ORGANIC LETTERS

2005
Vol. 7, No. 12
2301−2304

Reductive Coupling of Terpenic Allylic Halides Catalyzed by Cp_2TiCl: A Short and Efficient Asymmetric Synthesis of Onocerane Triterpenes

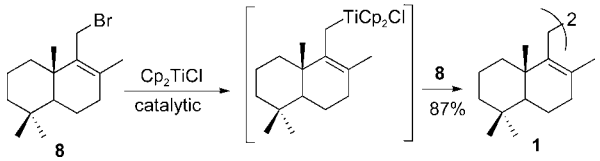
Alejandro F. Barrero,* M. Mar Herrador, José F. Quílez del Moral, Pilar Arteaga, Jesús F. Arteaga, María Piedra, and Elena M. Sánchez

Department of Organic Chemistry, Institute of Biotechnology, University of Granada, Avenida Fuentenueva, 18071 Granada, Spain

afbarre@goliat.ugr.es

Received February 17, 2005

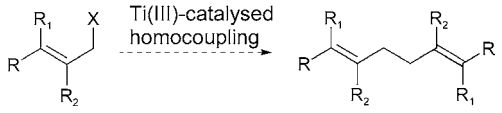
ABSTRACT



Titanocene chloride catalyzes the regioselective α,α′-homocoupling of terpenic allylic halides. This process has been employed in the short and effective synthesis of terpenoids such as *β*-onoceradiene (1), *β*-onocerin (2), and squalene (3). Evidence is presented for η^1-allyltitanium species being involved in the coupling.

To continue with our research into the use of bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl) in the synthesis of terpenoids,[1] we report here on our achievements in the development of a novel synthetic method based on a Ti(III)-catalyzed carbon−carbon coupling of allylic halogenated terpenoids (Scheme 1) and its application to the expeditious synthesis of triterpenoids such as squalene (**3**) and onocerane derivatives **1** and **2**.[2]

Scheme 1. General Approach



Titanocene monochloride[3] has been used in the past in the homolytic opening of oxiranes[4] and in pinacol coupling reactions.[5] This reagent has also provided good results in the reduction of glycosyl bromides[6] and *vic*-dibromides.[7] Furthermore, it has been reported that Cp_2TiCl promotes the homocoupling of benzylic and allylic halides.[8] Bearing in mind the mechanism of the above-mentioned reactions and the broad range of functional groups tolerated (alcohols, amines, amides, ketones, acids, esters),[6d] we thought that this reagent might efficiently mediate the homocoupling of terpenic allylic halides. A number of methods have already been developed to perform the homocoupling of allylic and alkyl halides[9] such as the reductive coupling of allylic halides by chlorotris(triphenylphosphine) cobalt(I)[9g] or Te^{2-} species,[9f] the reaction of allylic organometallic compounds with allylic halides,[9e] the coupling of π-methallylnickel(I) bromide with halides,[9c] the homocoupling of alkyl halides via activated copper,[9q] and so on. In the field of terpenoid synthesis, the

(1) (a) Justicia, J. J.; Rosales, A.; Oller-López, J. L.; Valdivia, M. V.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778−1788. (b) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074−4078. (c) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J.Org. Chem.* **2002**, *67*, 2566−2571. (d) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935−1938. (e) Barrero, A. F.; Cuerva, J. M.; Álvarez-Manzaneda, E. J.; Oltra, J. E.; Chahboun, R. *Tetrahedron Lett.* **2002**, *43*, 2793−2796.

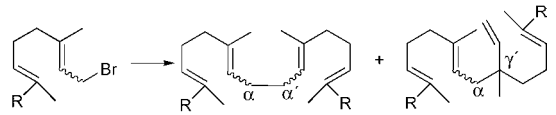
(2) Connolly, J. D., Hill, R. A., Eds. In *Dictionary of Terpenoids*; Chapman & Hall: London, U.K, 1991; Vol. 2, pp 1405−1406.

10.1021/ol050335r CCC: $30.25
Published on Web 05/14/2005

homocoupling reaction of allylic halides using Rieke barium[10] is particularly interesting. This method has been reported to give good results in the coupling of (*E*,*E*)-farnesyl barium with farnesyl bromide,[11] although its aplication has been limited.

We started the development of this synthetic method by choosing the simplest terpenic allyl halides: geranyl bromide (**4a**) and its geometrical isomer neryl bromide (**4b**). When these compounds were exposed to an excess of Cp_2TiCl,[12] the α,α′ coupling products (**5a** and **5b**) were mainly obtained after only 2 min, together with the α,γ′ adduct (Table 1, entries 1 and 3).

Table 1. Coupling of Allylic Bromides[a] Using Cp_2TiCl_2/Mn



4a (*E*) R = CH_3
4b (*Z*) R = CH_3
4c (2*E*,6*E*) R = COOMe
4d (2*E*,6*Z*) R = COOMe

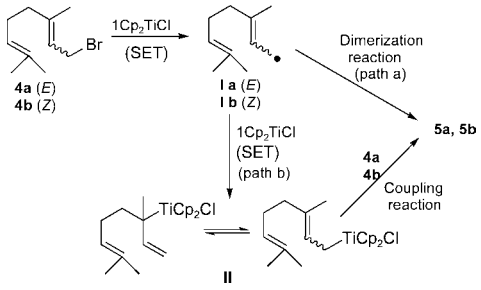
5a R = CH_3
5b R = CH_3
5c R = COOMe
5d R = COOMe

entry	allylic bromide	equiv of Cp_2TiCl_2[b]	time (min)	ratio[c] α,α′:α,γ′[d]	compd	yield[e] (%)
1	**4a**	3	2	70:30	**5a**	80
2	**4a**	0.2	15	64:36	**5a**	89
3	**4b**	3	2	74:26	**5b**	70
4	**4b**	0.2	15	73:27	**5b**	90
5	**4c**	3	2	77:23	**5c**	84
6	**4c**	0.2	10	74:26	**5c**	85
7	**4d**	3	2	85:15	**5d**	60
8	**4d**	0.2	10	81:19	**5d**	64
9[f]	**4c**	3	10	85:15	**5c**	67
10[g]	**4d**	0.05	20	78:22	**5d**	55

[a] Prepared by the reaction of corresponding alcohols with Ph_3P/CBr_4 in benzene except for the commercially available geranyl bromide. [b] Performed with 8 equiv of Mn, 0.07 M solutions, THF, rt. [c] Determined by GC analysis. [d] A certain degree of *E*/*Z* isomerization is observed. In most cases, the different isomers obtained in each coupling process could be isolated either by column chromatography on $AgNO_3$ (20%)−Si gel or by HPLC. For details, see Experimental Section. [e] Isolated yield after column chromatography. [f] Performed with 28 equiv of H_2O. [g] Performed with 2.5 equiv of 2,4,6-collidine hydrochloride.

To account for this result, the following mechanistic proposals might be postulated: the process would start by a fast single-electron transfer (SET) from Cp_2TiCl (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 **5** or suffer a second SET process to give an η^1-allyltitanium species (**II**), which would react with a molecule of unaltered halogenated derivative also to produce the coupling products **5** (Scheme 2).

Scheme 2



Evidence to help distinguish between the mechanistic paths proposed may be inferred from a further analysis of the results. Thus, although the geometry of the radical **Ia** might not be suitable to lead to a 6-*exo* cyclization with the 6,7 double bond, its geometrical isomer **Ib** should give rise to the formation of the corresponding *p*-menthanes. Since no derivative *p*-menthanes were ever detected, the mechanism via allyltitanium (**II**) would seem in principle more likely.[13] Continuing with the mechanistic aspects of this reaction, we prepared compounds **4c** and **4d**, in which the α,β-unsaturated methyl ester group (better nucleophilic radical acceptor) ought to favor the radical cyclization process.[14] When these α,β-unsaturated ester derivatives were made to react with

(3) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103−2112.

(4) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc*. **1988**, *110*, 8561−8562. (b) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc*. **1994**, *116*, 986−997. (c) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc*. **1998**, *120*, 12849−12859. (d) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, *16*, 2500−2520.

(5) (a) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem*. **1998**, 1923−1927. (b) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem*. **1998**, 2673−2676.

(6) (a) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem*. **1995**, *60*, 7055−7057. (b) Spencer, R. P.; Schwartz, J. *Tetrahedron Lett*. **1996**, *37*, 4357−4360. (c) Spencer, R. P.; Schwartz, J. *J. Org. Chem*. **1997**, *62*, 4204−4205. (d) Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. *J. Org. Chem*. **1999**, *64*, 3987−3995. (e) Hansen, T.; Krintel, S. L.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett*. **1999**, *40*, 6087−6090. (f) Hansen, T.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett.* **2000**, *41*, 8645−8649.

(7) Davies, S.; Thomas, S. E. *Synthesis* **1984**, 1027−1029.

(8) (a) Rasmus, J. E.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc*. **2004**, *126*, 7853−7864. (b) Yanlong, Q.; Guisheng, L.; Huang, Y. *J. Organomet. Chem*. **1990**, *381*, 29−34.

(9) (a) Corey, E. J.; Hamanaka, E. *J. Am. Chem. Soc*. **1964**, *86*, 1641−1642. (b) Corey, E. J.; Semmelhack, M. F. *Tetrahedron Lett*. **1966**, *7*, 6237−6240. (c) Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc*. **1967**, *89*, 2755−2757. (d) Baker, R. *Chem. Rev*. **1973**, *73*, 487−530. (e) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc*. **1978**, *100*, 6282−6284. (f) Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem*. **1982**, *47*, 1641−1647. (g) Momose, D.; Iguchi, K.; Sugiyama, T.; Yamada, Y. *Tetrahedron Lett*. **1983**, *24*, 921−924. (h) Calo, V.; López, L.; Pesce, G. *J. Chem. Soc., Perkin Trans.* 1 **1988**, 1301−1304. (i) Rieke, R. D.; Kavaliunas, A. V.; Rhyne, L. D. *J. Am. Chem. Soc*. **1979**, *101*, 246−248. (j) Merijanian, A.; Mayer, T. *J. Org. Chem*. **1972**, *37*, 3945−3947. (k) Benkeser, R. A. *Synthesis* **1971**, *7*, 347−358. (l) Courtois, G.; Miginiac, L. *J. Organomet. Chem*. **1974**, *69*, 1−44. (m) Kitagawa, Y.; Oshima, K.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett*. **1975**, 1859−1862. (n) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett*. **1977**, *43*, 3829−3830. (o) Nakanishi, S.; Oda, T.; Ueda, T.; Otsuji, Y. *Chem. Lett*. **1978**, 1309−1312. (p) Tokuda, M.; Satoh, K.; Suginome, H. *Chem. Lett*. **1984**, 6, 1035−1038. (q) Ginah, F. O.; Donovan, T. A.; Suchan, S. D.; Pfenning, D. R.; Ebert, G. W. *J. Org. Chem*. **1990**, *55*, 584−589. (r) Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem*. **2002**, *67*, 966−969.

(10) (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.-CH. *Tetrahedron Lett*. **1993**, *34*, 5995−5998.

(11) This process represented the first direct synthesis of squalene by the coupling of two (*E*,*E*)-farnesyl units.

(12) Procedure used in the opening of oxiranes; see ref 1b.

(13) Existence of η^1-allyltitanium species in equilibrium has been postulated previously: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc*. **1995**, *117*, 3881−3882.

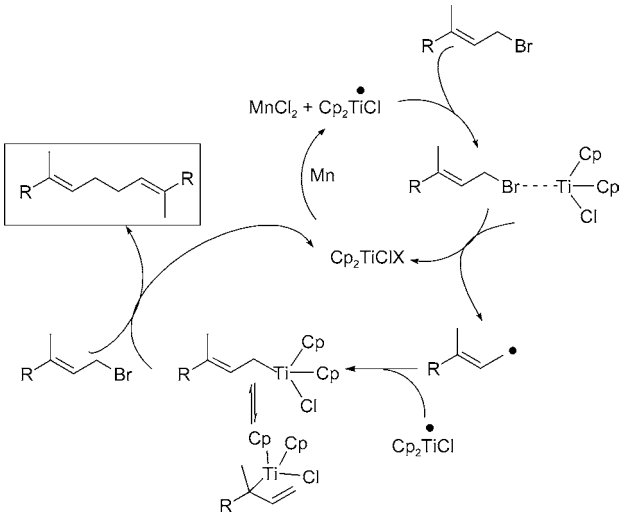
(14) Zhang, W. *Tetrahedron* **2001**, *57*, 7237−7262.

Ti(III) (Table 1, entries 5 and 7), the results were no different from those obtained with **4a** and **4b**. Thus, the homocoupling products **5c** and **5d** were obtained in yields of 84 and 60%, respectively, and no cyclization products were observed.

One final piece of evidence to denote the presence of the allyltitanium intermediate (**II**) was the formation of the corresponding reduction products[15] when **4c** and **4d** were made to react with species possessing electrophilic protons such as H_2O and 2,4,6-collidine hydrochloride.

Once we had established the presence of allyltitanium species as intermediates in this reaction, and bearing in mind that in these double SET processes $Cp_2TiClBr$ is released, we anticipated that the excess of Mn present in the medium should permit the regeneration of Ti(III) and thus the process would be susceptible to catalysis by titanium (Scheme 3).

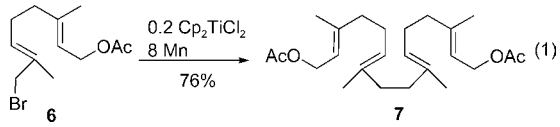
Scheme 3. Catalytic Cycle



Thus, we caused **4a**−**d** to react with 0.2 equiv of Cp_2TiCl_2 and an excess of Mn and found that these reactions took place rapidly (10−15 min), forming the corresponding coupling products (**5a**−**d**) as expected (Table 1, entries 2, 4, 6, and 8).

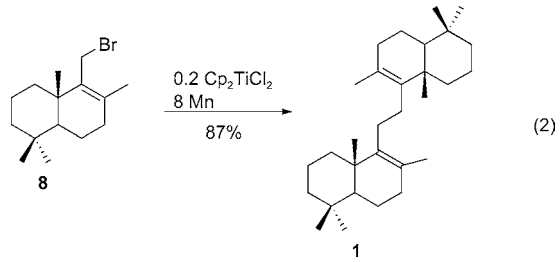
These results are in accordance with the proposed absence of radicals during the coupling process, given that, under these catalytic conditions, the concentration of radical **I** would be much lower and the probability of coupling would fall significantly versus the much more favorable cyclization process. It is also worth noting that the yields obtained with 0.2 equiv of Cp_2TiCl_2 were even higher than those obtained using the standard protocol (3 equiv of Cp_2TiCl_2) and that comparable results were also found when the quantity of organotitanium was reduced to 0.05 equiv. The fact that reaction yields did not depend on the quantity of Cp_2TiCl_2 employed might be more easily understood if **II** is presumed to associate with a second molecule of the halogenated derivative **4** via a Lewis acid−base interaction.

To widen the scope of this Ti(III)-catalytic procedure, we employed the bromo-derivative of geranyl acetate **6**. Similar results were also observed, and a 76% yield of coupling products was obtained, again as a mixture of α,α′ and α,γ′ isomers (4:1 ratio) (eq 1).



With these results in mind, we felt that different triterpenoids such as squalene, β-onoceradiene (**1**), and β-onocerin (**2**) could be synthesized using this catalytic procedure.[16] Thus, squalene was prepared in only one step from farnesyl bromide with 0.2 equiv of Ti(III) in a yield of 43%. This process represents a direct and catalytic synthesis of squalene by the coupling of two (*E*,*E*)-farnesyl units.

The enantiospecific synthesis of β-onoceradiene (**1**) was designed starting from natural (−)-drimenol.[17] Following a protocol reported elsewhere,[18] we achieved isomerization of the double bond to the Δ^8 position via the corresponding formyl derivative. Subsequent reduction and bromination afforded **8**.[19] The homocoupling reaction of **8** in the presence of catalytic quantities of Ti(III) afforded an excellent yield (87%) of **1** (eq 2).



The optical rotation and spectroscopic data of **1** coincide with those of the natural product.[20] The high regioselectivity attached to this process, presumably due to the inherent steric hindrance involved in the formation of the α,γ′ adduct, is noteworthy.

β-Onocerine (**2**) was enantioselectively synthesized from farnesyl acetate according to Scheme 4. Two key steps can be underlined in this synthesis: the radical cyclization of

(15) Reaction of **4c** with Ti(III) in the presence of water led to the formation of a 16% yield of methyl (2*E*,6*E*)-2,6-dimethyl-2,6-octadienoate. With **4d**, a 12% yield of methyl (2*E*,6*Z*)-2,6-dimethyl-2,6-octadienoate was obtained in the presence of 2,4,6-collidine hydrochloride. In both cases, the corresponding homocoupling products were also formed (Table 1, entries 9 and 10).

(16) Corey and co-workers have recently described a total synthesis of (+)-α-onocerin, see: Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290−11291. Previous syntheses of onocerane derivatives, most relying on numerous steps, can be found in references cited in the above-mentioned paper.

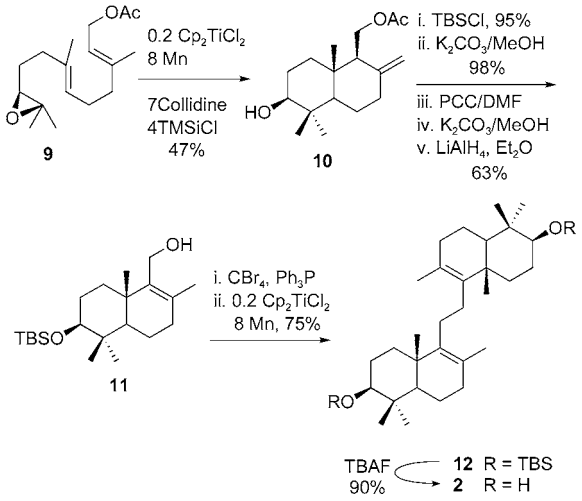
(17) Isolated from the bark of *Drimys winteri*. Appel, H. H.; Brooks, J. W.; Overton, K. H. *J. Chem. Soc.* **1959**, 3322−3332.

(18) Fernández-Mateos, A.; Burón, L. M.; Martín de la Nava, E. M.; González, R. R. *J. Org. Chem.* **2003**, *68*, 3585−3592.

(19) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635−5650.

(20) Masuda, K.; Shiojima, K.; Ageta, H. *Chem. Pharm. Bull.* **1989**, *37*, 263−265.

Scheme 4. Synthesis of β-Onocerin (**2**)



10*S*,11-epoxyfarnesyl acetate (**9**) catalyzed by Ti(III) and the homocoupling reaction of the corresponding allyl bromide in the presence of Ti(III) to give product **2**. Epoxide **9** was obtained by the enantioselective *cis*-dihydroxylation of farnesyl acetate using AD-mix-β followed by treatment of the diol with $MeSO_2Cl$-py and base.[21] Treatment of epoxide **9** with catalytic Ti(III) afforded the bicyclic alcohol **10** in a yield of 47%.[1a] Protection of the secondary hydroxyl group with TBSCl followed by isomerization of the double bond via the corresponding aldehyde[18] led to alcohol **11**. Bromination of **11** afforded the corresponding allyl bromide, which in the presence of catalytic Ti(III) suffered a homocoupling reaction to give 75% of the corresponding tetracyclic adduct. Finally, deprotection of the silyl group with TBAF afforded β-onocerin[22] (**2**) in a yield of 90%.

In conclusion, we present a new catalytic Ti(III)-mediated method for the homocoupling of allylic halides. It is noteworthy that the regioselectivity of the process increases considerably when cyclic allylic halides are used as substrates, as has been demonstrated with the highly efficient asymmetric synthesis of β-onoceradiene (**1**) and β-onocerine (**2**).

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology, Project BQU 2002-03211. Thanks go to our colleague Dr. J. Trout for revising our English text.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **1**−**3**, **4c**,**d**, **5a**−**d**, and **6**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050335R

(21) *cis*-Dihydroxylation of farnesyl acetate using AD-mix-β was previously reported by Vidari et al. to give the corresponding (10*R*)-diol in 98% ee; the optical rotation $[\alpha]_D^{20}$ measured for this compound was +12.3. See: Vidari, G.; Dapiaggi, A.; Zanoni, G.; Gaslaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485−6488. In our hands, this protocol led to similar results; thus, we obtained this diol with an $[\alpha]_D^{20}$ value of +12.1.

(22) Tanaka, T.; Tanaka, O.; Lin, Z.-W.; Zhou, J.; Ageta, H. *Chem. Pharm. Bull.* **1983**, *31*, 780−783.