JOC Article

Mild Ti^{III}- and Mn/Zr^{IV}-Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes†

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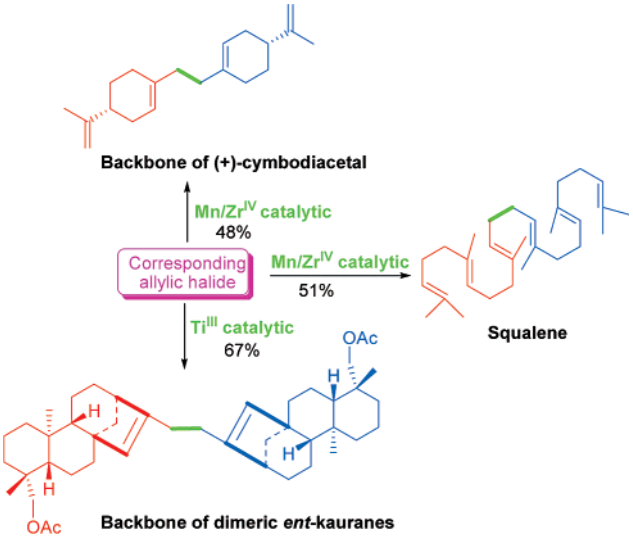

Two new efficient methods for the regioselective homocoupling of allylic halides using either catalytic Ti^{III} or the combination Mn/Zr^{IV} catalyst have been developed. The regio- and stereoselectivity of the process proved to increase significantly when the Mn/Zr^{IV} catalyst is used as the coupling reagent and when cyclic substituted allylic halides are used as substrates. The use of Lewis acids such as collidine hydrochloride allowed the quantity of catalyst to be lowered up to 0.05 equiv. We have proved the utility of these protocols with the synthesis of different terpenoids such as (+)-β-onoceradiene (**1**), (+)-β-onocerine (**2**), squalene (**5**), and advanced key-intermediates in the syntheses of (+)-cymbodiacetal (**3**) and dimeric *ent*-kauranoids as xindongnin M (**4a**).

Introduction

Several publications have described methods to achieve the homocoupling of both alkyl and allylic halides, including the electrochemical coupling of allylic halides by using a copper anode,[1] the coupling of two allylic moieties via the reaction of allylic or benzylic halides with SmI_2 in THF,[2] the reduction of organic halides with lanthanum metal,[3] the reaction of allylic organometallic compounds with allylic halides,[4] the coupling of π-methallylnickel(I) bromide with halides,[5] the homocoupling of alkyl halides via activated copper,[6] the reductive coupling of allylic halides by chlorotris(triphenylphosphine) cobalt(I),[7] the coupling of allylic halides promoted by Te^{2-} species,[8] and so on. Within the field of terpenoid synthesis, the homocoupling

† Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

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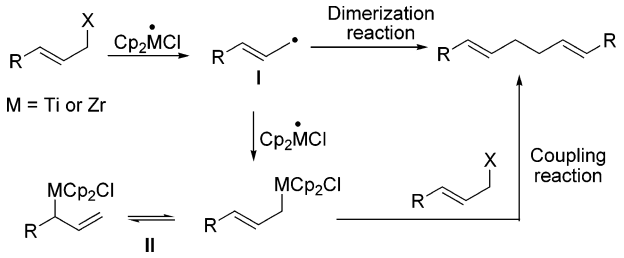
SCHEME 1. Possible Mechanistic Pathways for the Homocoupling of Allylic Halides



reaction of allylic halides using Rieke barium[9] is very interesting, giving satisfactory results in the coupling of (*E*,*E*)-farnesyl barium with farnesyl bromide. This process represents the first direct synthesis of squalene by the coupling of two *E*,*E*-farnesyl units. Most of the above-mentioned methods use stoichometric quantities of reducing species.

Titanocene chloride[10] has been widely used through SET processes in the homolytic opening of oxiranes[11] and in pinacol coupling reactions.[12] It has also been used in the reduction of glycosyl bromides[13]and vic-dibromides[14] and in the homocoupling of allylic and benzylic halides[15] with satisfactory results. These reactions take place under mild conditions and are tolerated by a large number of functional groups, such as alcohols, amines, amides, ketones, acids, and esters.[13d] By comparison with their Ti^{III} analogues, Zr^{III} complexes have been much less used in organic synthesis. Zirconocene chloride can be obtained by reduction of Cp_2ZrCl_2 with sodium-amalgam in THF or toluene.[16b,c,17] Cp_2ZrCl has been used to achieve pinacolinic couplings with aliphatic aldehydes.[17] These pinacolinic couplings have also been successfully achieved using catalytic amounts of Cp_2ZrCl_2 in the presence of Mg and TMSCl.[18] Cp_2ZrCl also provokes the slow reduction of glycosyl halides to glycals,[10,13d] although when this reagent was prepared in situ, it proved to be more efficient than Cp_2TiCl for the reduction of aliphatic halides.

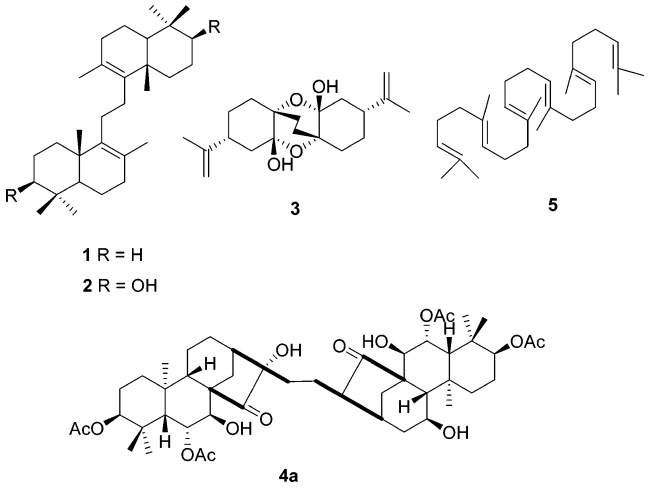


FIGURE 1. Natural dimeric structures.

Bearing in mind the mechanism proposed for the reactions mediated by these two reagents, we surmised that these species could well intervene efficiently in the homocoupling of allylic halides (Scheme 1).

In a previous paper[19a] we described the first results of a new catalytic method for the homocoupling of allylic bromides mediated by Ti^{III}, including the enantioselective preparation of onocerane derivatives **1** and **2**. We describe here the complete development of the process, the ability of Zr^{IV} to catalyze these homocouplings in the presence of manganese metal (to our knowledge no precedence of Zr^{IV} catalyzing these kind of processes can be found in the literature), and finally, new applications toward the synthesis of symmetric terpenes, such as the preparation of advanced key-intermediates in the syntheses of (+)-cymbodiacetal (**3**)[20] and dimeric *ent*-kauranoids (**4**), such as xindongnin M (**4a**),[21] and an improved synthetic way to prepare squalene (**5**) (Figure 1).

Results and Discussion

The development of these synthetic methods began with the use of geranyl bromide (**6**) and its geometric stereoisomer neryl bromide (**7**).[19a] The treatment of **6** and **7** in THF with an excess of Cp_2TiCl led rapidly to the formation of the homocoupling products being the $\alpha\alpha'$ coupling majority together with lesser quantities of the $\alpha\gamma'$ adduct (**8** and **9**) (Figure 2). Digeranyl and isodigeranyl, regioisomers derived from the coupling of **6** (obtained with 57% and 32%, respectively), are naturally occurring terpenes found in the commercially available bergamot oil.[22]

According to these results, we surmised that the process may well begin with a fast single-electron transfer (SET) from Cp_2-

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(9) (a) Wu, T.-C.; Hiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045−5051. (b) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893−5895. (c) Corey, E. J.; Noe, M. C.; Shieh, W.-C. *Tetrahedron Lett.* **1993**, *34*, 5995−5998.
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(22) Soucek, M.; Herout, V.; Sorm, F.; Ceskoslov, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2551−2556.

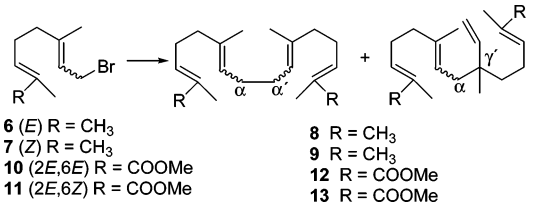


FIGURE 2. Coupling of allylic bromides using Cp_2TiCl_2/Mn.

TiCl (generated in situ) to the corresponding halogenated derivative to give an allylic radical species (**I**). This would then either dimerize to give the coupling products or suffer a second SET process to give an allyltitanium species (**II**), which would react with a molecule of unaltered halogenated derivative to also produce the coupling products (Scheme 1).

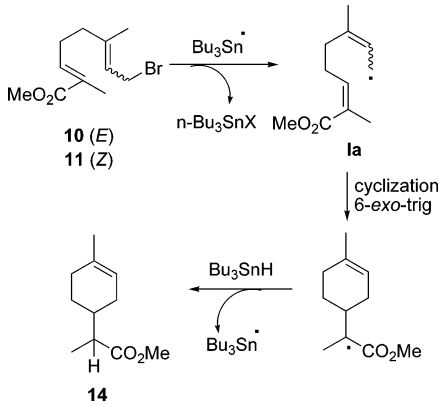
To provide more data about the mechanistic aspects of this coupling, we carried out the reaction with the compounds **10** and **11**, in which the α,β-unsaturated methyl ester group ought to favor the radical cyclization process.[23] The treatment of **10** and **11** with Ti^{III} produced similar results to those obtained with **6** and **7**, and the homocoupling products **12** and **13** were obtained in yields of 84% and 60%, respectively, and no cyclization products were observed. On the other hand, when **10** and its geometric stereoisomer **11** were treated with *n*-Bu_3SnH/AIBN in benzene at 80 °C under free-radical-forming conditions, the corresponding cyclization product, methyl 1-*p*-menthen-9-oate (**14**),[24] was formed via a 6-exo-trig process involving allylic radical **Ia** (Scheme 2). In both cases the cyclization yields were about 70%, together with a 10% yield of coupling products. Thus, the tendency of **Ia** to cyclize rather than to dimerize seems to confirm the involvement of an allyltitanium species in the formation of the coupling compounds. Additionally, this process constitutes an efficient and new mild method for the biomimetic preparation of *p*-menthanes starting from geraniol or nerol.

Once we had established the presence of the allyltitanium species as intermediates in this reaction and bearing in mind that in this double SET process $Cp_2TiClBr$ is released, we anticipated that the excess of Mn in the medium ought to permit the regeneration of Ti^{III} from $Cp_2TiClBr$ and thus render the process susceptible to catalysis by titanium. Gratifyingly, when **6** was made to react with 0.4 equiv of Cp_2TiCl_2 and an excess of Mn, the hoped-for conversion took place efficiently, producing 88% coupling products **8**. To our knowledge this protocol constitutes the only catalytic process involving the reduction of allylic halides.

To find out the extent to which the quantity of Ti^{III} could be reduced in this catalytic process, we made several assays lowering the proportion of Cp_2TiCl_2 used and deduced that the minimum quantity necessary for the reaction to take place was 0.2 equiv. Experiments made with lesser quantities of Ti^{III} invariably showed the presence of unaltered starting material even after prolonged reaction times.

To widen the scope of this catalytic procedure, apart from the previously reported allylic terpenic halides **6**, **7**, **10**, **11**, and **21**,[19a] other structurally varied allylic bromides such as **15**, **17**, **19**, and **23** and the secondary chloro derivative **25** (which is

SCHEME 2. 6-Exo-Trig Cyclization Reaction



easily obtained by regioselective chlorination of β-pinene)[25] were made to react with only 0.2 equiv of Cp_2TiCl_2 and an excess of Mn. It was then found that these reactions took place rapidly (5−15 min) to form the hoped-for coupling products (**8**, **9**, **12**, **13**, **16**, **18**, **20**, **22**, and **24**) (Table 1, entries 1, 2, 4−11), with acceptable selectivity and yields ranging from good to excellent (64−98%). The results obtained with compound **19** deserve special consideration. In this case, the starting material was recovered after 23 h of reaction (Table 1, entry 3). Nevertheless, when the concentration of the coupling reaction of **19** was increased from 0.07 to 0.8 M, 85% of the coupling products **20** was yielded in only 5 min (Table 1, entry 4). The need for a higher concentration in this case compared with the rest of the allylic halides studied may be attributed to the greater stability of the intermediate radical. This concentration effect may suggest that compounds **20** are formed by radical dimerization.

The results shown in Table 1 allowed us to extend the catalytic coupling reaction to different structures deriving from allylic halides and are in accordance with the proposed absence of radicals during the coupling process, given that under these catalytic conditions the concentration of radical **I** (Scheme 1) would be much lower and the probability of coupling would fall significantly versus the much more favorable cyclization process (Table 1, entries 5−9).

Once we had established the catalytic process, we began to study the possibility of further decreasing the quantities of Cp_2TiCl_2 and Mn by using electrophilic salts such as 2,4,6-collidine hydrochloride and LiCl (Table 2).

With allylic bromide **10** as the starting material, we reduced the initial quantity of Cp_2TiCl_2 to 0.1 equiv, obtaining 31% of homocoupling products and recovering 27% of **10** after 90 min (Table 2, entry 2). When using 0.05 equiv of Ti^{III} and 1.5 equiv of Mn, no reaction took place and the starting material was recovered after 90 min (Table 2, entry 3). Nevertheless, when 2,4,6-collidine hydrochloride (2.5 equiv) was added to the reaction medium, the homocoupling of **10** or **11** completed in 20 min (Table 2, entries 4 and 5), although the corresponding reduction product was formed to some extent (12%). If 2,4,6-collidine hydrochloride is replaced by LiCl (2.5 equiv) (Table 2, entry 6), the hoped-for homocoupling products **12** (38%) were now accompanied by the formation of the trans-halogenated derivative **27** (17%). It is believed that 2,4,6-collidine hydro-

(23) Zhang, W. *Tetrahedron* **2001**, *57*, 7237−7262.

(24) Compound **14** was obtained as a mixture of diastereoisomers at a 1:1 ratio.

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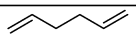
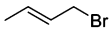
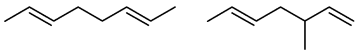
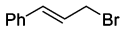
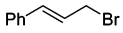
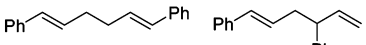
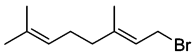
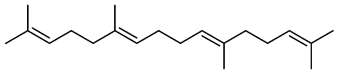
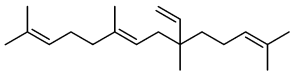
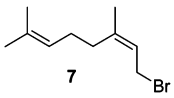
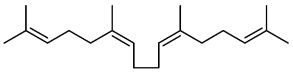
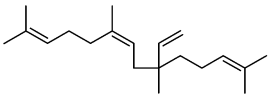
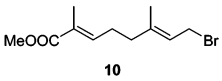
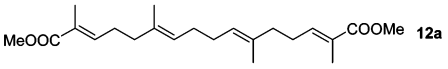
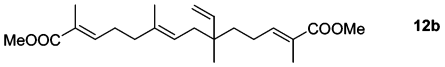
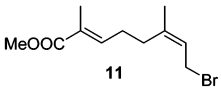
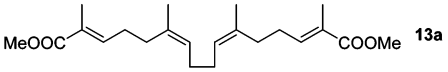
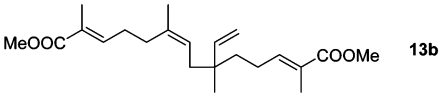
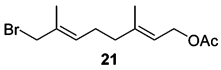
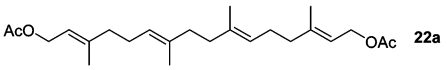
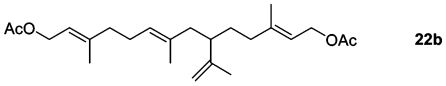
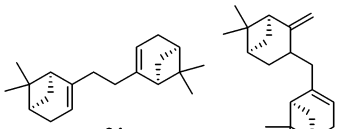
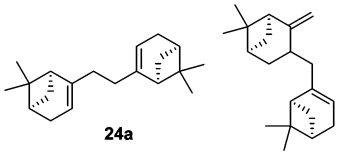
TABLE 1. Coupling of Allylic Halides[a] under Catalytic Conditions[b] of Ti^{III}

Entry	Allylic Halide	[M][c]	Compounds	Ratio[d] (αα′:αγ′)[e]	Yield[f] (%)
1	 **15**	0.07	 **16**		98[g]
2	 **17**	0.07	 **18a** **18b**	(76:24)	85[g]
3	 **19**	0.07	no reaction	–	–
4	 **19**	0.8	 **20a** **20b**	(45:55)	85[h]
5	 **6**	0.07	 **8a**  **8b**	(64:36)	89
6	 **7**	0.07	 **9a**  **9b**	(73:27)	90
7	 **10**	0.07	 **12a**  **12b**	(74:26)	85
8	 **11**	0.07	 **13a**  **13b**	(81:19)	64
9	 **21**	0.07	 **22a**  **22b**	(80:20)	76
10	 **23**	0.07	 **24a** **24b**	(61:39)	70
11	 **25**	0.07	 **24a** **24b**	(52:48)	90

[a] Prepared by the reaction of the corresponding alcohols with Ph_3P/CBr_4 in benzene except for the commercially available **6**, **15**, **17**, and **19** and for the secondary chloro derivative **25**, which is easily obtained by regioselective chlorination of β-pinene. [b] 0.2 equiv of Cp_2TiCl_2 and 8.0 equiv of Mn, THF, rt. [c] Molar concentration compared to the starting material. [d] Determined by GC−MS analysis. [e] A certain degree of *E*/*Z* isomerization was observed. In most cases the different isomers obtained in each coupling process could be isolated either by column chromatography on $AgNO_3$ (20%)−silica gel or by HPLC. [f] Isolated yield after column chromatography. [g] Determined by GC−MS analysis. [h] This yield includes 15% of the γγ′ regioisomer.

TABLE 2. Effect of 2,4,6-Collidine Hydrochloride and LiCl on the Reductive Coupling of Allylic Bromides

entry	allylic bromide	equiv of Cp_2TiCl_2	equiv of Mn	concn[a] (M)	time (min)	equiv of LiCl	equiv of 2,4,6-collidine hydrochloride	compd (yield, %)
1	**10**	0.2	8.0	0.07	10	0	0	**12** (85)
2	**10**	0.1	8.0	0.07	90	0	0	**12** (31)[b]
3	**10**	0.05	1.5	0.07	90	0	0	no reaction
4	**10**	0.05	1.5	0.07	20	0	2.5	**12** (58)[c]
5	**11**	0.05	1.5	0.07	20	0	2.5	**13** (55)[d]
6	**10**	0.05	1.5	0.07	60	2.5	0	**12** (38)[e]

[a] Molar concentration of the starting material. [b] 27% of **10** was recovered. [c] A 12% yield of the reduced product was obtained. [d] A 12% yield of the reduced product was obtained. [e] A 17% yield of the trans-halogenated compound **27** was also obtained.

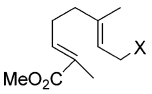
TABLE 3. Coupling of Allylic Bromides under Catalytic Conditions of Zr^{IV}

entry	allylic halide	Cp_2ZrCl_2	concn[a] (M)	time	coupling products	ratio[b] ($\alpha\alpha'/\alpha\gamma'$)	yield[c] (%)
1	**23**	0.2	0.07	28 h	no reaction		
2	**23**	0.2	0.8	21 h	**24**		35[d]
3	**23**	0.3	0.8	10 min	**24**	70:30	65
4	**6**	0.3	0.8	20 min	**8**	81:19	84
5	**19**	0.3	0.8	30 min	**20**	48:52	82[e]
6	**10**	0.3	0.8	20 min	**12**	82:18	78
7	**25**	0.3	0.8	24 h	no reaction		

[a] Molar concentration compared to the starting material. [b] Determined by GC−MS analysis. [c] Isolated yield after column chromatography. [d] Even after 21 h, 32% of starting material **23** was recovered. [e] This yield includes 14% of the $\gamma\gamma'$ regioisomer.

chloride or LiCl establish a Lewis acid−base interaction with the allylic bromide, which facilitates its reduction and subsequent coupling. Thus we conclude that the quantity of Cp_2TiCl_2 and Mn used in the standard protocol (3.0 and 8.0 equiv, respectively) can be considerably reduced to 0.05 equiv of Cp_2TiCl_2 and 1.5 equiv of Mn with no significant loss of efficiency in the process.

Another factor that has been analyzed during this work is the influence of the type of C−X bond (X = Cl, Br, I) upon the coupling reactions. As expected, the main difference observed was the lesser reactivity of the chloro derivative, **27**, compared to the bromo and iodo derivatives, **10** and **28**. Thus, while with **10** and **28** the coupling reaction completed in 10 and 5 min with yields of 85% and 84%, **27** generated 57% coupling products **12** in 75 min, with 10% of the starting material being recovered. The differences in reactivity found can be attributed to the different speeds at which radical **I** was formed due to the different dissociation energies of the C−X.[26]



10 X = Br
27 X = Cl
28 X = I

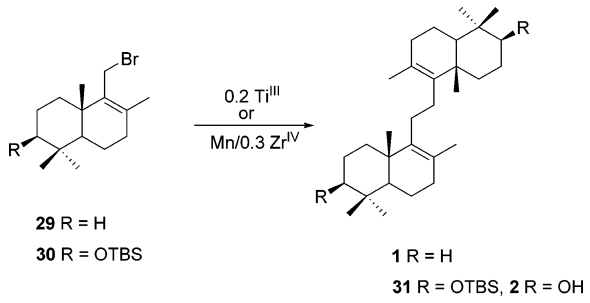
We then turned our attention to the behavior of the Zr^{III} species analogous to those of Ti^{III}. Bearing in mind both the antecedents of Zr^{III} chemistry and the similar electronic structure of Zr and Ti, we presumed that the Zr^{III} species could also affect the homocoupling of allylic halides. We began this study by making myrtenyl bromide (**23**) react under the standard catalytic conditions used with Ti^{III}, namely, 0.2 equiv of Cp_2ZrCl_2, 8 equiv of Mn, and THF (0.07 M). After 28 h, no coupling product was formed and **23** was recovered unaltered (Table 3, entry 1). Nevertheless, an increase to 0.8 M in the concentration of the starting material led to a 35% yield of the coupling products **24** with 32% of the starting material being recovered (Table 3, entry 2). However, although it has been reported that THF solutions of Cp_2ZrCl are deep red,[16b,17] in our case, the combination of Cp_2ZrCl_2 and Mn in THF remained colorless, which suggests that Zr^{III} species were not originated. Thus, with the aim of gaining an insight into the real active species in this process, we proceeded to reduce Cp_2ZrCl_2 with Na(Hg) amalgam[16b] to obtain a deep red solution, thus confirming the presence of Zr^{III} species. Addition of myrtenyl bromide to this Zr^{III} solution did not lead to any coupling adduct in our hands. Considering that Mn itself is not able to reduce allylically halogenated derivatives, an activation of the C−X bond by Cp_2ZrCl_2 (acting as an efficient Lewis acid) is proposed as the preliminary step to trigger this Cp_2ZrCl_2/Mn-mediated transformation.[27] The thus-activated C−X bond is now susceptible to be reduced by Mn to give the corresponding organomanganese derivatives (species represented in Scheme 1 by **II** with M now being Mn).

Additionally, we found that the yield of this process could be further improved when the reaction was carried out at the same molar concentration but increasing the quantity of Zr^{IV} from 0.2 to 0.3 equiv (Table 3, entry 3). In this case, the conversion is total, and **23** gave rise to the corresponding coupling products **24** after only 10 min with a 65% yield. ^1H NMR and GC−MS analyses of the coupling adducts showed a distribution of regioisomers 70:30 favoring the $\alpha\alpha'$ regioisomer. When these data were compared to those obtained with Ti^{III} (Table 1, entry 10), a noticeable increase of the reaction regioselectivity was observed when the combination Mn/Zr^{IV} catalyst was used, while the efficiency of the coupling showed

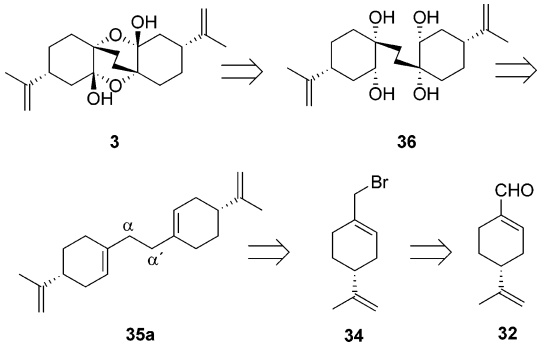
(26) (a) 83.2 kcal/mol (C−Cl), 70.9 kcal/mol (C−Br), and 57.6 kcal/mol (C−I). (b) Mc Givern, W. S.; North, S. W.; Francisco, J. S. *J. Phys. Chem. A* **2000**, *104*, 436−442. (c) Blansksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.

(27) (a) Ma, J.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 2499−2502. (b) Li, C.-J.; Meng, Y.; Yi, X. H. *J. Org. Chem.* **1998**, *63*, 7498−7504. (c) Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 2322−2330. (d) Hiyama, T.; Obayashi, M.; Nakamura, A. *Organomet.* **1982**, *1*, 1249−1251. (e) Cahiez, G.; Chavant, P.-Y. *Tetrahedron Lett.* **1989**, *30*, 7373−7376. (f) Suh, Y.; Lee, J.-S.; Hoi, S.; Rieke, R. D. *J. Organomet. Chem.* **2003**, *684*, 20−36.

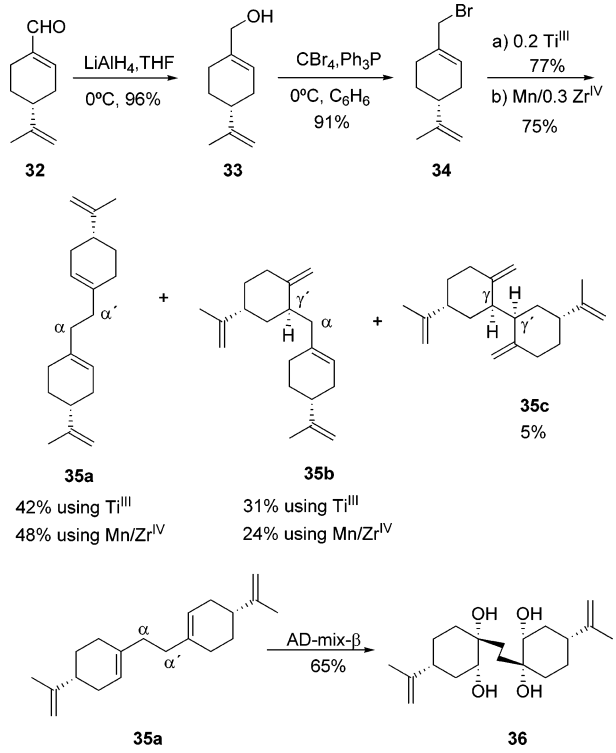
SCHEME 3



SCHEME 4. Approach to the Synthesis of (+)-Cymbodiacetal (3)

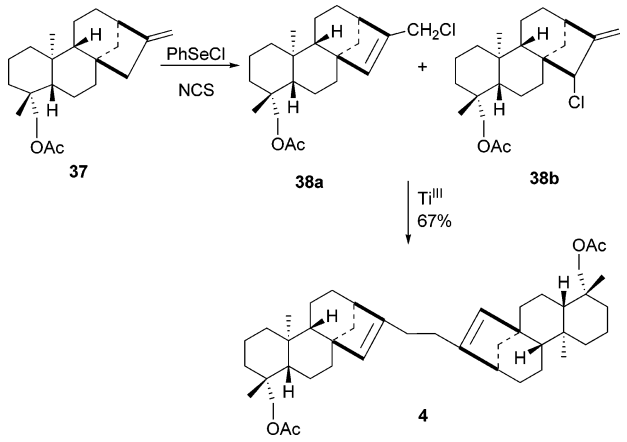


SCHEME 5. Homocoupling Reaction of (*R*)-Perillyl Bromide (34): Synthesis of the Advanced Intermediate 36



no substantial alteration. Similar results were found when either geranyl bromide (**6**) (Table 3, entry 4) or cinnamyl bromide (**19**) (Table 3, entry 5) was treated with 0.3 equiv of Zr^{IV}, which seems to confirm the increase of regioselectivity derived from the use of this reagent in all cases. Furthermore, a thorough analysis of the ^{1}H NMR and GC−MS of the homocoupling products now showed an almost complete geometric purity of the αα′ and αγ′ adducts, thus improving significantly the results

SCHEME 6. Preparation of Dimeric *ent*-Kauranoids



obtained with Ti.^{III} In fact, when geranyl bromide was used as the substrate, the 6:1 ratio of (6*E*,10*E*) and (6*Z*,10*E*) αα′ isomers obtained with Ti^{III} improved by up to 50:1 when Zr^{IV}/Mn mediated the coupling process. This seems to indicate that geometric isomerization (trans to cis) of the allylic manganese should be kept to a minimum during the coupling conditions, which makes this process particularly advantageous. Finally, as happened to be with the Ti^{III}-mediated reactions of allylic bromides **6** and **10**, when these compounds were exposed to the combination Mn/Zr^{IV} catalyst, only the corresponding homocoupling products were obtained (Table 3, entries 4 and 6). The absence of cyclization adducts seems to confirm again that these homocoupling processes should proceed via allylic manganese rather than via radical dimerization (Scheme 1).

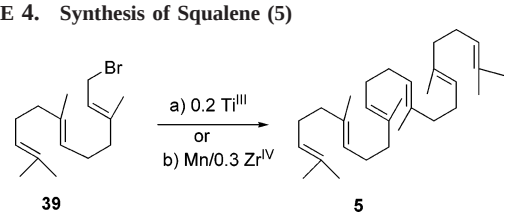
When the secondary allylic chloride **25** was treated under these catalytic procedure conditions, the homocoupling products **24** were not formed and the starting material was recovered unaltered even after prolonged reaction times (Table 3, entry 7). When **25** was exposed to catalytic Ti^{III}, a 90% yield of homocoupling products **24** was obtained in only 5 min (Table 1, entry 11).

Although we have already reported the synthesis of (+)-*β*-onoceradiene (**1**) and (+)-*β*-onocerine (**2**) via Ti^{III}-induced homocoupling of key intermediates **29** and **30**,[19a] we considered that these homocoupling products could also be achieved using Mn and catalytic Cp_2ZrCl_2, which would also allow the utility of this method to be tested. Thus, when **29** and **30** were treated using the combination Mn/Zr^{IV} catalyst, (+)-*β*-onoceradiene and (+)-*β*-onocerine were obtained in comparable yields to those obtained with Ti^{III} (Scheme 3).

We present here new applications of these catalytic homocoupling protocols, such as the preparation of compound **36**, an advanced key-intermediate in the enantioselective synthesis of (+)-cymbodiacetal (**3**) (Scheme 5), and the straightforward access to the framework of naturally occurring dimeric *ent*-kauranoids **4** (Scheme 6).

(+)-Cymbodiacetal (**3**) is a dihemiacetal bis-monoterpenoid isolated from the essential oil of *Cymbopogon martini*.[20] Several varieties of this plant are cultivated for use in soaps and perfumes. The enantioselective synthesis of (+)-cymbodiacetal (**3**) was designed starting from (*R*)-perillyl aldehyde (**32**) (Scheme 4). The key step of this strategy rests on the homocoupling reaction of (*R*)-perillyl bromide (**34**) catalyzed by Ti^{III} or Zr^{IV} to obtain the key intermediate 7,7′-bis((4*R*)-1,8-*p*-menthadiene) (**35a**).

TABLE 4. Synthesis of Squalene (5)



entry	allylic bromide[a]	Ti^{III}	Zr^{IV}	concn (M)	time (min)	coupling products yield (%)	squalene yield (%)
1	**39**	0.2	0	0.07	10	63	43
2	**39**	0	0.3	0.8	60	62	51

[a] Prepared by reaction of *trans*,*trans*-farnesol with Ph_3P/CBr_4 in C_6H_6.

Allylic bromide **34** was obtained by reduction of commercially available (*R*)-perillyl aldehyde (**32**) with $LiAlH_4$/THF and subsequent bromination with CBr_4/Ph_3P. (*R*)-Perillyl bromide (**34**) in the presence of 0.2 equiv of Ti^{III} or 0.3 equiv of Zr^{IV} underwent the expected homocoupling reaction to give 77% and 75%, respectively, of the corresponding coupling adducts, with the αα′ regioisomer **35a** being the major reaction product (Scheme 5). Moving forward with the synthetic planning, we found that compound **35a** could be chemo- and stereoselectively hydroxylated to efficiently lead to tetrol **36** as the only detectable stereoisomer using AD-mix-*β*,[28] as evidenced by the NOE effect observed between H2 and H4, both protons in an axial disposition in the most stable chair conformation of the cyclohexane ring in **36**. Even though preliminary dihemiacetal formation assays (PDC and Dess−Martin oxidations) were disappointing in that they furnished unacceptably low yields (approximately 5%) of the desired natural product **3**, the four-step sequence illustrated above for the preparation of **36** appears sufficiently promising to warrant completion of the synthesis.

Recently, the isolation of bioactive dimeric *ent*-kauranoids, such as xindongnins M−O,[21] lushanrubescensin J,[29] and bisrubescensins A−C[30] from different species of *Isodon rubescens*, called our attention. It was then envisioned that the dimeric framework of these structures could be easily constructed via the Ti^{III}- or Zr^{IV}/Mn-mediated homocoupling of the corresponding allylic halides (Scheme 6). We chose as the starting material *ent*-kaur-16-en-19-ol isolated from *Odontites longiflora*.[31] When its acetate derivative **37** was treated with PhSeCl and NCS,[25] the mixture of allylic chlorides **38** was obtained. When this mixture was exposed to catalytic Ti^{III}, we found the octacyclic structure **4**, although unreacted starting material **38** remained unaltered even after prolonged reaction times. It was nevertheless found that when 1.1 equiv of Cp_2TiCl was used, the reaction was completed after only 5 min and a 67% yield of dimer **4** was obtained.

Finally, we previously reported that squalene (**5**) can be prepared from *trans*,*trans*-farnesyl bromide (**39**) using 0.2 equiv of Ti^{III} in only one step in 43% yield (Table 4, entry 1). Bearing in mind the higher degree of regioselectivity and geometric purity of the Mn/Zr-mediated couplings, we hoped that this yield could be improved using these metals. Gratifyingly, the exposure of **39** to 0.3 equiv of Zr^{IV} and 8 equiv of Mn led to a 51% yield of squalene (Table 4, entry 2). In fact, the ^1H NMR and GC−MS analyses of the coupling products in both cases showed that the 66:22:12 ratio of αα′(*EE*)/αα′(*ZE*)/αγ′(*E*) regioisomers obtained with Ti^{III} improved considerably in the Zr^{IV}-mediated process, where no *E*/*Z* isomerization was noticed and a 82:18 ratio of αα′(*EE*)/αγ′(*E*) regioisomers was obtained. This catalytic process probably constitutes one of the easiest and most efficient synthetic ways to prepare squalene.

Conclusion

In conclusion, we present new catalytic methods for the homocoupling of allylic halides mediated either by Ti^{III} or by Mn/Zr^{IV} species with good to excellent yields. Thus, on the one hand, the range of applicability of the previously published Cp_2-TiCl-protocol coupling has been widened with the successful homocoupling of a number of allylic halides. Furthermore, it was found that the use of Lewis acids such as 2,4,6-collidine hydrochloride allows for the lowering of the quantity of Ti^{III} up to 0.05 equiv. On the other hand, the results obtained in the use of the combination Mn and Cp_2ZrCl_2 catalyst are presented. Both methods are very mild and should tolerate most functional groups. It is noteworthy that the regioselectivity of the process increases significantly when the combination Mn/Zr^{IV} catalyst is used as the reagent and when cyclic substituted allylic halides are used as substrates. These reagents have been employed in the efficient synthesis of symmetric terpenes, such as the onocerane derivatives (**1** and **2**), the preparation of an advanced key-intermediate in the enantioselective synthesis of (+)-cymbodiacetal (**3**), the framework of dimeric *ent*-kauranoids (**4**), and the synthesis of squalene (**5**).

Experimental Section

Homocoupling Reactions. Catalytic Protocol with Ti^{III}. A mixture of Cp_2TiCl_2 (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) and under Ar atmosphere was stirred at rt until the red solution turned green. The corresponding allylic halide (3.68 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp_2TiCl solution. The reaction mixture was stirred for 15 min, quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel to afford the corresponding coupling products.

Representative Example. (*R*)-Perillyl bromide (**34**) (2644 mg, 12.3 mmol) was subjected to the Ti^{III} catalytic procedure conditions (631 mg, 2.46 mmol of Cp_2TiCl_2 and 5412 mg, 98.4 mmol of Mn), and the resulting crude product was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford 1275 mg (77% yield) of a mixture of the corresponding coupling products **35** (αα′/(αγ′ + γγ′) at a 54:46 ratio). The corresponding mixture was subjected to flash column chromatography on $AgNO_3$ (20%)−silica gel (hexane/*t*-BuOMe, 99:1), and two fractions were obtained, the first containing the αα′ coupling product 7,7′-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) and the second containing the αγ′ coupling product (4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-yl)-1,8-*p*-menthadiene (**35b**). Finally, *t*-BuOMe was added and the γγ′ coupling product (**35c**) could be isolated.

Catalytic Protocol with Zr^{IV}. A mixture of Cp_2ZrCl_2 (462 mg, 1.58 mmol) and Mn dust (2323 mg, 42.20 mmol) in deoxygenated THF (9 mL) and under Ar atmosphere was stirred at rt. The

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(31) Barrero, A. F.; Riu, M. V.; Ramirez, A.; Altarejos, J. *An. Quim.* **1988**, *84C*, 203−206.

corresponding allylic bromide (5.28 mmol) in strictly deoxygenated THF (1 mL) was then added (TLC monitoring). The reaction mixture was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel to afford the corresponding coupling products **35**.

Representative Example. (*R*)-Perillyl bromide (**34**) (240 mg, 0.95 mmol) was subjected to the Zr^{IV}/Mn catalytic procedure conditions (56 mg, 0.19 mmol of Cp_2ZrCl_2 and 421 mg, 7.67 mmol of Mn), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford 192 mg (75% yield) of a mixture of the corresponding coupling products **35** ($\alpha\alpha'/(\alpha\gamma' + \gamma\gamma')$ at a 63:37 ratio).

7,7′-Bis((4*R*)-1,8-*p*-menthadiene) (35a). $[\alpha]_D$ +75.9 (*c* 2.65, CH_2Cl_2); ν (film) 3080, 2962, 2921, 2854, 1644, 1455, 1436, 1373, 886 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.48 (2H, ddd, $J = 5.6$, 11.3, 17.1 Hz), 1.75 (6H, s), 1.80−1.85 (2H, m), 1.87−2.15 (10H, m), 2.06 (4H, bs), 4.73 (4H, bs), 5.43 (2H, bs) ppm; δ_C (100 MHz, $CDCl_3$) 20.9, 28.0, 29.0, 30.9, 36.1, 41.3, 108.5, 120.3, 137.6, 150.3 ppm; EIMS (70 eV) *m*/*z* (relative intensity) 270 (15), 227 (35), 187 (22), 159 (18), 145 (32), 134 (25), 119 (55), 105 (61), 93 (95), 91 (100), 79 (73), 67 (42), 44 (45).

7,7′-Bis(1(*R*),2(*R*)-dihydroxy-8-*p*-menthene) (36). 7,7′-Bis((4*R*)-1,8-*p*-menthadiene) (**35a**) (285 mg, 1.06 mmol) was added to a solution of AD-mix-β (2968 mg) and $CH_3SO_2NH_2$ (207 mg, 2.11 mmol) in *t*-BuOH/H_2O 1:1 (10 mL) at 0 °C and stirred. After 7 h, $Na_2S_2O_3$ (2385 mg) was added to the reaction mixture while stirring for 10−20 min was continued at rt. The *t*-BuOH was removed and extracted with EtOAc. The organic phase was washed with 6 N NaOH (3 × 100 mL) and brine, then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, with the crude product thus obtained being purified by column chromatography on silica gel (*t*-BuOMe) to give **36** (230 mg, 65%). $[\alpha]_D$ +9.96 (*c* 0.5, MeOH); ν (film) 3399, 3327, 2941, 2916, 2854, 1642, 1441, 1261, 1161, 1062, 880, 749 cm^{-1}; δ_H (400 MHz, DMSO) 1.10−1.65 (16H, m), 1.66 (6H, s), 1.80−1.90 (2H, m), 3.20 (2H, m), 4.22 (2H, d, $J = 6.7$ Hz), 4.63 (2H, s), 4.64 (2H, s) ppm; δ_C (100 MHz, DMSO) 20.7, 25.7, 32.3, 33.5, 35.3, 43.2, 71.6, 72.9, 108.4, 149.5 ppm; HRFABMS calcd for $C_{20}H_{34}O_4Na$ $[M + Na]^+$ 361.2355, found 361.2354.

17,17′-Bis(19-acetoxy-*ent*-isokaurene) (4). A mixture of Cp_2TiCl_2 (37 mg, 0.14 mmol) and Mn dust (53 mg, 0.96 mmol) in strictly deoxygenated THF (1 mL) was stirred at room temperature until the red solution turned green. Then **38a** and **38b** (46 mg, 0.12 mmol) in strictly deoxygenated THF (1 mL) were added to the solution of Cp_2TiCl. The reaction mixture was stirred for 5 min, quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 20:1) to afford a 67% yield of the coupling product **4**. $[\alpha]_D$ −42.0 (*c* 1.0, CH_2Cl_2); ν (film) 2926, 2865, 1739, 1456, 1371, 1238, 1031 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.94 (6H, s), 1.04 (6H, s), 1.20−1.90 (36H, m), 2.04 (6H, s), 2.20 (4H, s), 2.39 (2H, bs), 3.87 (1H, d, $J = 11.0$ Hz), 4.22 (2H, d, $J = 11.0$ Hz), 5.07 (2H, bs) ppm; δ_C (100 MHz, $CDCl_3$) 18.3, 18.5, 19.1, 19.7, 21.3, 25.8, 27.7, 28.1, 36.6, 37.3, 39.6, 40.2, 40.7, 43.8, 44.0, 49.1, 49.3, 56.8, 67.4, 134.3, 147.0, 171.6 ppm; HRFABMS calcd for $C_{44}H_{66}O_4$ $[M + Na]^+$ 681.4859, found 681.4857.

Procedure for Radical Cyclization Reaction of 10 and 11. A solution of tributyltin hydride (228 mg, 0.76 mmol) and AIBN (7 mg, 0.04 mmol) in dry, degassed benzene (14 mL) was added dropwise (10 mL/h) to a solution of the bromide (**10** or **11**) (100 mg, 0.38 mmol) in dry, degassed benzene (136 mL) heated to 80 °C under an atmosphere of argon. After the addition time plus an additional hour (TLC monitoring), the cooled mixture was evaporated under reduced pressure, and the residue was dissolved in diethyl ether. An aqueous saturated KF solution (5 mL) was added, and the mixture was stirred for 2 h at rt. After filtration through Celite, the biphasic filtrate was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether after separation. The combined organic extracts were concentrated under reduced pressure, and the crude product was purified by column chromatography (petroleum ether/diethyl ether, 20:1) on silica gel to afford 50 mg (72%) of the cyclized compound methyl 1-*p*-menthen-9-oate (**14**).

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **4**, **8b**, **14**, **20a**, **20b**, **23**, **24**, **25**, **27**, **34**, **35a**−**c**, **36**, **38a**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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