samarium Barbier[30] procedures, or with allylzinc[31] and allylindium[32] reagents, the equatorial attack prevails. Our Ti-catalyzed allylation of **30**, on the other hand, led mainly to the product derived from axial attack, which is comparable to the results obtained by Reetz et al. using previously prepared allyltitanium reagents.[33] This observation suggested that, for the intermolecular allylation of ketones at least, an alternative mechanism via an allyl-Ti^{IV} intermediate and subsequent nucleophilic attack to the carbonyl group could not be ruled out. As we will see later, this seems to be the case for the intermolecular prenylation of ketones (for a detailed mechanistic discussion see the above section devoted to Barbier-type prenylation reactions). Additionally, the considerable stereoselectivity observed for the Ti-catalyzed synthesis of **41** followed the same trend as the recently reported allylation of cyclohexenone **34** with stoichiometric proportions of allylmagnesium and allylindium species.[34] Our Ti-catalyzed procedure has the advantage that it does not require the preparation of stoichiometric quantities of any organometallic reagent. Finally, it should be noted that no cyclopropane rearrangement products were detected in the allylation of cyclopropyl ketone **33**.[35]

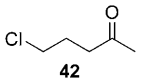
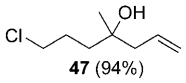
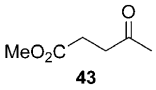
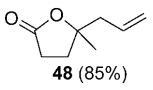
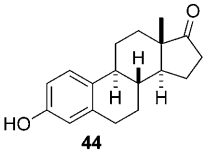
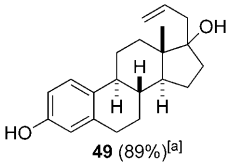
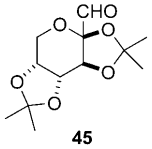
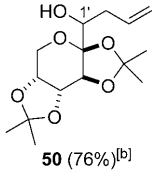
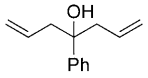
The results summarized in Table 4 indicate that under the mild conditions used the Ti-catalyzed procedure is compati-

Table 3. Titanocene(III)-catalyzed Barbier-type allylation of ketones **28**–**34**.

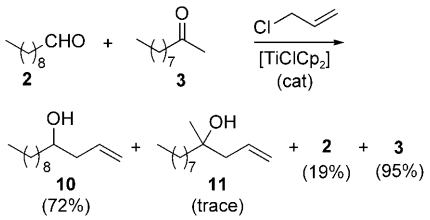
Ketone	X[a]	Product (yield)
 **28**	**8**	 **35** (98%)
 **29**	**9**	 **36** (85%)
 **30**	**9**	 **37** (98%)[b]
 **31**	**9**	 **38** (84%)
 **32**	**8**	 **39** (67%)
 **33**	**8**	 **40** (86%)
 **34**	**9**	 **41** (90%)[c]

[a] Alkyl halide. [b] Mixture of axial and equatorial attack products in a 2:1 ratio. [c] Together with the main product **41**, a minor proportion (8%) of its C-1 epimer was obtained.

Table 4. Titanocene(III)-catalyzed Barbier-type allylation of functionalized carbonyl derivatives **42**–**46**.

Substrate	X	Product (yield)
 **42**	**9**	 **47** (94%)
 **43**	**9**	 **48** (85%)
 **44**	**9**	 **49** (89%)[a]
 **45**	**9**	 **50** (76%)[b]
 **46**	**9**	 **51** (56%)

[a] Mixture of α and β-allyl derivatives at a ratio of 2:1. [b] 3:2 mixture of *R* and *S* epimers at C-1′.



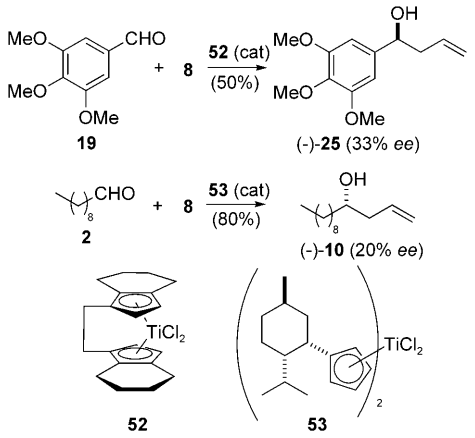
Scheme 4. Chemoselective Ti-catalyzed allylation of aldehyde **2** in the presence of ketone **3**.

ble with different functional groups, including alkyl halides, phenols, and ketals. Moreover, the easy lactonization that occurred after the allylation of keto ester **43** suggested that this procedure might become a useful tool for the synthesis of γ-lactones. Finally, the Ti-catalyzed allylation of benzoyl chloride **46** gave an acceptable 56% yield of the considerably labile, benzylic tertiary alcohol **51**, thus highlighting the mildness of our method.

Selectivity is one of the most desirable properties for novel methods in organic synthesis.[36] Therefore we assayed the capacity of this procedure for discriminating between aldehydes and ketones. The results of the competing experiment depicted in Scheme 4 indicated that the Ti-catalyzed allylation of aldehyde **2** was much faster than that of ketone **3**. This phenomenon might be advantageously exploited for the selective allylation of aldehydes in the presence of ketones.

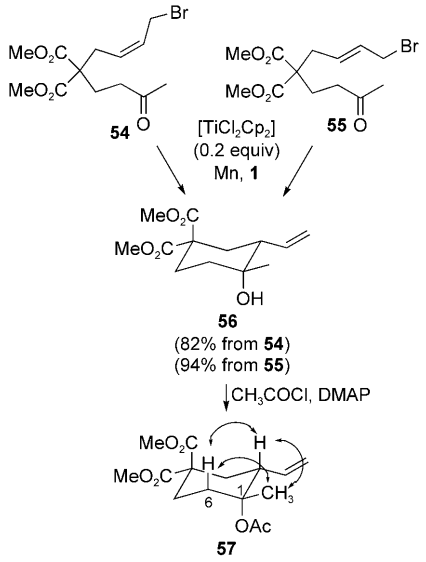
Asymmetric catalysis plays a crucial role in contemporary organic synthesis.[37] Therefore, we decided to assay some enantiomerically pure titanium catalysts to check the possibility of achieving enantioselective allylation processes using our Ti-catalyzed method. To this end we chose the commercial Brintzinger complex dichloro(*R*,*R*)-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)titanium(IV) (**52**) and Kagan's complex **53** prepared in our laboratory.[38]

Allylation of 3,4,5-trimethoxybenzaldehyde (**19**) catalyzed by **52** gave a 50% yield of (*S*)-(−)-**25**,[39] with a 33% enantiomeric excess (*ee*) (Scheme 5).[40] Moreover, the allylation of **2** catalyzed by **53** afforded an 80% yield of (*S*)-(−)-**10**,[41] with a 20% *ee*.[40] Despite these moderate *ee* values, the optical activity observed for products (−)-**10** and (−)-**25** demonstrated for the first time that Ti-catalyzed Barbier-type allylations can be conducted in an enantioselective manner by using chiral titanium catalysts.[12]



Scheme 5. Ti-catalyzed enantioselective allylations of **2** and **19**.

Ti-catalyzed intramolecular Barbier-type crotylations—stereoconvergent cyclization of allylic halides: The γ-regioselectivity and considerable diastereoselectivity of intermolecular carbonyl allylations with stoichiometric proportions of crotyltitanium reagents are well documented.[9,42] To the best of our knowledge, however, there is no precedent for intramolecular Barbier-type crotylations (cyclizations) catalyzed by any metal. In this context, we decided to assay the intramolecular version of our Ti-catalyzed procedure. Thus we prepared isomeric crotyl-type bromides **54** and **55**, and treated them with a substoichiometric proportion of [$TiClCp_2$] at room temperature (Scheme 6). In both cases

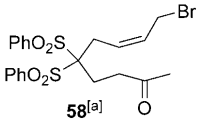
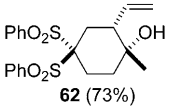
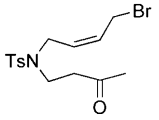
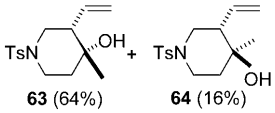
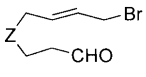
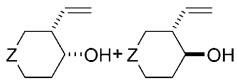
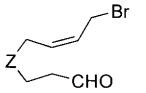


Scheme 6. Ti-catalyzed Barbier-type intramolecular allylation (cyclization) of **54** and **55** (double arrows indicate reciprocal NOEs observed for **57**).

we obtained good yields of vinyl cycloalkanol **56** (82 and 94% respectively) with excellent stereoselectivity (the 1*S**,2*R** diastereomer **73** was not detected). The relative configuration of **56** was assigned by comparing the chemical shift of its equatorial methyl group with that of sulfone **62** (vide infra)[43] and was confirmed by the NOE signals observed between the equatorial methyl group and the axial hydrogen atoms H-2 and H-6β of acetyl derivative **57** (Scheme 6). These results revealed the stereoconvergent character of this Ti-catalyzed cyclization process.

To gain information about the scope and limitations of the cyclization process we prepared ketones **58** and **59** together with isomeric aldehydes **60** and **61** and treated them with [$TiClCp_2$] (Table 5).

Table 5. Ti-promoted/catalyzed Barbier-type cyclization of aldehydes and ketones.

Substrate	Products (yield)	
 **58**[a]	 **62** (73%)	
 **59**[b]	 **63** (64%)	**64** (16%)
 **60**[b] Z=C(CO2Me)2	 **65** (30%)	**66** (27%)
 **61**[b] Z=C(CO2Me)2	**65** (36%)	**66** (34%)

[a] A stoichiometric proportion of [$TiClCp_2$] was used in this case. [b] A substoichiometric proportion of [$TiClCp_2$] was used in this case.

Ti-catalyzed cyclization of ketones **58** and **59** led mainly to products **62** and **63** respectively (Table 5), confirming the usefulness of this procedure for the stereoselective synthesis of not only cycloalkanols, but also piperidine derivatives. Additionally, tertiary alcohol **62** crystallized from diethyl ether and thus its structure and relative configuration could be established unambiguously by X-ray diffraction analysis (Figure 1). Moreover, the cyclization of sulfone **58** promoted by a substoichiometric quantity of [$TiClCp_2$] gave a 38% yield of **62** together with a minor proportion of **67**, its C-1 epimer (12%). Therefore, we could compare the physical properties of both diastereomers, including their NMR data.[43]

Intriguingly, the Ti-catalyzed cyclization of aldehydes **60** and **61** gave roughly 1:1 mixtures of isomers **65** and **66** with an almost complete loss of stereoselectivity. These results strongly suggested that the methyl groups of ketones **54**, **55**, **58**, and **59** played a crucial role in controlling the stereo-

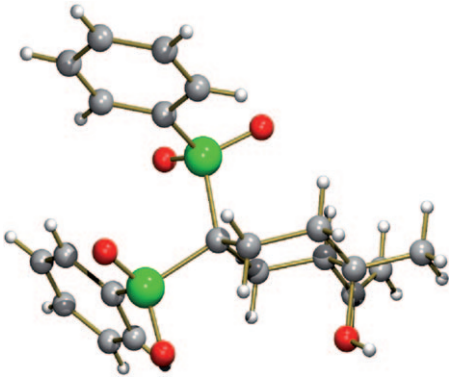
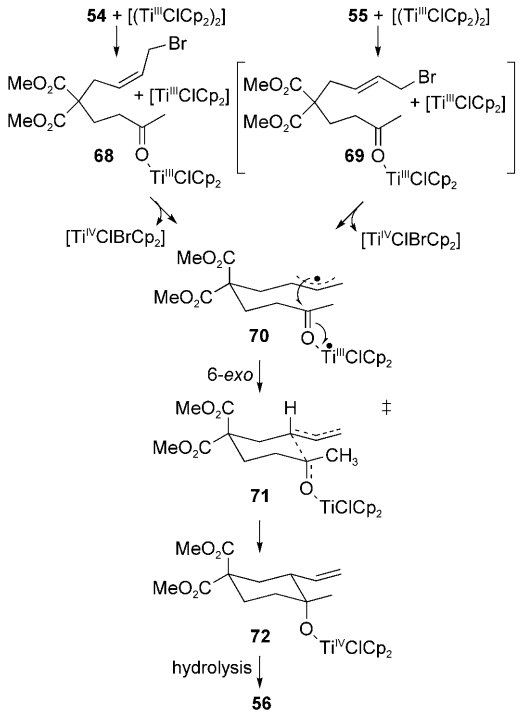


Figure 1. Three-dimensional structure of alcohol **62** established by X-ray diffraction analysis: C = gray, H = white, O = red, S = green.

chemistry of the cyclization process. The above observations are the basis for our mechanistic proposal in Scheme 7 outlined for isomeric ketones **54** and **55**.

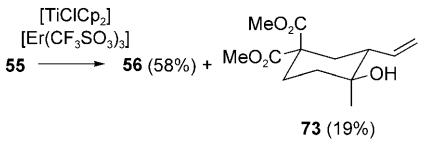


Scheme 7. Proposed mechanism for Ti-catalyzed Barbier-type cyclization of ketones (outlined for isomers **54** and **55**).

Our analysis commences with the coordination of the carbonyl group by the dimer species $[(TiClCp_2)_2]$ with the concomitant release of a monomer $[TiClCp_2]$ species in close proximity to the corresponding allylic halide.[10] Thus, despite of using substoichiometric proportions of the titanium catalyst, the dimer species can account for both carbonyl coordination and the subsequent halogen-atom abstraction processes. Ti–carbonyl coordination is essential for the activation of the carbonyl group and for the irreversible termination of the 6-*exo* radical cyclization,[44] which takes place immediately after the formation of the allylic radical **70**. Formation of the same radical intermediate (**70**) from both coordinated species **68** and **69** results in the stereoconvergent nature of our process. Finally, the stereoselectivity of the cyclization is governed by the pseudo-equatorial disposition of the methyl group in the transition state **71**. This enforces the radical attack from the *si* face of the ketone. In the case of aldehydes **60** and **61**, which lack the methyl group, radical attack can take place from both prochiral faces of the carbonyl group, resulting in an unselective overall reaction.

According to the above mechanism, Ti^{III} plays a triple role: it acts as a Lewis acid for carbonyl coordination, as a halogen-atom-trapping reagent for the generation of allylic radicals, and finally enforces the reductive termination of the overall process.

In this context it is interesting to use a second, redox-inactive, Lewis acid to compete with $[TiClCp_2]$ for carbonyl coordination, thus making the radical cyclization process reversible.[44] In this case, the allylic radical formed by Ti^{III} abstraction of the halogen atom could be trapped by a second Ti^{III} species, giving rise to an organometallic crotyl–Ti^{IV} intermediate. It is known that in the presence of a Lewis acid the reaction between crotyl–Ti^{IV} complexes and carbonyl compounds provides mixtures of diastereomers.[42a] Therefore, the decrease in stereoselectivity in the cyclization of a model ketone such as **55** can be regarded as a probe indicating the participation of an alternative mechanism via a crotyl-Ti^{IV} intermediate, followed by nucleophilic attack on the carbonyl group. As we expected, the treatment of **55** with a stoichiometric proportion of $[TiClCp_2]$ (2 equiv)[45] in the presence of the Lewis acid $[Er(CF_3O_3S)_3]$ (2 equiv) gave a mixture of isomers **56** (58% yield) and **73** (19%; d.r. = 3:1; Scheme 8). The minor isomer arises from the cyclization of



Scheme 8. Ti-promoted cyclization of **55** in the presence of Er^{III}.

a crotyl–Ti^{IV} intermediate. Moreover, when we treated **55** with $[TiClCp_2]$ in the presence of BF_3 etherate, a harder Lewis acid than $[Er(CF_3O_3S)_3]$,[46] we obtained a mixture of **56** (51%) and an increased proportion of **73** (33%; d.r. = 1.5:1), supporting the idea that the addition of Lewis acids can shift the cyclization mechanism from the radical coupling depicted in Scheme 7 to a nucleophilic γ-attack by a preformed crotyl–Ti^{IV} intermediate. The experiments described above allowed us to isolate the equatorial alcohol **73** and compare its physical properties, including NMR data, with those of the axial isomer **56**.[43]

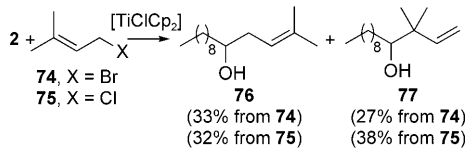
We subsequently assayed the cyclization of model ketone **55** with other titanium catalysts. Thus, the cyclization of **55** catalyzed by $[Ti^{III}Cl_2Cp]$ (generated in situ by stirring com-

mercial [$Ti^{IV}Cl_3Cp$] with Mn dust) gave a 64% yield of **56** (no **73** was detected) with the same stereoselectivity observed for [$TiClCp_2$]. In contrast, when we employed dichloro(*R*,*R*)-ethylenebis(4,5,6,7-tetrahydro-1-indenyl)titanium(IV) (**52**) as pre-catalyst we obtained a mixture of diastereomers (−)-**56** (36% yield; 20% *ee*)[47] and (−)-**73** (29%; 19% *ee*)[47] with a diastereomeric ratio (d.r. = 1.2:1) close to that obtained from the [$TiClCp_2$]-promoted cyclization in the presence of BF_3. These results suggest that the bulky Ti^{III} complex formed from **52** has considerably lower ketone-coordination ability than [$TiClCp_2$] or [$TiCl_2Cp$]. Moreover, it should be noted that the optical activity observed for both (−)-**56** and (−)-**73** strongly supports the idea that the titanium catalyst actually participates in the crucial C−C bond-forming step of the cyclization process.

To the best of our knowledge, this is the first metal-catalyzed Barbier-type cyclization described to date.

Barbier-type prenylations promoted and catalyzed by [$TiClCp_2$]: Isoprene units constitute the building blocks of natural terpenoids, in which they are generally linked in a "head-to-tail" manner, although occasionally they lie "head-to-head" (e.g., the central bonds of squalene and phytoene). In both cases, however, at least one of the isoprene units is linked at the α-position.[48] Therefore, α-prenylation reactions might facilitate the chemical synthesis of this valuable family of natural products. Unfortunately, few methods have been described for carbonyl α-prenylation and they require stoichiometric proportions of preformed organometallic complexes derived from light rare-earth elements, relatively expensive Sm, or reactive Ba, and generally provide mixtures containing variable amounts of γ-addition byproducts.[30,49] Moreover, it is known that both crotyl–Ti^{IV} and prenyl–Ti^{IV} complexes are prone to add to carbonyl compounds at the γ-position.[42] Nevertheless, we deemed that because of the potential free-radical nature of the coupling step of Ti^{III}-mediated Barbier-type allylations (see Scheme 1) this kind of reaction might afford a convenient procedure for the α-prenylation of carbonyl derivatives.[50]

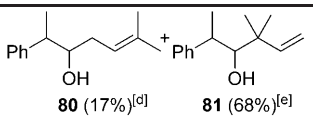
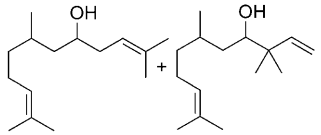
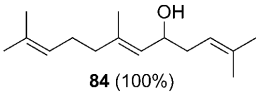
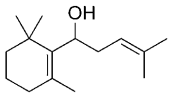
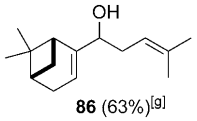
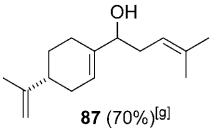
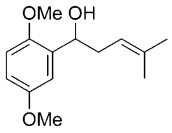
To check our hypothesis we treated decanal (**2**) with prenyl bromide (**74**) and prenyl chloride (**75**) in the presence of [$TiClCp_2$] (2.2 equiv; Scheme 9).



Scheme 9. Barbier-type prenylation of decanal (**2**) promoted by [$TiClCp_2$].

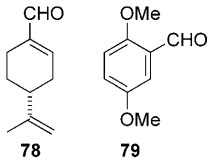
In both cases we obtained mixtures of α-addition (**76**) and γ-addition (**77**) products at a ratio of close to 1:1. We subsequently treated α-substituted (**17**) and β-substituted (**18**) aldehydes under similar conditions, thus obtaining mixtures of α- and γ-addition products at ratios of about 1:4 and 2:3 respectively (Table 6). However, Ti-promoted Barbier-type prenylation of conjugated aldehydes **6**, **20**, **21**, **78**, and **79**

Table 6. Ti-promoted Barbier-type prenylation of aldehydes.

S[a]	X[b]	Products (yield)	Y[c]
17	**74**	 **80** (17%)[d] **81** (68%)[e]	1:4
18	**75**	 **82** (39%)[f] **83** (58%)[g]	2:3
6	**75**[h]	 **84** (100%)	1:0
20	**74**[h]	 **85** (89%)	1:0
21	**75**[h]	 **86** (63%)[g]	1:0
78	**75**[h]	 **87** (70%)[g]	1:0
79	**75**[h]	 **88** (92%)	1:0

[a] S = substrate. [b] X = halide that provided the best yield. [c] Y = α/γ-prenylation products ratio. [d] 9:1 mixture of diastereomers. [e] 2:3 mixture of diastereomers. [f] 7:3 mixture of diastereomers. [g] 1:1 mixture of diastereomers. [h] A mixture of aldehyde and prenyl halide in THF was slowly added into a THF solution of [$TiClCp_2$].

generated only the desired α-prenylation products (**84**–**88**; Table 6). Regio- and stereospecific synthesis of product **84** showed the potential viability of this procedure to build "head-to-head" isoprene linkages in the synthesis of terpenoids.



We subsequently assayed the Ti-catalyzed version of our prenylation process. Thus, we treated aldehydes **2**, **6**, **18**, and **79** with halides **74** or **75** in the presence of a mixture of a substoichiometric proportion of [$TiCl_2Cp_2$] (0.2 equiv),[10] Mn dust, and a combination of Me_3SiCl and 2,4,6-collidine

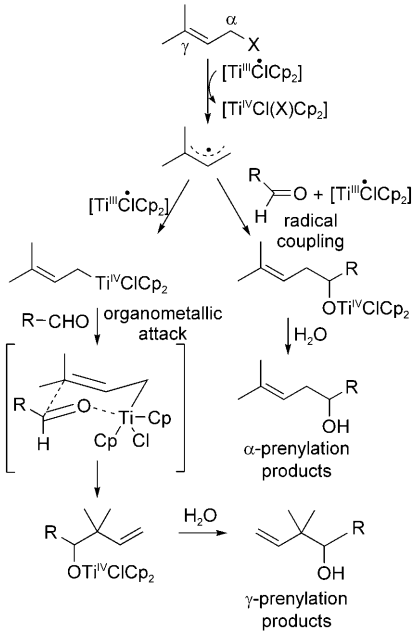
to form the titanocene-regenerating agent **1**.[26] In this way we obtained prenylation products **76**, **77**, **82–84**, and **88** (Table 7). The yields and regiochemical trends (α/γ-addition ratios) were similar to those obtained by using stoichiometric amounts of $[TiClCp_2]$ (Table 6), thus confirming the validity of the Ti-catalyzed procedure. What is more, the Ti-catalyzed version provided a slightly higher proportion of the preferred α-prenylated isomer **76**.

Table 7. Ti-catalyzed Barbier-type prenylation of aldehydes.

S[a]	X[b]	Products (yield)	Y[c]
2	**74**	**76** (38%) + **77** (16%)	7:3
18	**75**	**82** (36%)[d] + **83** (55%)[d]	2:3
6	**74**[e]	**84** (83%)	1:0
79	**74**[e]	**88** (89%)	1:0

[a] S = substrate. [b] X = halide employed. [c] Y = α/γ-prenylation products ratio. [d] 1:1 mixture of diastereomers. [e] A mixture of aldehyde and prenyl halide in THF was slowly added into a THF solution of a substoichiometric proportion of $[TiCl_2Cp_2]$, Mn dust, and **1**.

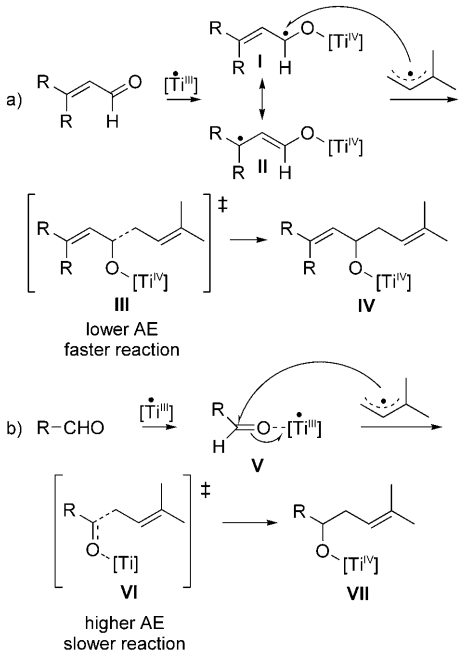
The dichotomy of the reaction is easily rationalized. The α-prenylation products are derived from the coupling between a prenyl radical and a carbonyl compound,[50] whereas γ-prenylation products originate from the nucleophilic attack of an organometallic prenyl–Ti^{IV} intermediate, via a cyclic transition state analogous to that reported by Sato et al. (Scheme 10).[51]



Scheme 10. Divergent pathways towards α- and γ-addition products from Ti-promoted Barbier-type prenylations.

Prenyl radical coupling to conjugated aldehydes is postulated to be fast and irreversible. Thus, prenyl radicals would not have the opportunity to be trapped by $[TiClCp_2]$ to form prenyl–Ti^{IV} derivatives and so only α-prenylation products were obtained. Prenyl radical coupling to nonconjugated aldehydes, and especially to those sterically hindered by α-substitution, such as **17**, may be assumed to be considerably slower than with conjugated aldehydes. Therefore, prenyl radicals could accumulate and be eventually trapped by $[TiClCp_2]$ to form prenyl–Ti^{IV} intermediates. Consequently, mixtures of α- and γ-prenylation products would be obtained, as was in fact observed.

The higher reactivity of conjugated aldehydes was confirmed by the following experiment. When we treated an equimolar mixture of decanal (1 equiv) and conjugated aldehyde **79** (1 equiv) with prenyl bromide (1 equiv) in the presence of $[TiClCp_2]$, we obtained only **88** (82% yield), the α-prenylation product from **79**. Products **76** and **77**, potentially deriving from the prenylation of decanal, were not detected. This difference in reactivity must be put down to a substantial difference between the activation energies (AEs) of the radical coupling steps for conjugated and nonconjugated aldehydes. In turn, the difference in AE may well derive from the different nature of the reactive intermediates involved in each coupling step (Scheme 11).

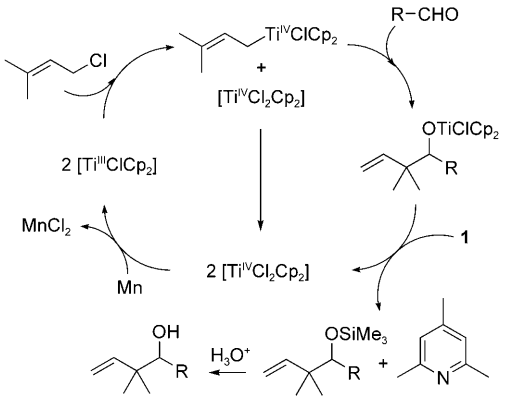


Scheme 11. Hypothetical reactive intermediates involved in the radical coupling step for a) conjugated and b) non-conjugated aldehydes.

It is believed that conjugated aldehydes are reduced by $[TiClCp_2]$ to mesomerically stabilized ketyl-type radicals that are also involved in the pinacol coupling reaction undergone by these aldehydes in the presence of titanocene-(III).[14] Therefore, the prenyl radical coupling of conjugated aldehydes (Scheme 11a) could have the character of a very fast radical–radical coupling, with a very low AE.[52] On the other hand, $[TiClCp_2]$ does not promote pinacol couplings of nonconjugated aldehydes because the corresponding ketyl-type radicals are not formed through single-electron transfer from Ti^{III}. Therefore, in the radical coupling step of

nonconjugated aldehydes (Scheme 11b) the π-bond of the Ti^{III}-coordinated carbonyl group has to be broken and consequently the energy of transition state **VI** increases. So it seems that in the prenyl radical coupling of nonconjugated aldehydes Ti^{III} also plays a triple role: it serves as a Lewis acid to activate the aldehydes towards radical attack, as a halide-abstracting reagent to generate prenyl radicals, and finally serves as a radical terminator to render the radical coupling step irreversible. In α-substituted aldehydes, such as **17**, carbonyl–Ti^{III} coordination is less favored due steric factors. Consequently the carbonyl π-bond is stronger and the radical coupling step slower, thus providing an increased proportion of γ-prenylation products.

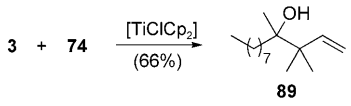
At this point, the possibility of two competing catalytic cycles for Ti-mediated Barbier-type prenylations (and probably also for simple allylations) of nonconjugated aldehydes should be considered. One of these, closely related to that depicted in Scheme 1, would proceed through the irreversible coupling between prenyl radicals and Ti^{III}-coordinated aldehydes, thus providing α-prenylation products. Another would proceed via a prenyl–Ti^{IV} intermediate and subsequent nucleophilic attack upon the carbonyl group, thus generating γ-prenylation isomers (Scheme 12).



Scheme 12. Alternative catalytic cycle for Barbier-type prenylation of non-conjugated aldehydes.

We were subsequently interested in the regiochemistry of Ti-promoted prenylation of ketones, which are intrinsically subject to higher steric hindrance than aldehydes. Therefore we treated 2-decanone (**3**) with prenyl bromide (**74**) in the presence of a stoichiometric proportion of [$TiClCp_2$]. In this way we obtained only γ-prenylation product **89** (66% yield; Scheme 13), whereas the corresponding α-prenylation isomer was not detected.

This result did not surprise us. It seems that carbonyl–Ti^{III} coordination in ketones is weaker than in nonconjugated aldehydes. Therefore, prenyl radical coupling is much slower and prenyl radicals are trapped by [$TiClCp_2$] to form prenyl–Ti^{IV} derivatives. In consequence, α-prenylation products cannot be formed and this represents one of the main limitations of the Ti-promoted α-prenylation method.



Scheme 13. Ti-promoted Barbier-type prenylation of ketone **3**.

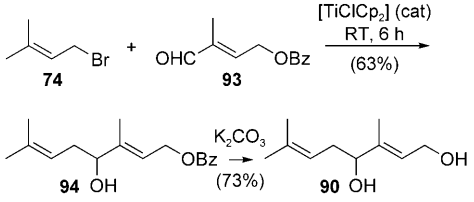
Finally, we assayed the α-prenylation of conjugated aldehyde **79** by using commercial complex **52** as a chiral titanium pre-catalyst. In this way we obtained a 21% yield of alcohol (−)-**88** (29% *ee*).[47] No γ-prenylation product was detected. The optical activity observed for (−)-**88** confirmed that the titanium catalyst actually participated in the crucial C–C bond-forming step of the intermolecular coupling process.

To the best of our knowledge the Ti-catalyzed α-prenylation procedure described above is the first metal-catalyzed α-prenylation method reported so far. The reaction proceeds at room temperature under mild conditions and in many cases might be more convenient than the previously reported carbonyl prenylation methods,[30,49] which require stoichiometric proportions of metal complexes that are not always easy to prepare. Moreover, in the case of conjugated aldehydes, the Ti-catalyzed method exclusively provides the desired α-addition product (regiospecificity), which is unusual among previously reported methods.

Ti-catalyzed synthesis of rosiridol, shikalkin, and 12-hydroxysqualene: The synthesis of natural products constitutes one of the most demanding tests of the viability of a new method in organic synthesis. Therefore we decided to try out Ti-catalyzed prenylation procedure by synthesizing some natural products. To this end we chose rosiridol (**90**), shikalkin (**91**), and 12-hydroxysqualene (**92**) as target molecules.

Rosiridol (**90**), a monoterpenoid isolated from different plants, has in the past been synthesized by heating to reflux a preformed prenyl–zinc complex with an isoprenic aldehyde closely related to **93** in THF (b.p. 66 °C) for 72 h.[53a] Shorter reaction times or lower temperatures provided a γ-prenylation product instead of the desired α-prenylation one, suggesting that the coupling reaction gave the γ-addition product, which, subject to prolonged heating, rearranged itself into the α-addition isomer.[53a] More recently, Lindel et al. have synthesized rosiridol through a BCl_3-promoted coupling between isoprenic aldehydes and a stoichiometric quantity of a previously prepared (from halides **74** or **75**) prenyl–tin complex at −78 °C.[53b]

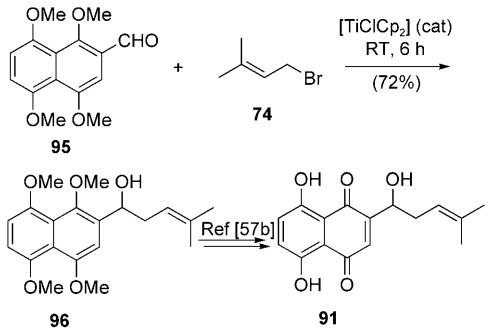
Using our novel method, we directly obtained rosiridol from halide **74** and aldehyde **93** (Scheme 14). The key Ti-



Scheme 14. Ti-catalyzed synthesis of rosiridol (**90**).

catalyzed, regiospecific α-prenylation step took place in 6 h at room temperature. To the best of our knowledge this is the first metal-catalyzed synthesis of rosiridol that proceeds at room temperature and does not require stoichiometric quantities of any organometallic reagent. This result highlights the usefulness of this procedure in constructing "head-to-tail" isoprene linkages for the synthesis of terpenoids.

Shikalkin (**91**) is a racemic mixture of (*R*)-shikonin and (*S*)-alkannin, metabolites derived from the roots of the oriental medicinal herb *Lithospermum erythrorhizon*[54] and the European plant *Alkanna tinctoria*.[55] These products have proved to possess a plethora of pharmacological uses, including anti-inflammatory, antibacterial, antifungal, antitumoral, analgesic and antipyretic, antithrombotic, immunostimulatory, angiostatic, and wound healing properties.[56] They have, therefore, been synthesized by several researchers.[55–57] One of the most convenient synthesis, conducted by Torii et al.,[57b] proceeds via alcohol **96**, prepared from the well-known aldehyde **95**[57a] in three steps and produces an overall yield of 46%. In contrast, the Ti-catalyzed prenylation of **95** directly provided a 72% yield of **96**. Thus we completed the formal synthesis of shikalkin (Scheme 15) and improved

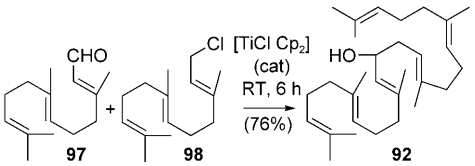


Scheme 15. Ti-catalyzed formal synthesis of shikalkin (**91**).

considerably upon Torii's procedure.

12-Hydroxysqualene (**92**), the major product from the biotransformation of presqualene diphosphate catalyzed by the enzyme squalene synthase in the absence of NADPH, is apparently produced by water attack upon the carbocation intermediate precursor of squalene biosynthesis.[58] Yamamoto and co-workers are responsible for the only chemical synthesis of **92** described to date, by treating (*E*,*E*)-farnesal (**97**) with an stoichiometric proportion of the preformed allylic barium complex derived from (*E*,*E*)-farnesyl chloride (**98**).[49b] This reaction demands a very low temperature (−95 °C) and affords a 75% yield of **92**.

In our laboratory, Ti-catalyzed Barbier-type coupling between **97** and **98** at room temperature, directly provided a 76% yield of (*E*,*E*,*E*,*E*)-12-hydroxysqualene (**92**; Scheme 16). No regio- or stereoisomers were detected, thus demonstrating the regio- and stereospecific character of the process. To the best of our knowledge, this is the first metal-



Scheme 16. Ti-catalyzed synthesis of 12-hydroxysqualene (**92**).

catalyzed synthesis of 12-hydroxysqualene, which proceeds at room temperature and does not require stoichiometric quantities of any organometallic reagent. This result confirms that our method can be employed for the coupling not only of simple isoprene units, but also more complex polyprene moieties. This capacity might be usefully exploited for the synthesis of higher terpenoids.

Conclusion

We have demonstrated that titanocene(III) complexes, easily generated in situ from commercial Ti^{IV} precursors, can promote and catalyze Barbier-type allylations, intramolecular crotylations (cyclizations), and prenylations of carbonyl compounds, including a wide range of aldehydes and ketones. These reactions take place at room temperature under mild conditions compatible with many functional groups, provide good yields of open-chain and cyclic homoallylic alcohols, including heterocyclic derivatives, afford moderate-to-high diastereoselectivity, and can be conducted enantioselectively by using chiral titanium catalysts.

Ti-catalyzed Barbier-type cyclizations and intermolecular reactions with conjugated aldehydes seem to be relatively fast and irreversible radical-coupling processes. The former probably proceeds through intramolecular coupling between a crotyl-type radical and a Ti^{III}-coordinated carbonyl group. The latter possibly occurs by intermolecular coupling between an allylic and a Ti^{IV}-bonded ketyl-type radical. Intermolecular reactions with ketones are the slowest processes described here. Their mechanism presumably proceeds via the generation of an organometallic allyl–Ti^{IV} intermediate followed by nucleophilic attack upon the carbonyl derivative. Intermolecular reactions with nonconjugated aldehydes are medium-rate processes in which both radical coupling and organometallic attack (summarized in Schemes 1 and 12 respectively) would seem to participate.

As a probable consequence of the radical coupling mechanism, the Ti-catalyzed α-prenylation of conjugated aldehydes is regiospecific. This unusual property was advantageously exploited for the straightforward synthesis of the natural products rosiridol, shikalkin, and 12-hydroxysqualene.

In recent years the development of enantioselective allylation reactions has become an important goal in chemical synthesis.[59] In this work we have paved the way to Ti-catalyzed, enantioselective Barbier-type allylation, cyclization, and prenylation reactions. Nevertheless, currently

available titanium complexes only afforded moderate *ee*. At the moment, we are engaged in the rational design and synthesis of novel, more efficient chiral titanium catalysts.

Experimental Section

General details: For all reactions with titanocene, solvents and additives were thoroughly deoxygenated prior to use. The following known compounds were isolated as pure samples and showed NMR spectra matching those of the reported compounds: **10**,[60] **11**,[17] **12**,[60] **13**,[42b] **15**,[61] **22**,[62] **23**,[63] **24**,[17] **25**,[64] **27**,[65] **37**,[66] **38**,[67] **39**,[68] **41**,[34] **47**,[69] **48**,[70] **49**,[71] **51**,[72] **65**,[17] **66**,[17] **73**,[17] **77**,[73] **81**,[74] **89**,[17] **90**,[53] **92**,[58] **95**,[56] and **96**.[57b]

General procedure for Ti^{III}-mediated Barbier-type allylations of nonconjugated aldehydes and ketones (GP1): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehyde (1 mmol) in THF (1 mL) was added. Subsenquently, a solution of allylic halide (2 mmol) in THF (1 mL) was slowly added over a period of 1 h and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 1 (products **10** and **11**) and in the Supporting Information (products **22**–**24**, **35**–**37**, and **47**–**50**).

General procedure for Ti^{III}-mediated Barbier-type allylations of conjugated aldehydes and ketones (GP2): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehyde (1 mmol) and allylic halide (2 mmol) in THF (1 mL) was slowly added over a period of 1 h and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 1 (products **12**–**15**) and in the Supporting Information (products **25**–**27**, **38**–**41**, and **51**).

General procedure for Ti^{III}-catalyzed Barbier-type allylations of nonconjugated aldehydes and ketones (GP3): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehyde (1 mmol) and 2,4,6-collidine (7 mmol) in THF (1 mL), and Me_3SiCl (4 mmol) were added. Subsequently, allylic halide (2 mmol) in THF (1 mL) was slowly added over a period of 1 h and the mixture was stirred for 6 h. The reaction was then quenched with saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **10**–**11**, **22**–**24**, **35**–**37**, and **47**–**50** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Scheme 3 and Tables 2–4. In some experiments, trimethylsilyl derivatives were observed. In these cases, the residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine, and dried (anhyd Na_2SO_4), and the solvent was removed.

General procedure for Ti^{III}-catalyzed Barbier-type allylations of conjugated aldehydes and ketones (GP4): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (0.2 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehyde (1 mmol), 2,4,6-collidine (7 mmol), and allylic halide (2 mmol) in THF (2 mL), and Me_3SiCl (4 mmol) were slowly added and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **12**–**15**, **25**–**27**, **38**–**41**, and **51** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Scheme 3 and Tables 2–4. In some experiments, trimethylsilyl derivatives were observed. In these cases, the residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed.

Ti-catalyzed chemospecific coupling of allyl chloride with decanal in the presence of 2-decanone: Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (32 mg, 0.13 mmol) and Mn dust (282 mg, 5.13 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of decanal (100 mg, 0.64 mmol), 2-decanone (100 mg, 0.64 mmol), and 2,4,6-collidine (621 mg, 5.13 mmol) in THF (2 mL), and Me_3SiCl (279 mg, 2.56 mmol) were added. Subsequently, allyl chloride (49 mg, 0.64 mmol) in THF (1 mL) was slowly added over a period of 1 h and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was purified by flash chromatography (hexane/EtOAc, 9:1) to yield **10** (97 mg, 72%), **11** (trace) and the starting materials **2** (19 mg, 19%) and **3** (95 mg, 95%).

Preparation of compound 14: Following GP2 and GP4, compound **14** was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.84$ (ddd, $J = 19.2$, 13.6, 9.6 Hz, 2H), 5.14 (m, 3H), 4.41 (q, $J = 8.4$ Hz, 1H), 2.31 (br t, $J = 9.2$ Hz, 2H), 2.13 (br t, $J = 8.8$ Hz, 2H), 2.06 (m, 2H), 1.71 (s, 6H), 1.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta = 137.7$ (C), 133.5 (CH), 130.6 (C), 126.0 (CH), 122.9 (CH), 116.8 (CH_2), 66.7 (CH), 41.2 (CH_2), 38.5 (CH_2), 25.34 (CH_2), 24.7 (CH_3), 16.7 (CH_3), 15.6 ppm (CH_3); HRMS FAB: *m/z* calcd for $C_{13}H_{22}ONa$ $[M+Na]^+$: 217.1724; found: 217.1567.

Preparation of compound 26: Following GP2 and GP4, compound **26** was obtained as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.58$ (ddt, $J = 16.4$, 10.6, 6.8 Hz, 1H), 5.15 (d, $J = 16.4$ Hz, 1H), δ 5.12 (d, $J = 10.3$ Hz, 1H), 4.30 (dd, $J = 10.6$, 3.2 Hz, 1H), 2.67–2.59 (m, 1H), 2.32–2.26 (m, 1H), 1.96–1.92 (m, 2H), 1.87 (s, 3H), 1.59–1.52 (m, 2H), 1.47–1.39 (m, 2H), 1.16 (s, 3H), 1.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta = 138.3$ (C), 135.4 (CH), 130.6 (C), 116.2 (CH_2), 69.2 (CH), 40.4 (CH_2), 38.9 (CH_2), 33.6 (C), 33.0 (CH_2), 27.6 (CH_3), 27.0 (CH_3), 20.1 (CH_3), 18.3 ppm (CH_2); HRMS FAB: *m/z* calcd for $C_{13}H_{22}ONa$ $[M+Na]^+$: 217.3058; found: 217.0932.

Preparation of compound 35: Following GP1 and GP3, compound **35** was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.90$ (ddd, $J = 20$, 14, 10 Hz, 2H), 5.16 (m, 2H), 5.12 (m, 1H), 2.73 (br d, $J = 9.6$ Hz, 2H), 2.08 (m, 6H), 1.71 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.53 (m, 2H), 1.21 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta =$ 135.6 (C), 134.3 (CH), 131.6 (C), 124.5 (CH), 124.5 (CH), 118.7 (CH_2), 72.4 (C), 46.6 (CH_2), 41.8 (CH_2), 39.9 (CH_2), 26.9 (CH_3), 25.9 (CH_3), 22.7 (CH_2), 17.9 (CH_3), 16.2 ppm (CH_3), (one carbon signal was not observed); HRMS FAB: *m/z* calcd for $C_{16}H_{28}ONa$ $[M+Na]^+$: 259.3861; found: 259.2132.

Preparation of compound 36: Following GP1 and GP3, compound **36** was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.88$ (ddt, $J = 17.3$, 10.3, 7.7 Hz, 1H), 5.13 (br d, $J = 10.3$ Hz, 1H), 5.10 (br d, $J = 17.3$ Hz, 1H), 2.17 (d, $J = 7.7$ Hz, 2H), 1.80–1.40 ppm (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta = 134.0$ (CH), 118.7 (CH_2), 75.6 (C), 34.1 (CH_2), 26.8 (CH_2), 26.4 (CH_2), 23.7 (CH_2), 23.5 (CH_2), 21.2 ppm (CH_2); HRMS FAB: *m/z* calcd for $C_{13}H_{24}ONa$ $[M+Na]^+$: 219.1827; found: 219.1833.

Preparation of compound 40: Following GP2 and GP4, compound **40** was obtained as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$ (d, $J = 7.7$ Hz, 2H), 7.38 (t, $J = 7.7$ Hz, 2H), 7.28 (t, $J = 7.7$ Hz, 1H), 5.71 (ddt, $J = 13.7$, 8.1, 6.7 Hz, 1H), 5.18 (d, $J = 13.7$ Hz, 1H), 5.14 (d, $J = 8.1$ Hz, 1H), 2.82 (dd, $J = 13.8$, 6.7 Hz, 1H), 2.64 (dd, $J = 13.7$, 8.1 Hz, 1H), 1.32 (quint, $J = 7.1$ Hz, 1H), 0.52 (m, 2H), 0.37 ppm (dt, $J = 10.9$ Hz,

7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 146.3 (C), 133.8 (CH), 128.0 (CH), 126.7 (CH), 125.6 (CH), 119.4 (CH_2), 47.3 (CH_2), 21.7 (CH), 1.6 (CH_2), 0.6 ppm (CH_2) (one carbon signal was not observed); IR (film) ν_{max} = 3472, 3007 cm^{-1}; HRMS EI: *m/z* calcd for $C_{13}H_{15}O$ $[M-H]^+$: 187.1123; found: 187.1122.

Preparation of compound 50 (3:2 mixture of diastereomers): Following GP1 and GP3, compound **50** was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03–5.86 (m, 2H), 5.21–5.10 (m, 4H), 4.68–4.59 (m, 2H), 4.54 (d, *J* = 2.6 Hz, 1H)*, 4.39 (d, *J* = 2.6 Hz, 1H), 4.28–4.25 (m, 4H), 3.98–3.62 (m, 3H), 2.51–2.25 (m, 4H), 1.60 (brs, 2H; both OH), 1.59 (s, 3H)*, 1.58 (s, 3H), 1.55 (s, 3H)*, 1.50 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H)*, 1.39 (s, 3H)*, 1.38 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 136.2 (CH)*, 135.6 (CH), 117.9 (CH_2), 116.7 (CH_2)*, 109.4 (C)*, 109.2 (C), 108.7 (C), 108.5 (C)*, 104.8 (C), 104.4 (C)*, 75.4 (CH), 72.8 (CH)*, 72.3 (CH), 71.1 (CH), 70.8 (CH)*, 70.6 (C), 70.2 (CH)*, 61.5 (CH_2), 61.2 (CH_2)*, 35.9 (CH_2), 35.7 (CH_2)*, 26.6 (CH_3), 26.5 (CH_3)*, 26.0 (CH_3), 26.0 (CH_3)*, 25.9 (CH_3)*, 25.8 (CH_3), 24.2 (CH_3), 24.0 ppm (CH_3)* (one carbon signal was not observed) (signals with asterisk correspond to the minor diastereomer); HRMS FAB: *m/z* calcd for $C_{15}H_{24}O_6Na$ $[M+Na]^+$: 323.3386; found: 323.3382.

General procedure for the synthesis of allylic bromides 54, 55, and 58–61 (GP5): PBr_3 (2 mmol) was added to a solution of the corresponding allylic alcohol (1 mmol; for the preparation of these allylic alcohols see Supporting Information) in Et_2O (20 mL) at 0 °C. The mixture was stirred at room temperature for 4 h. Then, the mixture was diluted with Et_2O, washed with brine, and dried (anhyd Na_2SO_4) and the solvent was removed. The residue was used in the next step without further purification.

Preparation of allylic bromide 54: Following GP5, compound **54** was obtained as a colorless oil (48 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75–5.70 (m, 1H), 5.39–5.33 (m, 1H), 3.99 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 6H), 2.65 (d, *J* = 8 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.12 (t, *J* = 8.4 Hz, 2H), 2.11 ppm (s, 3H). This compound is quite unstable and we could obtain neither ^{13}C NMR nor HRMS data.

Preparation of allylic bromide 55: Following GP5, compound **55** was obtained as a colorless oil (226 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.70 (dt, *J* = 15.0, 5.7 Hz, 1H), 5.52 (dt, *J* = 15.0, 5.7 Hz, 1H), 3.91 (d, *J* = 6.6 Hz, 2H), 3.70 (s, 6H), 2.62 (d, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 8.0 Hz, 2H), 2.12 (s, 3H), 2.11 ppm (t, *J* = 7.5 Hz, 2H). This compound is quite unstable and we could obtain neither ^{13}C NMR nor HRMS data.

Preparation of allylic bromide 58: Following GP5, compound **58** was obtained as a colorless oil (126 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (brd, *J* = 7.5 Hz, 4H) 7.72 (brt, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 4H), 5.86 (m, 1H), 5.73 (m, 1H), 3.83 (d, *J* = 8.3 Hz, 2H), 2.98 (dd, *J* = 6.4, 1.6 Hz, 2H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.50 (brt, *J* = 7.6 Hz, 2H), 2.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 206.1 (C), 136.7 (C), 135.1 (CH), 131.6 (CH), 129.4 (CH), 129.1 (CH), 126.4 (CH), 89.4 (C), 38.0 (CH_2), 30.2 (CH_3), 28.1 (CH_2), 25.8 (CH_2), 23.8 ppm (CH_2).

Preparation of allylic bromide 59: Following GP5, compound **59** was obtained as a colorless oil (476 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.3, 2H) 7.24 (d, *J* = 8 Hz, 2H), 5.78 (m, 1 H-*cis*), 5.32 (m, 1H), 3.89 (d, *J* = 8.4 Hz, 2H), 3.84 (d, *J* = 7 Hz, 2H), 3.25 (t, *J* = 7 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 2.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): δ = 206.8 (C), 143.7 (C), 136.2 (C), 129.9 (CH), 129.5 (CH), 129.3 (CH), 127.3 (CH), 45.3 (CH_2), 43.6 (CH_2), 42.9 (CH_2), 30.3 (CH_3), 25.5 (CH_2), 21.6 ppm (CH_3).

Preparation of allylic bromide 60: Following GP5, compound **60** was obtained as a colorless oil (72%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 5.76–5.69 (m, 1H), 5.57–5.49 (m, 1H), 3.91 (d, *J* = 6.6 Hz, 2H), 3.76 (s, 6H), 2.66 (d, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.19 ppm (t, *J* = 7.3 Hz, 2H). This compound is quite unstable and we could obtain neither ^{13}C NMR nor HRMS data.

Preparation of allylic bromide 61: Following GP5, compound **61** was obtained as a colorless oil (65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 5.79–5.72 (m, 1H), 5.42–5.37 (m, 1H), 3.96 (d, *J* = 8.4 Hz, 2H), 3.73 (s, 6H), 2.74 (d, *J* = 6.8 Hz, 2H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.21 (t, *J* = 8.4 Hz, 2H). This compound is quite unstable and we could obtain neither ^{13}C NMR nor HRMS data.

General procedure for Barbier-type cyclizations promoted by [TiClCp$_2$] (GP6): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of substrate **58** (1 mmol) in THF (1 mL) was slowly added over a period of 15 min and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Product **62** (73%) was purified by flash chromatography on silica gel (hexane/EtOAc 8:2) and characterized by spectroscopic techniques.

General procedure for Barbier-type cyclizations catalyzed by [TiClCp$_2$] (GP7): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (7 mmol), and Me_3SiCl (4 mmol) were added. Finally, a solution of the corresponding substrate (**54**, **55**, and **58–61**; 1 mmol) in THF (1 mL) was slowly added over a period of 15 min and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **56**, and **62–67** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 5 and the body text.

Preparation of compound 56: Following GP7, compound **56** was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (ddd, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.21 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.15 (dd, *J* = 17.1, 0.9 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.40–1.98 (m, 5H), 1.73 (dt, *J* = 14.1, 3.3 Hz, 1H), 1.54 (td, *J* = 14.1, 4.5 Hz, 1H), 1.20 ppm (s, 3H); NOE-diff. experiment: proton irradiated, (NOEs observed): H-7, (H_2–8, H_3–9); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): δ = 172.7 (C), 171.8 (C), 137.9 (CH), 117.6 (CH_2), 69.4 (C), 54.9 (C), 52.9 (CH_3), 52.7 (CH_3), 46.7 (CH), 36.3 (CH_2), 31.8 (CH_2), 29.4 (CH_3), 26.6 ppm (CH_2); HRMS ES: *m/z* calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 279.1202; found: 279.1192; the relative configuration of **56** was established on the basis of NOE-diff. experiments performed on its acetyl derivative **57**.

Preparation of compound 57: Treatment of **56** with acetyl chloride in the presence of 4-dimethylaminopyridine (DMAP) generated compound **57** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.68 (m, 1H), 5.22–5.10 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.02 (dt, *J* = 14.8, 3.2 Hz, 1H), 2.29 (s, 3H), 2.26–2.19 (m, 2H), 2.15 (dt, *J* = 11.2, 3.2 Hz, 1H), 2.03–1.93 (m, 1H), 1.86–1.77 (m, 1H), 1.54 (s, 3H), 1.41 ppm (td, *J* = 14.8, 3.6 Hz, 1H); NOE-diff. experiment: proton irradiated, (NOEs observed): H-6β, (H_3–9, H-2, H-6α), H_3–9, (H-2, H-6α, H-6β) , H-6α, (H-6β, H_3–9); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): δ = 172.3 (C), 171.6 (C), 167.3 (C), 137.0 (CH), 118.1 (CH_2), 83.2 (C), 54.4 (C), 52.9 (CH_3), 52.9 (CH_3), 49.2 (CH), 32.7 (CH_2), 31.3 (CH_2), 26.7 (CH_2), 25.6 (CH_3), 24.2 ppm (CH_3).

Preparation of disulfone 62: Following GP6 and GP7, compound **62** was obtained as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.9 Hz, 2H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.69 (m, 2H), 7.58 (m, 4H), 5.80 (m, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 5.15 (d, *J* = 17.4 Hz, 1H), 2.92 (m, 1H), 2.68 (dt, *J* = 14.1, 5.1 Hz, 1H), 2.62 (t, *J* = 12.8 Hz, 1H), 2.31 (dt, *J* = 13.8, 4.5 Hz, 1H), 2.20 (dd, *J* = 14.8, 2.1 Hz, 1H), 2.08 (dt, *J* = 14.4, 3.2 Hz, 1H), 1.72 (ddd, *J* = 8.8, 5, 2 Hz, 1H), 1.24 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): δ = 139.6 (CH), 139.2 (C), 138.7 (C), 137.1 (CH), 136.9 (CH), 134.1 (CH), 133.7 (CH), 131.1 (CH), 131.0 (CH), 120.8 (CH_2), 90.3 (C), 71.2 (C), 48.0 (CH), 37.6 (CH_2), 31.3 (CH_3), 29.8 (CH_2), 24.9 ppm (CH_2).

Preparation of piperidine 63: Following GP7, compound **63** was obtained as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.83 (m, 1H), 5.20 (m, 2H), 3.28 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.17 (m, 1H), 3.03 (m, 1H), 2.90 (dd, *J* = 11.5, 6.7 Hz, 1H), 2.43 (s, 3H), 2.26 (m, 1H), 1.79 (m, 1H), 1.63 (m, 1H), 1.08 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): δ = 143.6 (C), 135.3 (CH), 133.5 (C), 129.8 (CH) ,127.7 (CH), 118.8 (CH_2), 69.6 (CH), 50.9 (CH), 47.3 (CH_2), 43.2 (CH_2), 36.8 (CH_2), 29.8 (CH_2), 25.1 (CH_3), 21.6 ppm

(CH_3); HRMS FAB: *m/z* calcd for $C_{15}H_{21}NO_3SNa$ $[M+Na]^+$: 318.1139; found: 318.1137.

Preparation of piperidine 64: Following GP7, compound **64** was obtained as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.61$ (d, $J = 8$ Hz, 2H), 7.28 (d, $J = 8$ Hz, 2H), 5.70 (m, 1H), 5.18 (dd, $J = 10.5$, 1.3 Hz, 1H), 5.12 (d, $J = 17.4$ Hz, 1H), 3.53 (td, $J = 13.4$, 2.1 Hz, 1H), 3.48 (ddd, $J = 11.3$, 4.3, 1.7 Hz, 1H), 2.61 (dt, $J = 11.8$, 3.24 Hz, 1H), 2.48 (t, $J = 11.4$ Hz, 1H), 2.40 (s, 3H), 2.26 (ddd, $J = 12$, 8.5, 4.4 Hz, 1H), 1.67 (m, 2H), 1.15 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): $\delta = 143.7$ (C), 134.7 (CH), 133.6 (C), 129.9 (CH), 127.8 (CH), 119.4 (CH_2), 116.9 (CH), 68.3 (CH), 49.6 (CH), 46.3 (CH_2), 42.3 (CH_2), 38.6 (CH_2), 28.7 (CH_3), 21.7 ppm (CH_3) (one carbon signal was not observed); HRMS FAB: *m/z* calcd for $C_{15}H_{21}NO_3SNa$ $[M+Na]^+$: 318.1139; found: 318.1137.

Preparation of disulfone 67: Following GP7, compound **67** was obtained as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J = 7.9$ Hz, 2H), 8.00 (d, $J = 7.9$ Hz, 2H), 7.72 (m, 2H), 7.58 (m, 4H), 5.75 (m, 1H), 5.25 (d, $J = 10.3$ Hz, 1H), 5.20 (d, $J = 17.4$ Hz, 1H), 2.98 (m, 1H), 2.68 (dt, $J = 14.1$, 5.1 Hz, 1H), 2.50–2.25 (m, 3H), 1.80–1.50 (m, 1H), 1.30–1.20 (m, 2H), 1.10 ppm (s, 3H).

Ti-promoted Barbier-type cyclizations of model allylic bromide 55 in the presence of Lewis acids: Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of substrate **55** (1 mmol) and the Lewis acid ($[Er(CF_3O_3S)_3]$ or BF_3 etherate; 2 mmol) in THF (1 mL) was added dropwise and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **56** and **73** were purified by flash chromatography on silica gel (hexane/EtOAc 8:2) and characterized by spectroscopic techniques. Yields obtained are reported in the body text.

Barbier-type cyclizations of model allylic bromide 55 catalyzed by $[TiCl_2Cp]$: Strictly deoxygenated THF (20 mL) was added to a mixture of commercial $[TiCl_3Cp]$ (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (7 mmol), and Me_3SiCl (4 mmol) were added. Finally, a solution of **55** (1 mmol) in THF (1 mL) was slowly added over a period of 15 min and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Product **56** (64% yield) was purified by flash chromatography on silica gel (hexane/EtOAc 8:2).

Barbier-type cyclizations of model allylic bromide 55 catalyzed by the Brintzinger's complex 52: Strictly deoxygenated THF (20 mL) was added to a mixture of commercial Brintzinger's complex (**52**; 0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (7 mmol), and Me_3SiCl (4 mmol) were added. Finally, a solution of **55** (1 mmol) in THF (1 mL) was slowly added over a period of 15 min and the mixture was stirred for 6 h. The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was submitted to flash chromatography on silica gel (hexane/EtOAc 8:2) yielding products (−)-**56** (36% yield, 20% *ee*) and (−)-**73** (29% yield, 19% *ee*).[47]

General procedure for Barbier-type prenylations of nonconjugated aldehydes and ketones promoted by Ti^{III} (GP8): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of carbonyl compound (1 mmol) in THF (1 mL) was added. Subsequently, prenyl halide (2 mmol) in THF (1 mL) was slowly added and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **76**, **77**, and **80**–**83** and **89** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Scheme 9 and Scheme 13, and in Table 6.

General procedure for Barbier-type prenylations of nonconjugated aldehydes catalyzed by Ti^{III} (GP9): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of carbonyl compound (1 mmol) and 2,4,6-collidine (7 mmol) in THF (2 mL), and Me_3SiCl (4 mmol) were added. Subsequently, prenyl halide (2 mmol) was slowly added and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **76**, **77**, **82**, and **83** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 7. In some experiments, trimethylsilyl derivatives were observed. In these cases, the residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed, thus obtaining the corresponding homoallylic alcohols.

General procedure for Barbier-type prenylations of conjugated aldehydes promoted by Ti^{III} (GP10): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (2.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of carbonyl compound (1 mmol) and prenyl halide (2 mmol) in THF (2 mL) was slowly added and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **84**–**88** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 6.

General procedure for Barbier-type prenylations of conjugated aldehydes catalyzed by Ti^{III} (GP11): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (7 mmol) and Me_3SiCl (4 mmol) were added. Subsequently, a solution of carbonyl compound (1 mmol) and prenyl halide (2 mmol) in THF (2 mL) was slowly added over a period of 1 h and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. Products **84** and **88** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques. Yields obtained are reported in Table 7. In some experiments, trimethylsilyl derivatives were observed. In these cases, the residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed, thus obtaining the corresponding homoallylic alcohols.

Ti-catalyzed chemospecific coupling of prenyl bromide (74) with 2,5-dimethoxybenzaldehyde (79) in the presence of decanal (2): Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (299 mg, 1.2 mmol) and Mn dust (264 mg, 4.81 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned lime green (after about 15 min). Then, a solution of **2** (94 mg, 0.60 mmol), **79** (100 mg, 0.60 mmol), and **74** (90 mg, 0,60 mmol) in THF (2 mL) was slowly added and the mixture was stirred for 6 h. The reaction was then quenched with brine and extracted with EtOAc. The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed. Prenylation product **88** (82% yield) and unchanged decanal were isolated by flash chromatography (hexane/EtOAc, 8:2).

Preparation of compound 76: Following GP8 and GP9, compound **76** was obtained as a pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.17$ (t, $J = 6.8$ Hz, 1H), 3.60 (m, 1H), 2.15 (m, 2H), 1.75 (s, 3H), 1.65 (s, 3H), 1.26 (brs, 16H), 0.89 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): $\delta = 135.2$ (C), 120.3 (CH), 71.8 (CH), 36.9 (CH_2), 36.3 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.0 (CH_3), 25.9

(CH_2), 22.8 (CH_2), 18.1 (CH_3), 14.2 ppm (CH_3); HRMS FAB: *m/z* calcd for $C_{15}H_{30}ONa$ $[M+Na]^+$: 249.2194; found: 249.2196.

Preparation of compound 80 (9:1 mixture of diastereomers): Following GP8, compound **80** was obtained as a colorless oil. Only signals for the major isomer are described; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=7.22$ (m, 5H), 5.07 (t, $J=7.2$ Hz, 1H), 3.60 (m, 1H), 2.70 (quint, $J=7.2$ Hz, 1H), 1.97 (m, 2H), 1.64 (s, 3H), 1.50 (s, 3H), 1.27 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): $\delta=144.7$ (C), 135.2 (C), 128.4 (CH), 127.7 (CH), 126.3 (CH), 120.2 (CH), 76.1 (CH), 45.3 (CH), 33.8 (CH_2), 25.9 (CH_3), 17.9 (CH_3), 16.4 ppm (CH_3); MS (70 eV): *m/z* (%): 204 (5) $[M]^+$, 186 (5), 171 (4), 143 (8), 135 (47), 117 (48), 106 (93), 91 (94), 81 (84), 70 (100).

Preparation of compound 82 (7:3 mixture of diastereomers): Following GP8 and GP9, compound **82** was obtained as a colorless oil; ^1H NMR ($CDCl_3$, 400 MHz): $\delta=5.16$ (dt, $J=6.8$, 1.2 Hz, 1H), 5.09 (t, $J=6.8$ Hz, 1H), 3.69 (m, 1H), 2.20–1.90 (m, 4H), 1.73 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.50–1.06 (m, 4H), 0.91 (d, $J=6.4$ Hz, 3H) 0.90 ppm (d, $J=6.4$ Hz, 3H)*; ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): $\delta=135.3$ (C)*, 131.3 (C), 124.9 (CH), 120.3 (CH)*, 120.3 (CH), 69.9 (CH), 69.5 (CH)*, 44.5 (CH_2), 44.4 (CH_2)*, 38.0 (CH_2)*, 37.1 (CH_2)*, 36.9 (CH_2), 36.6 (CH_2), 29.5 (CH_3), 29.2 (CH_3)*, 26.0 (CH_3), 25.8 (CH_3), 25.6 (CH_2)*, 25.5 (CH_2), 20.4 (CH_3), 19.3 (CH_3)*, 18.1 (CH_3)*, 17.7 ppm (CH_3) (signals with asterisk correspond to the minor diastereomer); HRMS FAB: *m/z* calcd for $C_{15}H_{27}O$ $[M-H]^+$: 223.2061; found: 223.2065.

Preparation of compound 83 (1:1 mixture of diastereomers): Following GP8 and GP9, compound **83** was obtained as a colorless oil; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=5.81$ (dd, $J=10.8$, 2 Hz, 1H), 5.09 (m, 2H), 3.34 (d, $J=10.8$ Hz, 1H), 2.10–1.86 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.50–1.10 (m, 4H), 1.00 (s, 6H), 0.94 (d, $J=6.8$ Hz, 3H), 0.88 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT): $\delta=145.5$ (CH), 131.1 (C), 124.9 (CH), 124.8 (CH), 113.3 (CH_2), 76.0 (CH), 75.6 (CH), 41.7 (C), 41.5 (C), 39.0 (CH_2), 38.6 (CH_2), 38.4 (CH_2), 35.7 (CH_2), 29.8 (CH_3), 29.2 (CH_3), 25.7 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 23.1 (CH_3), 23.0 (CH_3), 22.0 (CH_3), 21.9 (CH_3), 20.8 (CH_3), 18.8 (CH_3), 17.6 ppm (CH_3) (some carbon signals were not observed); HRMS FAB: *m/z* calcd for $C_{15}H_{27}O$ $[M-H]^+$: 223.2061; found: 223.2065.

Preparation of compound 84: Following GP10 and GP11, compound **84** was obtained as a pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): $\delta=5.21$ (d, $J=8.5$, 1H), 5.14 (m, 2H), 4.36 (ddd, $J=14.1$, 7.6, 1.3 Hz, 1H), 2.27 (m, 1H), 2.12 (m, 5H), 1.72 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 1.60 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz; DEPT): $\delta=145.3$ (C), 138.5 (C), 134.9 (C), 127.4 (CH), 124.5 (CH), 119.9 (CH), 68.6 (CH), 39.6 (CH_2), 36.6 (CH_2), 26.5 (CH_2), 26.0 (CH_3), 25.8 (CH_3), 18.1 (CH_3), 17.8 (CH_3), 16.7 ppm (CH_3); HRMS FAB: *m/z* calcd for $C_{15}H_{26}ONa$ $[M+Na]^+$: 245.1881; found: 245.1876.

Preparation of compound 85: Following GP10, compound **85** was obtained as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.24$ (t, $J=6.8$ Hz, 1H), 4.23 (dd, $J=10.6$, 3.2 Hz, 1H), 2.65 (ddd, $J=14.7$, 9.4, 5.3 Hz, 1H), 2.14 (br d, $J=4.5$ Hz, 1H), 1.97–1.91 (m, 1H), 1.87 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H), 1.63–1.38 (m, 4H), 1.09 (s, 3H), 0.95 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): $\delta=139.6$ (C), 134.5 (C), 131.4 (C), 121.9 (CH), 71.1 (CH), 40.0 (CH_2), 35.8 (CH_2), 34.7 (C), 34.1 (CH_2), 28.7 (CH_3), 28.1 (CH_3), 26.0 (CH_3), 21.2 (CH_3), 19.4 (CH_2), 18.1 ppm (CH_3); IR (film) $\nu_{max}=3447$, 2927 cm^{-1}; HRMS EI: *m/z* calcd for $C_{15}H_{26}O$ $[M]^+$: 222.1984; found: 222.1986.

Preparation of compound 86: Following GP10, compound **86** was obtained as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.43$ (m, 1H), 5.09 (m, 1H), 3.97 (t, $J=6.9$ Hz, 1H), 2.43–2.08 (m, 8H), 1.72 (s, 3H), 1.62 (s, 3H), 1.28 (s, 3H), 0.83 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): $\delta=149.9$ (C), 134.5 (C), 120.3 (CH), 117.7 (CH), 74.4 (CH), 42.3 (CH), 41.1 (CH), 37.8 (C), 33.8 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 26.2 (CH_3), 25.9 (CH_3), 21.5 (CH_3), 18.0 ppm (CH_3); MS (70 eV): *m/z* (%): 202 (32) $[M-H_2O]^+$, 187 (12), 159 (30), 151 (62), 131 (46), 117 (75), 105 (76), 91 (100).

Preparation of compound 87 (1:1 mixture of diastereoisomers): Following GP10, compound **87** was obtained as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.66$ (br s, 1H), 5.10 (br t, $J=10$ Hz, 1H), 4.67 (s, 2H), 3.93 (t, $J=9$ Hz, 1H), 1.73–2,24 (m, 9H), 1.71 (s, 6H), 1.62 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta=149.9$ (C), 149.8 (C), 139.4 (C), 139.2 (C), 134.97 (C), 134.8 (C), 122.7 (CH), 121.7 (CH), 120.3 (CH), 120.1 (CH), 108.6 (CH_2), 75.7 (CH), 75.5 (CH), 41.4 (CH), 41.2 (CH), 34.4 (CH_2), 34.2 (CH_2), 30.6 (CH_2), 30.4 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 26.0 (CH_3), 25.9 (CH_3), 24.7 (CH_2), 24.1 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 18.1 ppm (CH_3) (two carbon signals were not observed); HRMS FAB: *m/z* calcd for $C_{15}H_{24}ONa$ $[M+Na]^+$: 243.1724; found: 243.1724.

Preparation of compound 88: Following GP10 and GP11, compound **88** was obtained as a colorless oil; ^1H NMR ($CDCl_3$, 300 MHz): $\delta=6.95$ (d, $J=2.8$ Hz, 1H), 6.75 (m, 2H), 5.22 (t, $J=7.4$ Hz, 1H), 4.87 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.61 (d, $J=5.8$ Hz, 1H), 2.42 (m, 2H), 1.71 (s, 3H), 1.60 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz; DEPT): $\delta=153.8$ (C), 150.6 (C), 134.7 (C), 133.6 (C), 120.5 (CH), 112.9 (CH), 112.4 (CH), 111.4 (CH), 70.3 (CH), 36.4 (CH_2), 36.3 (CH_2), 25.9 (CH_3), 17.9 ppm (CH_3); HRMS FAB: *m/z* calcd for $C_{14}H_{20}O_3Na$ $[M+Na]^+$: 259.1412; found: 259.1407.

Barbier type α-prenylation of conjugated aldehyde 79 catalyzed by the Brintzinger's complex 52: Strictly deoxygenated THF (20 mL) was added to a mixture of commercial complex **52** (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (7 mmol) and Me_3SiCl (4 mmol) were added. Subsequently, a solution of **79** (1 mmol) and **74** (2 mmol) in THF (2 mL) was slowly added over a period of 1 h and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was solved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with EtOAc, washed with brine, and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was submitted to flash chromatography on silica gel (hexane/EtOAc, 8:2) yielding product (−)-**88** (21% yield, 29% *ee*).[47]

Preparation of aldehyde 93: A sample of MnO_2 (188 mg, 2.16 mmol) was added to a solution of (*E*)-4-hydroxy-3-methylbut-2-enyl benzoate (150 mg, 0.72 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred for 8 h at RT. Then, the solution was filtered and the solvent was removed. The residue was purified by flash chromatography (hexane/EtOAc, 8:2) to yield aldehyde **93** (147 mg, 100%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta=9.47$ (s, 1H), 8.06 (d, $J=6.8$ Hz, 2H), 7.57 (t, $J=7.6$ Hz, 1H), 7.45 (t, $J=8$ Hz, 2H), 6.22 (dt, $J=5.6$, 1.2 Hz, 1H), 5.14 (d, $J=6$ Hz, 2H), 1.85 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT): $\delta=194.2$ (C), 166.2 (C), 145.8 (CH), 140.6 (C), 133.4 (CH), 129.7 (CH), 128.5 (CH), 61.3 (CH_2), 9.6 ppm (CH_3).

Ti-catalyzed prenylation of 93: Following the general procedure GP11, alcohol **94** was obtained (84 mg, 63%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta=8.09$ (dd, $J=10$, 1.2 Hz, 2H), 7.59 (t, $J=10$ Hz, 1H), 7.47 (t, $J=10$ Hz, 2H), 5.77 (t, $J=9.2$ Hz, 1H), 5.15 (t, $J=9.6$ Hz, 1H), 4.93 (d, $J=9.2$ Hz, 2H), 4.10 (t, $J=8.4$ Hz, 1H), 2.32 (t, $J=9.2$ Hz, 2H), 1.82 (s, 3H), 1.75 (s, 3H), 1.68 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=166.6$ (C), 143.1 (C), 135.4 (C), 132.9 (CH), 130.5 (C), 129.7 (CH), 128.4 (CH), 119.7 (CH), 119.5 (CH), 76.3 (CH), 61.5 (CH_2), 34.3 (CH_2), 25.9 (CH_3), 18.1 (CH_3), 12.6 ppm (CH_3); HRMS FAB: *m/z* calcd for $C_{17}H_{22}O_3Na$ $[M+Na]^+$: 297.1469; found: *m/z* 297.1463.

Synthesis of rosidirol (90): K_2CO_3 (160 mg, 1.16 mmol) was added to a solution of alcohol **94** (84 mg, 0.3 mmol) in MeOH (5 mL), and the mixture was stirred for 24 h at RT. Then, AcOEt was added and the mixture was washed with water, dried (anhyd Na_2SO_4) and the solvent was removed. The crude was purified by flash chromatography (hexane/EtOAc, 1:1) to yield rosiridol (**90**)[53] (38 mg, 73%).

Ti-catalyzed prenylation of 95: Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (27 mg, 0.11 mmol) and Mn dust (239 mg, 4.35 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehyde **95** (150 mg, 0.54 mmol), 2,4,6-collidine (527 mg, 4.35 mmol), and **74** (162 mg, 1.09 mmol) in THF (2 mL), and Me_3SiCl (232 mg, 2.14 mmol) were simultaneously added and the solution was stirred for 6 h. The reaction was then quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic

layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was submitted to flash chromatography (hexane/EtOAc, 7:3) to give **96** (153 mg, 72%).

Synthesis of aldehyde 97: Dess-Martin periodinane (771 mg, 1.82 mmol) was added to a solution of *trans*,*trans*-farnesol (200 mg, 0.909 mmol) in CH_2Cl_2 (15 mL). The suspension was stirred for 4 h at RT. Then, the solvent was partially removed, Et_2O (20 mL) was added and the mixture was washed with a 1:1 mixture of saturated solution of $NaHCO_3$ and 10% $Na_2S_2O_3$ and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was submitted to flash chromatography (hexane/EtOAc, 85:15) to give **97** (164 mg, 82%) as a colorless oil.

Ti-catalyzed "head to head" coupling between 97 and 98. Synthesis of 92: Strictly deoxygenated THF (20 mL) was added to a mixture of $[TiCl_2Cp_2]$ (23 mg, 0.09 mmol) and Mn dust (198 mg, 3.6 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, 2,4,6-collidine (436 mg, 3.6 mmol) in THF (1 mL) and Me_3SiCl (232 mg, 2.14 mmol) were simultaneously added. Subsequently, a solution of **97** (100 mg, 0.45 mmol) and commercial **98** (217 mg, 0.9 mmol) in THF (2 mL) were slowly added and the mixture was stirred for 6 h. The reaction was then quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4), and the solvent was removed. The residue was submitted to flash chromatography (hexane/EtOAc, 8:2) to give **92** (145 mg, 76%) as a colorless oil.

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