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Zirconium-Mediated Intramolecular Ester Transfer Reaction: Synthesis of α-Substituted γ-Aminobutyric Acid (GABA) Derivatives

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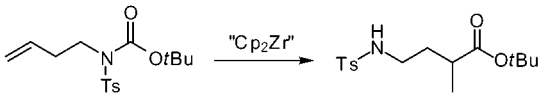
ABSTRACT



The zirconium-mediated intramolecular ester transfer reaction of *N*-alkenyl carbamate derivatives proceeded to give α-substituted γ-aminobutyric acid (GABA) derivatives in good to excellent yields. Quenching experiments of the reaction mixture with iodine or O_2 indicated the presence of a cyclopropane intermediate. The resulting iodide was converted to 2-substituted pyrrolidine-3-carboxylate and/or α-alkylidene-γ-aminobutyric acid derivatives in a stereospecific manner.

Low-valent zirconium-mediated intramolecular coupling reaction of unsaturated functional groups has been widely developed as a powerful tool for the construction of cyclic compounds.[1] Although many reports on intramolecular coupling reaction of alkene, alkyne, and imine derivatives have appeared, to the best of our knowledge, there is no example of a zirconium-mediated intramolecular coupling reaction between alkene and carbonyl moieties. On the other hand, low-valent titanium-mediated intramolecular coupling reaction of the carbon−carbon multiple bond with a carbonyl group to afford cycloalkanol, cycloalkanone, lactone and related compounds has been reported.[2,3] Furthermore, some catalytic approaches to the intramolecular coupling reaction of alkene with a carbonyl group by using titanocene derivatives were successfully achieved.[4] In particular, titanium-mediated intramolecular nucleophilic acyl substitution (INAS) reaction of alkene with a carbonate moiety is a useful tool for the construction of lactone derivatives.[5] Contrary to such a low-valent titanium chemistry, the use of a zirconocene equivalent (zirconocene butene complex, "Cp_2Zr")[6] in these reactions would be difficult due to the high oxophilicity of the zirconium atom resulting in the attack of the butene ligand on the carbonyl group prior to the butene−alkene ligand exchange reaction. We anticipated that both electronic and steric features of the carbonyl moiety would affect its reactivity toward the zirconocene equivalent, and thus *N*-alkenyl-*N*-substituted *tert*-butyl carbamate (**1** or **3**) was chosen as the substrate for the intramolecular coupling reaction due to the relatively lower reactivity of this sterically hindered carbamate than that of ketone or ester. Moreover, the substituent on the nitrogen atom would control the reaction pathway depending on its ability as a leaving group.

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(1) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 1163.

(2) For early works on titanium-mediated intramolecular coupling reaction of a carbon−carbon multiple bond with carbonyl compounds, see: Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684.

(3) For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

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(5) (a) Lee, J.; Kim, Y. G.; Bae, J. G.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878. (b) Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. See also ref 3.

(6) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

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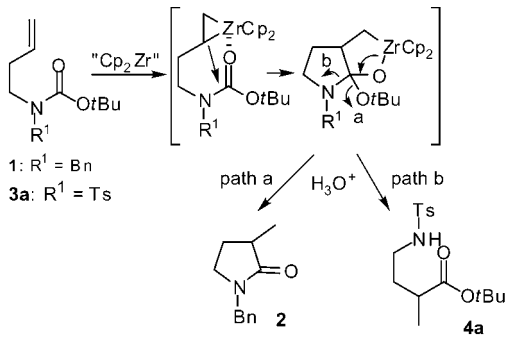
That is, as shown in Scheme 1, lactam derivative **2** would be formed from the substrate **1** having an electron-donating

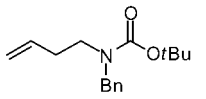
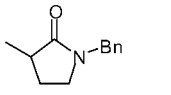
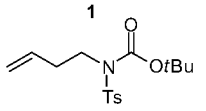
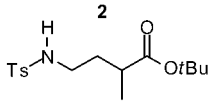
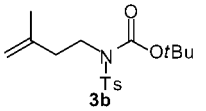
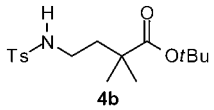
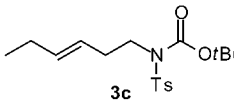
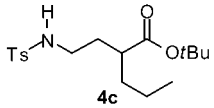
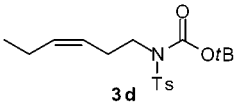
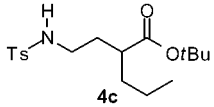
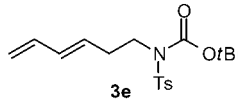
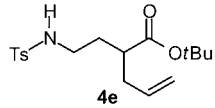
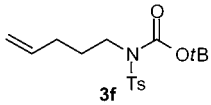
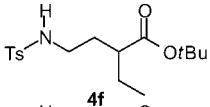
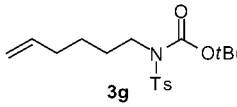
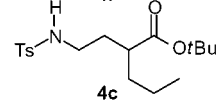
Scheme 1



group, while γ-amino carboxylic acid derivative **4** would be obtained from the substrate **3** with an electron-withdrawing group such as a sulfonyl group. We report herein an efficient synthetic method for the selective construction of lactam derivatives and α-substituted γ-aminobutyric acid (GABA) derivatives through Cp_2Zr-mediated intramolecular coupling reaction of alkene and carbamate moieties (Scheme 1).[7]

Preliminary results are summarized in Table 1. The zirconium-mediated intramolecular coupling reaction of *N*-benzyl carbamate derivative **1** smoothly proceeded to give pyrrolidine derivative **2** in 75% yield through path a (entry 1). A similar reaction of **3a** having an electron-withdrawing group (*p*-toluenesulfonyl group) with Cp_2Zr also efficiently proceeded through path b to give the γ-amino ester derivative **4a** in excellent yield (entry 2).[8] The present coupling reaction could be applied to the substrates with a disubstituted olefin part, **3b**−**e**, to give the products **4b**−**e** in slightly lower yields (entries 3, 5, 7, and 8). As shown in entries 4 and 6, toluene, instead of THF, was a more effective solvent for the substrate that has a hindered olefin part. The coupling reaction of 4-pentenyl carbamate **3f** proceeded smoothly *after migration of zirconium to a more hindered inner site* in a way to form the five-membered ring intermediate (entry 9 and Scheme 2).[9,10] One more carbon-elongated 5-hexenyl carbamate **3g** was also reacted intramolecularly after the migration of

Table 1. Zirconium-Mediated Intramolecular Ester Transfer Reaction[a]

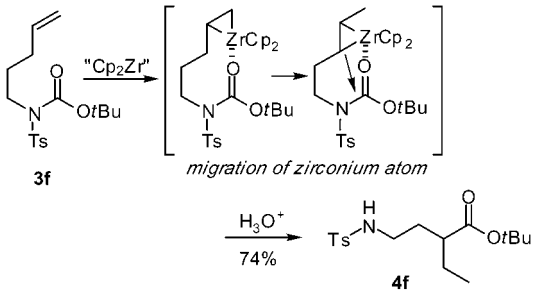
entry	substrate	product	yield[b]
1	 **1**	 **2**	75
2	 **3a**	 **4a**	95
3	 **3b**	 **4b**	51
4			71[c]
5	 **3c**	 **4c**	41
6			56[c]
7	 **3d**	 **4c**	82
8	 **3e**	 **4e**	50
9	 **3f**	 **4f**	74
10	 **3g**	 **4c**	50

[a] Compound **1** or **3** (0.5 mmol), Cp_2Zr prepared from Cp_2ZrCl_2 (0.6 mmol) and *n*-butyllithium (1.2 mmol), THF, rt. [b] Isolated yield. [c] Toluene was used as the solvent.

zirconium to give the α-propyl-γ-amino ester **4c** (entry 10). These substrates **3a**−**g** were easily prepared by the Mitsunobu reaction of the corresponding alken-1-ol with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide.[11]

To clarify the reaction mechanism and to introduce an additional functional group into the product, we examined the quenching of the intermediate with electrophiles. Although the reaction of alkylzirconium with oxygen has been

Scheme 2



(7) Zirconium-mediated intermolecular coupling reaction of alkyne with chloroformate to obtain the α,β-unsaturated esters was reported. Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K.; *J. Am. Chem. Soc.* **2000**, *122*, 3228.

(8) *Typical Experimental Procedure for the Intramolecular Ester Transfer Reaction.* Under an argon atmosphere, a solution of *n*-butyllithium (1.48 M in hexane, 0.81 mL, 1.2 mmol) was added to a solution of zirconocene dichloride (175 mg, 0.6 mmol) in THF (2 mL) at −78 °C, and the reaction mixture was stirred at the same temperature for 1 h. A solution of compound **3** (0.5 mmol) in THF (2 mL) was added to the reaction mixture at −78 °C, and the mixture was stirred at ambient temperature for 1 h. To the reaction mixture was added 4% hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography.

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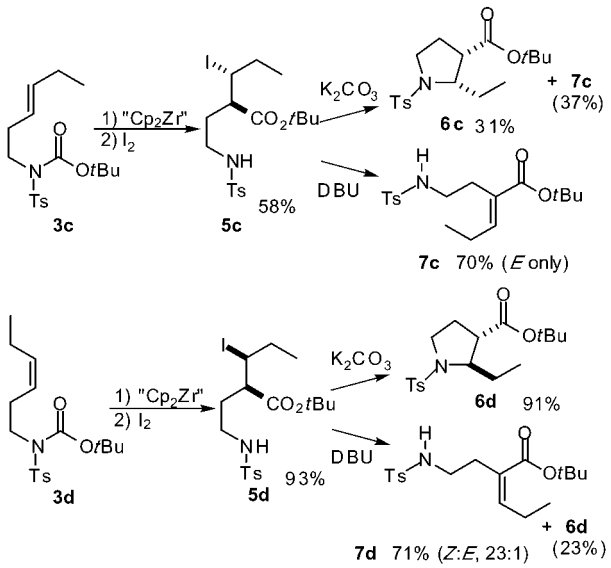
(10) In the case of titanium-mediated intramolecular reaction of 4-pentenyl carbonate reported by Sato et al., a complex mixture without any desired product was obtained. See ref 5b.

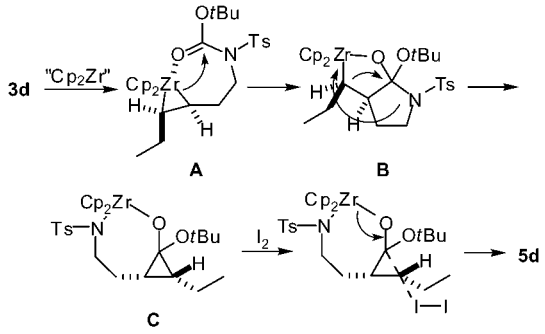
reported as a useful method for the conversion of the carbon−zirconium bond to a hydroxyl group,[12] no oxygenated product was detected by treating the reaction mixture with O_2 before the aqueous workup. On the other hand, iodination was accomplished by the addition of iodine to the reaction mixture. The iodide **5c** and **5d** derived from (*E*)-isomer **3c** and (*Z*)-isomer **3d** were obtained as single stereoisomers, respectively (Scheme 3). These compounds

Scheme 3



could be converted stereospecifically to the pyrrolidine derivatives **6c** and **6d**, respectively, upon treatment with potassium carbonate and to the α,β-unsaturated esters **7c** and **7d**, respectively, by reaction with DBU. The stereochemistry of **5c** was determined on the basis of the stereochemistries of the pyrrolidine derivative **6c** and α,β-unsaturated ester **7c** formed via S_N2 and E2 mechanisms, respectively. Likewise, the stereochemistries of **6d** and **7d** were the basis for the structure determination of **5d**. Our proposed reaction mechanism is shown in Scheme 4. The ligand exchange reaction of the zirconocene equivalent with the carbon−carbon double bond in the substrate **3d** gave zirconacyclopropane intermediate **A**, which then coupled with the carbonyl moiety intramolecularly to form a bicyclic intermediate **B**. It is known that the iodination of an alkylzirconium intermediate proceeds with complete retention of configuration.[13] However, the observed stereochemistry of

Scheme 4. Proposed Reaction Mechanism



the chiral center bearing the iodine atom in the product **5d** was inverted, if the intermediate **B** was trapped with iodine. Presumably, the bicyclic intermediate **B** easily converted to the cyclopropane intermediate **C** due to the facile cleavage of the bridgehead carbon−nitrogen bond by attacking the nucleophilic carbon center bearing the zirconium atom. Similar cyclopropane formation reaction has been reported in the titanium-mediated inter- or intramolecular coupling reaction of alkene with an ester group, in which an alkyltitanium intermediate cyclized intramolecularly to form cyclopropanol derivatives.[3] We also reported zirconium-mediated cyclopropanation by the attack of an alkylzirconium species on the oxocarbenium ion.[14] Subsequently, this intermediate **C** reacts with iodine via inversion of the stereocenter to afford the iodide **5d** (Scheme 4).[15] The participation of the cyclopropane intermediate **C** in this reaction is possibly supported not only by the stereochemical outcome of the iodide **5d** but also by the result of the quenching reaction with oxygen, instead of iodine, (vide supra) indicating that there is no zirconium−carbon bond in the intermediate.

In conclusion, we have developed a useful preparative method for α-substituted γ-aminobutyric acid derivatives via a zirconium-mediated intramolecular ester transfer reaction of *N*-alkenyl-*N*-tosyl carbamates. 2-Substituted pyrrolidine-3-carboxylic acid derivative **6** and α,β-unsaturated carboxylate **7** could be obtained in a stereospecific manner through the iodination of the intermediate followed by treatment with base.

Supporting Information Available: Typical experimental procedure and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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