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Intramolecular Tandem Michael-Type Addition/Aldol Cyclization Induced by $TiCl_4$–R_4NX Combinations

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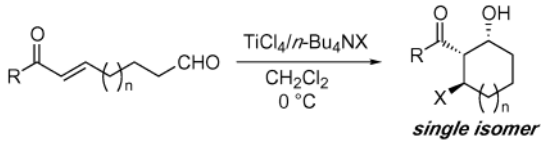
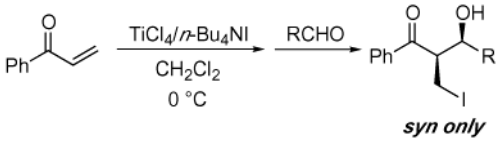
ABSTRACT



Treatment of formyl α,β-enones with a $TiCl_4$–R_4NX combination induces an intramolecular aldol cyclization to furnish 2-acyl-3-halocyclohexanol with three controlled consecutive stereogenic centers. The reaction of bis-α,β-enones with the combination provides cyclic diketones with high stereoselectivity via an intramolecular Michael addition reaction.

Efficient and stereoselective cyclization is a powerful means to construct cyclic structures of natural and nonnatural compounds. In this context, stereoselective tandem conjugate addition−cyclization reactions have been extensively explored.[1] In particular, intramolecular aldol and Michael cyclizations are useful strategies.[2] We have recently developed a highly stereoselective coupling reaction between α,β-unsaturated ketones and aldehydes via a sequential Michael addition−aldol reaction with the use of halides as nucleophiles (Scheme 1).[3,4] We then anticipated that this reaction would be applied to an intramolecular variant. Herein, we describe a highly stereoselective intramolecular aldol reaction of formyl α,β-enones to furnish 2-acyl-3-halocycloalkanols with three consecutive stereogenic centers by the action of a $TiCl_4$−R_4NX combination.[5] This combination also achieved a stereoselective cyclization of bis-α,β-enones via an intramolecular double-Michael addition reaction.

Scheme 1



Under an argon atmosphere, a solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 0.6 mL, 0.6 mmol) was added dropwise to a solution

(1) (a) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315. (b) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010.

(2) For recent examples of aldol and Michael cyclizations, see: (a) Enholm, E. J.; Xie, Y.; Abboud, K. A. *J. Org. Chem.* **1995**, *60*, 1112. (b) Baik, T.-G.; Luis, A. L.; Wang, L. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (c) Chiu, P.; Szeto, P.-C.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901. (d) Nagaoka, Y.; Tomioka, K. *Org. Lett.* **1999**, *1*, 1467. (e) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 6979. (f) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199. (g) Kamenecka, T. M.; Overman, L. E.; Ly Sakata, S. K. *Org. Lett.* **2002**, *4*, 79. (h) Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403. (i) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, 1302.

(3) For the use of combinations of $TiCl_4$−R_4NI and related mixtures in similar reactions, see: (a) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383. (b) Han, Z.; Uehira, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7854. (c) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406. (d) Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390.

(4) For the use of TiX_4 alone as both a Lewis acid and a halogen source for Michael-type addition/aldol reactions, see: (a) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. (b) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617. (c) Wei, H.-X.; Kim, S. H.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397.

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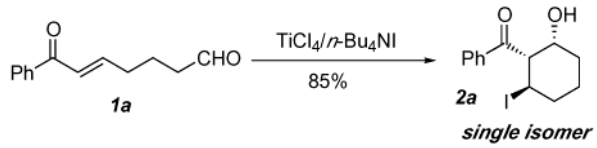
of *n*-Bu_4NI (222 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) at 0 °C, and the resulting dark-red solution was stirred for 10 min. To the reaction mixture was added a solution of **1a** (101 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was poured into saturated aqueous ammonium chloride (30 mL). Extraction followed by silica gel column purification afforded adduct **2a** in 85% yield with high stereoselectivity (Scheme 2). None of the other isomers were detected in the reaction mixture.[6]

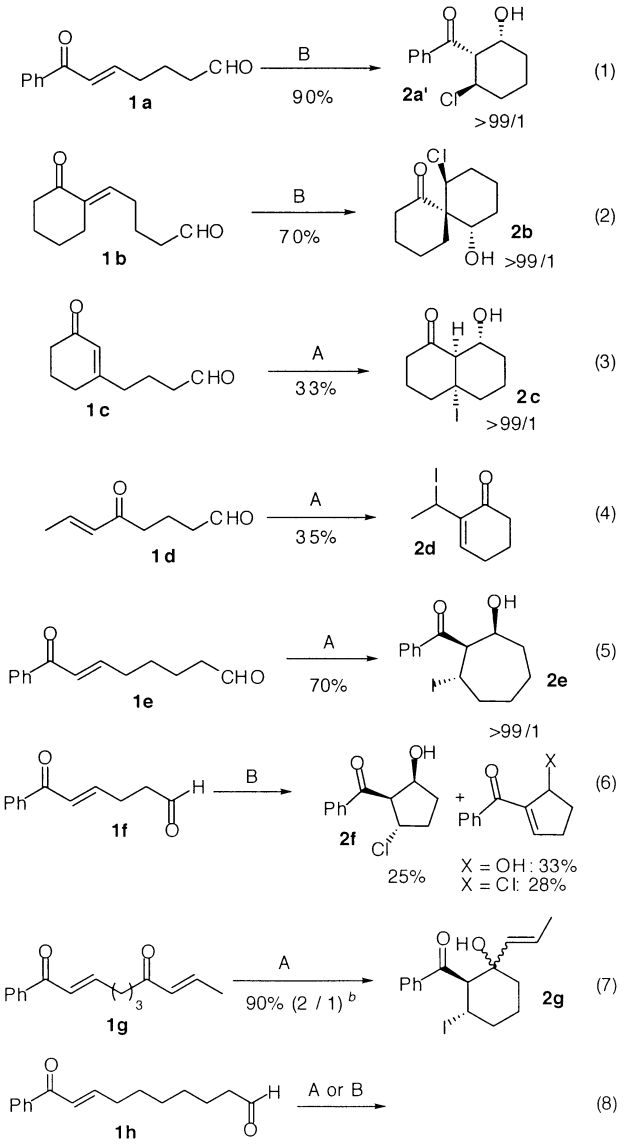
Scheme 2



We examined several formyl α,β-enones (Scheme 3) to clarify the scope and limitations. Several characteristics of this cyclization are noteworthy. Benzylammonium chloride also worked efficiently as a halide source, and achieved excellent stereoselectivity (eq 1). The use of benzylammonium bromide provided the corresponding bromide in 53% yield along with chloride **2a′** (27%). The addition of ammonium halide is essential. In the absence of ammonium halide, treatment of **1a** with $TiCl_4$ at 0 °C provided the desired product **2a′** in a low yield (<10% yield). Starting from alkylidencyclohexanone **1b** afforded spiro compound **2b** in good yield (eq 2). The reaction of β-substituted cyclohexenone **1c** was sluggish and yielded a Decalin derivative **2c** in a low yield (eq 3). Formyl α,β-enone **1e** provided seven-membered hydroxy ketone **2e** in good yield as a single isomer (eq 5). In the case of **1f**, five-membered hydroxy ketone **2f** was not so stable and dehydration and dehydrochlorination products accompanied (eq 6). Diketone **1g** also furnished hydroxy ketone **2g** in good yield. The product was decomposed during silica gel column purification via a retro-aldol reaction. The reaction of **1h** provided a complex mixture containing mainly the starting material. The stereochemistry of the hydroxy ketones was assigned by the examination of the coupling constants on the basis of the Karplus relationship[2b] and confirmed by X-ray crystallographic analysis in the case of **2b** (Figure 1).[8]

Treatment of **1a** with Et_2AlI instead of $TiCl_4$−*n*-Bu_4NI provided unsaturated ketone **4** in 80% yield via intramolecular Baylis−Hillman-type cyclization (Scheme 4).[7,8] Treatment of dimethyl acetal **3** with the $TiCl_4$−*n*-Bu_4NI combi-

Scheme 3[a]



[a] Condition A: enone (0.5 mmol), $TiCl_4$ (0.6 mmol), *n*-Bu_4NI (0.6 mmol), CH_2Cl_2 (5 mL), 0 °C. Condition B: enone (0.5 mmol), $TiCl_4$ (0.6 mmol), $BnNEt_3Cl$ (0.6 mmol), CH_2Cl_2 (5 mL), 0 °C. [b] NMR yield with Bn_2O as an internal standard.

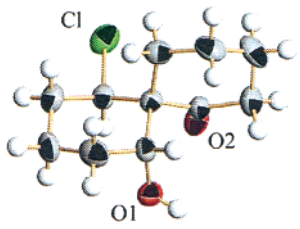


Figure 1. ORTEP drawing of **2b**.

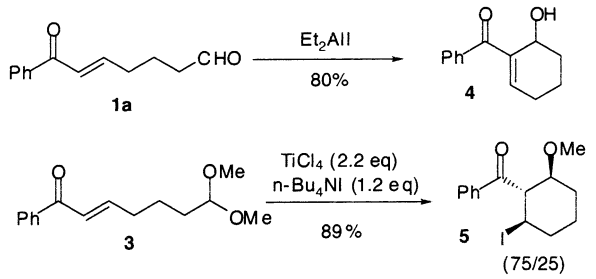
(5) (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767. (b) Yachi, K.; Maeda, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 5161. (c) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 8121. (d) Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066. (e) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987. (f) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 978.

(6) The diastereomer could not be detected by ^1H or ^{13}C NMR.

(7) For the use of Et_2AlI in Michael-type addition reactions, see: Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274. For Michael/aldol cyclization with Et_2AlSPh, see: Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361.

(8) For recent examples of Baylis−Hilman cyclization, see: (a) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (b) Wang, L. C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402 and references therein.

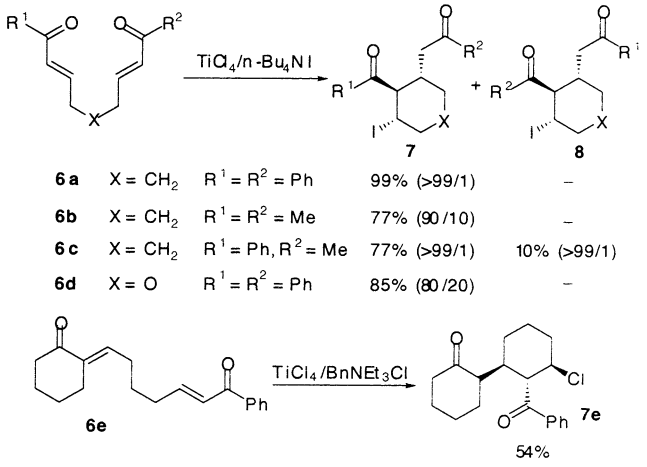
Scheme 4



nation afforded the decomposed product containing aldehyde **1a**. However, the use of excess $TiCl_4$ yielded the cyclized product **5** in good yield.[9] It is notable that the major isomer has the opposite stereochemistry to **2a** at the methoxy-substituted carbon atom, although the stereoselectivity is not satisfactory.

The $TiCl_4$−ammonium halide combination also effects the cyclization of bis-α,β-enones **6**, providing cyclic diketones **7** with high stereoselectivity via an intramolecular Michael addition.[10] The results are summarized in Scheme 5. Treatment of unsymmetrical diketone **6c** yielded **7c** predominantly via enolate formation at the phenyl-substituted α,β-enone.

Scheme 5[a]



[a] Diketone (0.5 mmol), $TiCl_4$ (0.6 mmol), ammonium salt (0.6 mmol), CH_2Cl_2 (5 mL), 0 °C.

The use of oxygen-tethered diketone **6d** lowered the stereoselectivity. The stereochemistry of the cyclized diketones were assigned by the examination of the coupling constants and confirmed by X-ray crystallographic analysis in the case of **7e** (Figure 2).[11]

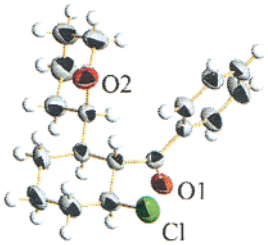
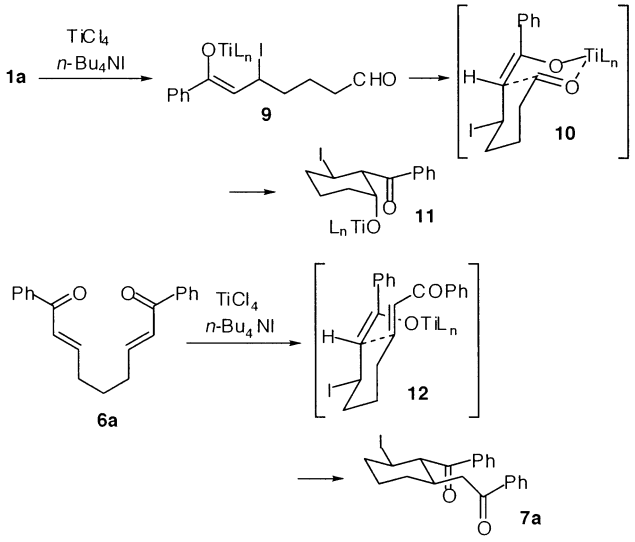


Figure 2. ORTEP drawing of **7e**.

We propose a plausible mechanism to explain the stereochemical outcome of these processes (Scheme 6).[12] 1,4-Addition of titanium iodide species to the α,β-enone moiety furnishes iodo titanium enolate **9**. The enolate **9** then undergoes the intramolecular aldol reaction via a chelated six-membered transition state **10** and provides hydroxy ketone with the axial hydroxy group. In the case of **6a**, iodo titanium enolate cyclizes to diketone with an all-equatorial orientation via an intramolecular Michael addition.

Scheme 6



(9) This result can be explained as follows: $TiCl_4$−*n*-Bu_4NI affords an iodo titanium enolate, and the excess $TiCl_4$ converts dimethoxy acetal to an oxocarbenium ion. The $TiCl_4$−*n*-Bu_4NI combination does not have enough Lewis acidity to activate an acetal.

(10) **General Procedure.** To a solution of *n*-Bu_4NI (222 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) was added TiCl4 (0.6 mL, 1.0 M solution in CH_2Cl_2, 0.6 mmol) dropwise at 0 °C. After 10 min, a solution of **6a** (152 mg, 0.5 mmol) in CH_2Cl_2 (2.0 mL) was introduced dropwise for 1 min at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and poured into saturated aqueous NH_4Cl (30 mL). The mixture was extracted with ether, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration and purification afforded **7a** (214 mg) in 99% yield.

(11) Crystallographic data for the structures reported herein have been deposited with the Cambridge Crystallographic Data Center (CCDC 186739 and 186740 for **2b** and **7e**, respectively). Copies of this data can be obtained, free of charge, upon application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: 44-1223-3360033. E-mail: deposit@ccdc.cam.ac.uk.

(12) A similar model to account for the stereochemical outcome has been proposed. See ref 2h.

In conclusion, we have developed a highly stereoselective cyclization via intramolecular aldol and Michael reactions with a $TiCl_4-R_4NX$ combination.

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Supporting Information Available: Experimental procedures and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.

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