Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2867-2870, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00484-X

Efficient Synthesis of 7-, 8- and 9-Membered Cyclic Allyltitanium Compounds and Their Stereoselective Addition Reaction with Aldehydes and Imines

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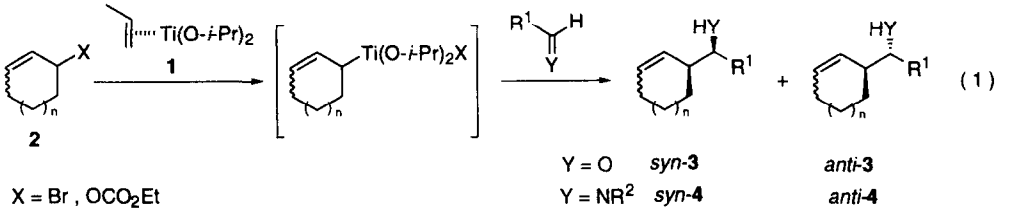
Abstract: *Reaction of 7-, 8- and 9-membered cyclic allylic compounds* **2** *with (η^2-propene)Ti(O-i-Pr)$_2$* (**1**) *via an oxidative addition pathway provides the corresponding allylic titanium compounds, which, in turn, react with aldehydes and imines stereoselectively, thus providing an efficient and stereoselective method for synthesizing cycloalkenes having a side chain at the allylic position.*

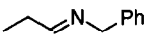
Reaction of acyclic allylic compounds such as halides, acetates and carbonates with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), which is readily generated *in situ* from Ti(O-*i*-Pr)$_4$ and 2 equiv. of *i*-PrMgCl, results in an oxidative addition reaction to provide allylic titanium complexes in excellent yield. The allylic titanium complexes thus prepared exhibit good to excellent diastereoselectivities in their reaction with aldehydes[1a] and imines.[1b] With these results in hand, we were interested in expanding the reaction to cyclic allylic compounds **2** (*i.e.*, the reaction sequence shown in eq. 1), because the reaction might furnish a selective method for synthesizing cycloalkenes having a side chain at the allylic position.[2] We took particular interest in applying the reaction to **2** with a medium ring since development of stereoselective access to medium-ring carbocycles has attracted considerable attention.[3]



To determine the feasibility of the reaction under our conditions, we carried out the reaction of **1** with 6-, 7-, 8-, 9- and 12-membered **2** at -50 to -40 °C for 1.5 h in ether, the reaction mixture was then treated with propanal at around -40 °C for 1 h (eq. 1, Y = O, R^1 = C_2H_5). The results are summarized in Table 1 (entries 1-8).[4]

It can be seen from Table 1 that 6-membered substrates gave unsatisfactory results with respect to both yield and stereochemical outcome (entries 1 and 2). The bromide **2a** provided only 3% yield of the expected **3**

Table 1. Synthesis of cyclic allyltitanium compounds from **2** and their reaction with an electrophile[a]

Entry	Substrate **2**			Electrophile	Product (**3** or **4**)[b]	
	n	X			Yield (%) [c]	Diastereoselectivity [d] *syn : anti* [e]
1	1	Br	**a**	EtCHO	3[f]	not determined
2	"	OCO_2Et	**b**	"	26[g]	-- [h]
3	2	Br	**c**	"	14[f]	84 : 16
4	"	OCO_2Et	**d**	"	71	80 : 20
5	3	Br	**e**	"	85	95 : 5
6	"	OCO_2Et	**f**	"	83	95 : 5
7	4	"	**g**	"	98	90 : 10
8	7	"	**h**[i]	"	70	-- [j]
9	3	Br	**e**	PhCHO	93	97 : 3[k]
10	"	"	"		72	5 : 95[l]

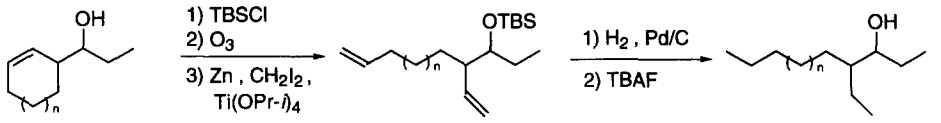
[a] The reaction was carried out with a reactant ratio of **2**:Ti(O-*i*-Pr)$_4$:*i*-PrMgCl: electrophile = 1:1.1:2.2:0.7. [b] The products have (*Z*)-olefin geometry (no (*E*)-isomer was detected) except for entry 8 which was confirmed by ^{1}H NMR analysis. [c] Isolated yields based on electrophile. [d] Determined by ^{1}H NMR. [e] Determination of the stereochemistry, see text. [f] The homocoupling product of **2** was obtained in 68% yield in entry 1 and 55% yield in entry 3. [g] The starting **2b** was recovered in 35% yield. [h] Two diastereomers were obtained in a 64:36 ratio. [i] The starting **2h** was an (*E*)- and (*Z*)-mixture in a ratio of 85:15. [j] At least three stereomixtures in a ratio of 4:2:1. [k] Determination of the stereochemistry was based on ^{1}H NMR analysis (ref. 5). [l] For the determination of stereochemistry, see ref 6.

(R^1= Et, n=1) and 68% yield of 1, 1'-bi(2-cyclohexene) which might be obtained by the coupling of the resulting allyltitanium complex and **2a** under the reaction conditions. The reaction with the carbonate **2b** resulted in a better yield, but it was still 26% and the diastereoselectivity was low. In this case, the starting **2b** was recovered in 35% yield, supposedly due to the lower reactivity of the carbonate. Seven-membered bromide **2c** also provided a self-coupling product mainly (entry 3); however, the corresponding carbonate **2d** afforded **3** (R^1= Et, n=2) in high yield and in an 80:20 diastereomeric ratio where the major product has *syn* stereochemistry with respect to the newly-created stereogenic centers (entry 4). Gratifyingly, the reaction with 8- and 9-membered substrates **2e-g** provided excellent results; the reaction, regardless of whether the starting compounds was bromide or carbonate, provided the corresponding **3** with (*Z*)- and *syn*-configuration with high selectivity and in excellent yields (entries 5, 6 and 7). Reaction of 12-membered carbonate **2h** also gave the expected adduct, but the products consisted of at least three compounds in a ratio of 4:2:1 (entry 8). This result indicated that the reaction afforded not only a mixture of diastereomers dependent on the newly-created stereogenic centers but also on olefinic stereochemistry. To ascertain that the reaction provided the mixture of olefinic isomers, we treated the allyltitanium intermediate derived form **2h** with non-prochiral acetone, and found the production of the corresponding adducts, (*E*)- and (*Z*)-2-(2-cyclododecen-1-yl)propan-2-ol, in a ratio of *E*/*Z*=7/3.

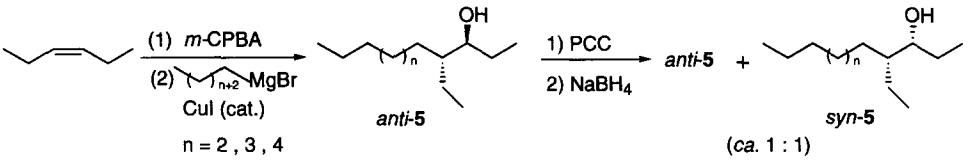
The result that the major product obtained by the reactions shown in entries 4-7 has *syn*-configuration was confirmed by derivatization to the corresponding acyclic 4-ethyl-3-alkanol **5**. Thus, each product was

converted into the corresponding **5** according to the procedure shown in Scheme 1, and it was found that the major product was coincident with the **5** having *anti*, and not *syn*, stereochemistry, both of which were synthesized unambiguously according to the procedure shown in Scheme 2.

Scheme 1: Derivatization of **3** to **5**



Scheme 2: Synthesis of authentic *syn*- and *anti*-**5**



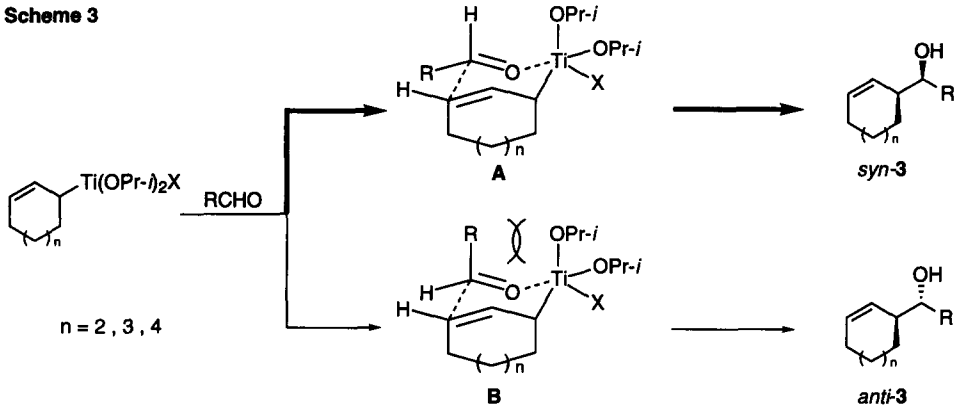
Several aspects of the reaction shown in Table 1 deserve further comment. The diastereoselectivity attained in the reaction with 8- and 9-membered **2** was far better than that observed for the reaction of acyclic allylic titanium complexes which was represented by the production of a 75:25 diastereomixture from a crotyltitanium complex and propanal.[1a] The production of the *syn*-adduct with respect to the newly-created stereogenic centers shown in entries 3-7 is seemingly a striking contrast to the reaction of acyclic allylic titanium complexes with aldehydes which affords *anti*-adduct predominantly. This result can be explained by assuming the generation of a cyclic allylic titanium complex with (*Z*)-stereochemistry from **2d-g** which is conformationally inevitable and/or favorable, but not (*E*)-allylic titanium complexes as is the case of acyclic allyltitaniums, and that the reaction with propanal proceeds *via* a cyclic six-membered transition state (**A**) rather than (**B**) as shown in Scheme 3.[7] The production of both olefinic isomers of the propanal adduct from 12-membered substrate **2h** can be explained by the formation of the allyltitanium complex having both (*E*)- and (*Z*)-stereochemistry.

With synthetically very useful results starting with 8- and 9-membered **2**, we then carried out the reaction of the allylic titanium complex derived from **2e** with benzaldehyde and *N*-benzylidenepropylamine. The reactions similarly proceeded with high stereoselectivity (the results also included in Table 1, entries 9 and 10). Thus, the reaction with benzaldehyde proceeded with 97 % diastereoselectivity to afford the *syn*-addition product. The reaction with *N*-benzylidenepropylamine was slow at -40 °C, but it proceeded readily at -40 ~ -20 °C, eventually affording amine **4** (R^1= Et, Y = NBn, eq. 1) having *anti*-stereochemistry with respect to the newly-created stereogenic centers in excellent diastereoselectivity of 95 %. The *anti*-stereochemistry observed here can be explained by the similar six-membered chair-like transition state shown in Scheme 3 in which the imine R^1 group occupies an axial position as was proposed by Yamamoto.[8, 1b]

In conclusion, the reaction of 7-, 8- and 9-membered **2** with **1** afforded the corresponding allylic titanium compounds in excellent yield. The allylic titanium compounds thus obtained react with aldehydes and

imines with high stereoselectivity, thus providing an efficient and stereoselective method for synthesizing cycloalkenes having a side chain at the allylic position.

Scheme 3



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2. Synthesis of cyclic allyltitanium complexes of the type Cp2Ti(η^3-cycloallyl) and their reactions with electrophiles have been reported, see: Kobayashi, Y.; Umeyama, K.; Sato, F. *J. C. S., Chem. Commun.* **1984**, 621-623; Szymoniak, J.; Pagneux, S.; Felix, D.; Moïse, C. *Synlett* **1996**, 46-48 and references cited therein.
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4. The following procedure is typical: To a stirred solution of Ti(O-*i*-Pr)4 (0.364 g, 1.28 mmol) and 3-bromocyclooctene (0.219 g, 1.16 mmol) in ether (8 mL) was added a 1.68 M ethereal solution of *i*-PrMgCl (1.52 mL, 2.56 mmol) at -50 °C. The reaction mixture was stirred at -45 ~ -50 °C for 1.5 h, and then propanal (0.047 g, 0.81 mmol) was added. The reaction mixture was stirred for 1 h at around -40 °C. The reaction was terminated by dropwise addition of 1 N HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (10 mL x 3). The combined organic layer was dried on MgSO4 and concentrated to an oil, which was chromatographed on silica gel to afford 1-(2-cycloocten-1-yl)propan-1-ol (0.117 g, 85 % yield).
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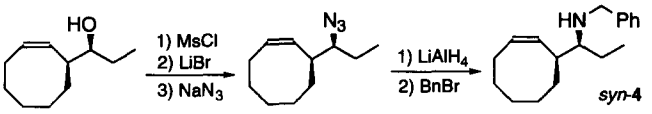
6. The *anti*-stereochemistry of the major isomer in entry 10 (Table 1) was confirmed by comparing its ^1H and ^{13}C NMR spectra with *syn*-**4** prepared as follows:



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(*Received in Japan* 3 *February* 1997; *revised* 5 *March* 1997; *accepted* 7 *March* 1997)