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Stereoselective Synthesis of Metalated Cyclobutyl Derivatives

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This paper is dedicated to Armin de Meijere for his 70th birthday.

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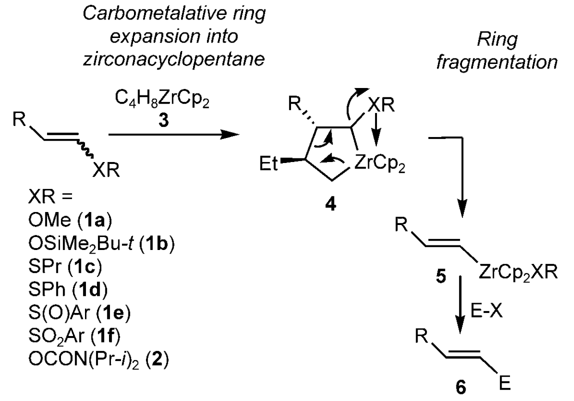
Abstract: Treatment of *Z*-vinyl carbamates with dicyclopentadienyl(diethyl)zirconium [Et_2ZrCp_2] leads to cyclobutyl-zirconocene derivatives in good yields and as a unique diastereoisomer. The reaction proceeds through a carbometalative ring-expansion followed by an intramolecular migratory insertion.

Keywords: carbometalation; cyclobutanes; enol carbamates; ring expansion; zirconocenes

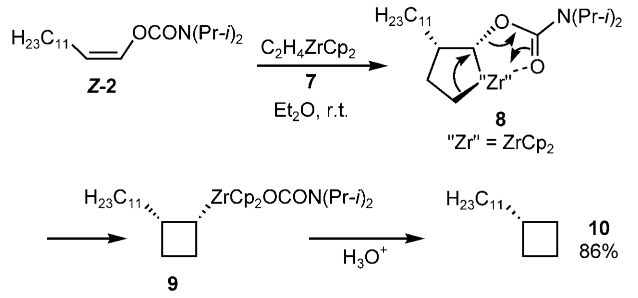
We have recently reported that *E*- and *Z*-heterosubstituted alkenes such as enol ether **1a**,[1] silyl enol ether **1b**,[2] vinyl alkyl (and aryl) sulfides **1c** and **1d**, vinyl sulfoxides **1e**, vinyl sulfones **1f**,[3] and vinyl carbamates **2**,[4] were excellent candidates for the stereoselective preparation of alkenylmetals[5] and conjugated dienyl[6] organometallic derivatives. Typically, the reactions proceed in a few hours at room temperature by treatment of heterosubstituted alkenes with the Negishi reagent $C_4H_8ZrCp_2$ (**3**)[1,7] (easily prepared *in situ* by reaction of the commercially available Cp_2ZrCl_2 with two equivalents of *n*-BuLi, Scheme 1).[8]



Scheme 1. General preparation of *E*-vinyl-zirconocene derivatives from heterosubstituted alkenes.

Interestingly, except for vinylic carbamate **2**, the reaction leads only to the *E*-vinyl-zirconocene regardless of the initial *E*- or *Z*-stereochemistry of the starting heterosubstituted alkenes **1a**–**f**. This isomerization has been rationalized through a carbometalative ring expansion between **1a**–**f** and **3**, leading to the corresponding five-membered ring zirconacycle **4** in which the carbon-heteroatom bond of the sp^3-metallated center isomerizes to produce the most stable intermediate. Then, by a skeletal rearrangement (or elimination),[9] the corresponding vinyl zirconocenes **5** were first obtained and after reaction with electrophiles, functionalized alkenes **6** were produced in excellent yields. This transformation represents the formal substitution of an sp^2 heteroatom (O, S) by an electrophile. This methodology was extended to conjugated unsaturated enol ethers *via* a subsequent C,H-bond activation-elimination sequence.[6,10]

As far as **2** is concerned, the higher configurational stability of the sp^3-metallated center in the zirconacycle **4** [XR = OCON(Pr-*i*)$_2$] slows down the isomerization[11] and *E*-**2** gave *E*-**6** whereas *Z*-**2** gave a mixture of two geometrical isomers of **6** in a *Z*/*E* ratio of 80/20 after reaction with iodine.[4] On the other hand, $C_2H_4ZrCp_2$ [**7**; prepared by reaction of Cp_2ZrCl_2 with 2 equivalents of EtMgBr or EtLi, known to give a zirconocene-ethylene complex $Cp_2Zr(CH_2{=}CH_2)$ in a similar way to **3**], leads to a different chemistry due to the presence of the ethylene ligand.[12] Indeed, the ethylene ligand reacts with various unsaturated com-



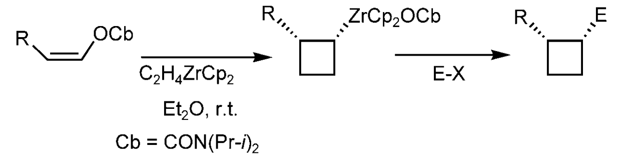
Scheme 2. Reaction of *Z*-enol carbamate **2** with $C_2H_4ZrCp_2$.

pounds and as it is usually incorporated in the reaction product, we thought that the outcome of the reaction of **2** with **7** could be completely different. We were pleased to see that indeed when **7** was added to *Z*-**2**, the formation of the vinyl-zirconocene species **5** $[XR=OCON(Pr\text{-}i)_2]$ was not observed but instead, and as expected, a cyclobutane derivative **10** was isolated after hydrolysis in very good yield as described in Scheme 2. This new outcome could be rationalized through an initial carbometalation reaction of **7** with **2** to lead to the corresponding intermediate zirconacyclopentane **8** (first step is similar to the one described in Scheme 1 but with $C_2H_4ZrCp_2$) but, instead of a ring fragmentation, a ring contraction of **8** occurs to give the corresponding metalated cyclobutane **9** (intramolecular migratory insertion)[13] and then cyclobutane derivative **10** after hydrolysis.

Straightforward methods for the stereoselective preparation of *metalated cyclobutane* species are relatively rare in the arsenal of synthetic tools[14] and this method represents, with the ones recently described by Barluenga, Fañanás, Rodríguez and co-workers,[15] a powerful entry to such species. It should also be noted that metalated cyclobutenes were also reported by ring contraction when a zirconocene species was added to an alkynyl halide.[16] The fundamental significance of zirconocene migratory insertion as a process permitting carbon-carbon bond formation is growing exponentially,[17] particularly when zirconocene carbenoid species are used.[18]

The reaction described in Scheme 2 shows that different alkyl groups can be present on the starting materials (see Table 1, entries 1 to 3). As the alkylzirconocene species presents some configurational stability,[19] the question of the stereochemistry of an sp^3 stereogenic center was then raised. As shown in entry 4 of Table 1, the addition of iodine to the metalated cyclobutyl derivative **9** leads only to the *syn*-diastereoisomer **13**. When a transmetalation reaction was performed by addition of a stoichiometric amount of CuCl, the transmetalation occurs with complete retention of configuration to yield the resulting configurationally stable organocopper species as judged by the stereochemistry of the reaction with allyl bromide (formation of **14**, Table 1, entry 5). The stereochemistry was determined by NMR experiments (see Experimental Section). Similarly, the addition of different electrophiles gave the corresponding functionalized cyclobutane derivatives **15** and **16** (entries 6 and 7, respectively, Table 1).

Table 1. Formation of disubstituted cyclobutanes.



Entry	R	E-X	E	*dr*[a]	Yield [%][b]
1	n-$C_{11}H_{23}$	H_3O^+	H (**10**)	–	86
2	$Ph(CH_2)_3$	H_3O^+	H (**11**)	–	80
3	$PhCH_2$	H_3O^+	H (**12**)	–	75
4	n-$C_{11}H_{23}$	I_2	I (**13**)	>98:2	65
5	n-$C_{11}H_{23}$	AllylBr[c]	C_3H_5 (**14**)	>98:2	55
6	$Ph(CH_2)_3$	D_2O	D (**15**)	>98:2	70
7	$Ph(CH_2)_3$	allylBr[c]	C_3H_5 (**16**)	>98:2	85

[a] Ratio determined by ^1H NMR spectroscopy of the crude mixture.

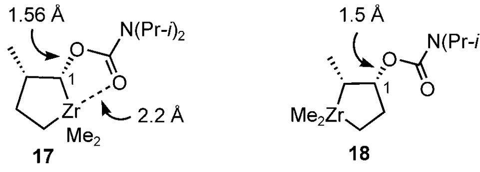
[b] Yield determined after purification by chromatography on silica gel.

[c] CuCl was first added to transmetalate the cyclobutyl-zirconocene derivatives into the corresponding organocopper species.

To have a better understanding of this intramolecular migratory insertion (**8** into **9**, Scheme 2), we have investigated the mechanism of the rearrangement by theoretical calculations.[20,21]

Two alternative zirconacycles (Scheme 3) were optimized and their energies compared. Zirconacycle **17** ("Zr" species α to carbamate carbon) is 21.6 kcal mol^{-1} more stable than its β analogue **18**, which rules out the formation of the latter. This stabilization can be attributed to the carbonyl-Zr chelation, which does not exist in **18** (see bond lengths on Scheme 3). Solvatation does not change this picture.

Thus, **17** with one Me_2O coordinated to $ZrMe_2$ is stabilized by 2.3 kcal mol^{-1} as compared to the gas phase, whereas **18**, coordinated to two Me_2O molecules, is stabilized by 3.7 kcal mol^{-1} relative to the gas phase. It can be safely concluded that **17** (but not **18**) is the zirconacycle intermediate in the reaction. We



Scheme 3. Model structures of **17** and **18**.

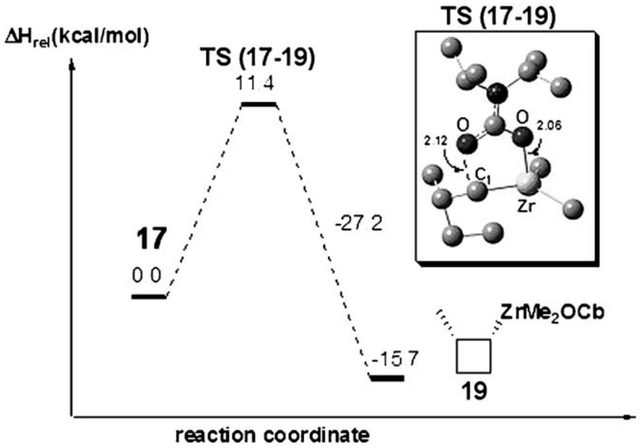


Figure 1. Potential energy profile for the ring contraction of **17** to form **19**.

have further found that the ring contraction of **17** is an exothermic process (15.7 kcal mol^{-1} are released), which indeed affords a zirconium-substituted cyclobutane species **19**. The transformation feasibility is confirmed by a reasonable energetic barrier of 11.4 kcal mol^{-1} (Figure 1). A structural comparison between **17** and the $TS_{\mathbf{17\text{-}18}}$ shows a shortening of the Zr–O bond along with an elongation of the C1–O bond (Figure 1 vs. Scheme 3). The mechanism depicted in Scheme 2 is therefore coherent with the computational results.

In conclusion, the treatment of *Z*-vinyl carbamate with Et_2ZrCp_2 leads to the cyclobutyl-zirconocene derivatives in good yields and as a unique diastereoisomer. The reaction proceeds through a carbometalative ring-expansion followed by an intramolecular migratory insertion. Applications to the synthesis of enantiomerically pure cyclobutyl-zirconocene derivatives are under study in our research group.

Experimental Section

General Procedure

A solution of ethylmagnesium bromide (2 equiv., 1 N solution in Et_2O) in diethyl ether was added slowly to a solution of bis(cyclopentadienyl)zirconium dichloride (1 equiv.) in dry diethyl ether at −78 °C. The reaction mixture was warmed to 0 °C, stirred for 5 min and cooled again to −78 °C. *Z*-Vinyl carbamate **2** (1 equiv.) was added slowly in dry diethyl ether (5 mL). The solution was allowed to warm to room temperature and stirred for 20 min. The formation of zirconacyclobutane derivative **9** was checked by TLC analysis after acidic hydrolysis of aliquots. The reaction was quenched with an aqueous solution of HCl (1 M). The phases were separated and the aqueous phase was extracted three times with ether. The combined organic layers were washed with saturated solution of $NaHCO_3$ and dried over anhydrous $MgSO_4$. Purification was performed by silica gel chromatography with pure hexane.

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References

[1] A. Liard, I. Marek, *J. Org. Chem.* **2000**, *65*, 7218.
[2] A. Liard, J. Kaftanov, H. Chechik, S. Farhat, N. Morlender-Vais, C. Averbuj, I. Marek, *J. Organomet. Chem.* **2001**, *624*, 26.
[3] S. Farhat, I. Marek, *Angew. Chem.* **2002**, *114*, 1468; *Angew. Chem. Int. Ed.* **2002**, *41*, 1410.
[4] H. Chechik-Lankin, I. Marek, *Synthesis* **2005**, 3311.
[5] a) S. Farhat, I. Zouev, I. Marek, *Tetrahedron* **2004**, *60*, 1329; b) N. Chinkov, H. Chechik, S. Majumdar, A. Liard, I. Marek, *Synthesis* **2002**, 2473.
[6] a) N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2002**, *124*, 10282; b) N. Nicka, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 13258; c) B. Canchegui, P. Bertus, J. Szymoniak, *Synlett* **2001**, 123.
[7] N. Chinkov, I. Marek, in: *Stereoselective Synthesis of Dienyl Zirconocene Complexes*, in: *Topics in Organometallic Chemistry*, (Ed.: I. Marek), Springer Verlag, Dublin, Heidelberg, **2004**, p 133.
[8] For reviews, see a) E. Negishi, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755; b) E. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124; c) E. Negishi, D. Y. Kondakov, *Chem. Soc. Rev.* **1996**, *25*, 417.
[9] a) J. P. Maye, E. Negishi, *Tetrahedron Lett.* **1993**, *34*, 3359; b) E. Negishi, J. P. Maye, D. Choueiry, *Tetrahedron* **1995**, *51*, 4447; c) T. Takahashi, T. Fujimori, T. Seki, M. Saburi, Y. Uchida, C. J. Rousset, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1990**, 182.
[10] a) N. Chinkov, S. Majumdar. I. Marek, *Synthesis* **2004**, 2411; b) I. Marek, N. Chinkov, A. Levin, *Synlett* **2006**, 501.
[11] For leading references of configurationally stable *sp*^{3} metallated carbamates, see: a) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282; b) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708.
[12] a) T. Takahashi, N. Suzuki, M. Kageyama, Y. Nitto, M. Saburi, E. Negishi, *Chem. Lett.* **1991**, 1579; b) T. Takahashi, Y. Nitto, T. Seki, M. Saburi, E. Negishi, *Chem. Lett.* **1990**, 2259.
[13] For an account on the insertion reaction of carbenoids with organozirconium species, see: S. Dixon, R. J. Whitby, in: *Titanium and Zirconium in Organic Synthesis*, (Ed.: I. Marek), Wiley-VCH, Weinheim, **2002**, p 86.
[14] *The Chemistry of Cyclobutanes*, in: *The Chemistry of Functional Groups*, (Eds.: Z. Rappoport, J. F. Liebman), Wiley, Chichester, **2005**.

[15] a) J. Barluenga, J. Calleja, M. J. Antón, L. Alvarez-Rodrigo, F. Rodríguez, F. J. Fañanás, *Org. Lett.* **2008**, *10*, 4469; b) J. Barluenga, L. Álvarez-Rodrogo, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2004**, *116*, 4022; *Angew. Chem. Int. Ed.* **2004**, *43*, 3932; c) F. J. Fañanás, F. Rodríguez, *Eur. J. Org. Chem.* **2008**, 1315; d) J. Barluenga, F. Rodríguez, L. Alvarez-Rodrigo, F. Fañanás, *Chem. Soc. Rev.* **2005**, *34*, 762.

[16] K. Kasai, Y. Liu, R. Hara, T. Takahashi, *Chem. Commun.* **1998**, 1989.

[17] E. Negishi, S. Huo, in: *Synthesis and Reactivity of Zirconocene Derivatives*, in: *Titanium and Zirconium in Organic Synthesis*, (Ed.: I. Marek), Wiley-VCH, **2002**.

[18] For selected examples, see: a) E. Negishi, B. Akiyoshi, K. O'Conner, G. Takagi, G. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 3089; b) S. F. Fillery, G. J. Gordon, T. Luker, R. J. Whitby, *Pure Appl. Chem.* **1997**, *69*, 633; c) A. N. Kasatkin, R. J. Whitby, *J. Am. Chem. Soc.* **1999**, *121*, 7039; d) A. N. Kasatkin, R. J. Whitby, *Tetrahedron Lett.* **1999**, *40*, 9353; e) A. N. Kasatkin, R. J. Whitby, *Tetrahedron Lett.* **2000**, *41*, 5275; f) E. Thomas, S. Dixon, R. J. Whitby, *Angew. Chem.* **2006**, *118*, 7228; *Angew. Chem. Int. Ed.* **2006**, *45*, 7070; g) E. Thomas, S. Dixon, R. J. Whitby, *Tetrahedron Lett.* **2006**, *47*, 9181; h) D. Norton, R. J. Whitby, E. Griffen, *Chem. Commun.* **2004**, 1214.

[19] R. A. Bubnik, J. K. Kochi, *J. Organomet. Chem.* **1976**, *116*, C3.

[20] All the systems under study underwent full geometry optimization and analytical frequencies calculations to ensure real minima ($N_{imag}=0$) and transition states ($N_{imag}=1$) at the B3LYP/LANL2DZ theoretical level. The transition state was further confirmed by internal reaction coordinate (IRC) calculations. All the energies are ZPE corrected and reported in kcal mol^{-1}. $ZrMe_2$ served as a model for $ZrCp_2$ and Me represents the alkyl substituent.

[21] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03, Revision C.02*, Gaussian, Inc., Wallingford CT, **2004**.