

Check fo updates

Diastereoselective Synthesis of Spiro[2.3]hexanes from Methylenecyclopropane and Cyanoalkenes Catalyzed by a Tin-ate Complex

Itaru Suzuki^[a], Jun-ya Shimazu^{[a],[b]}, Shinji Tsunoi^[a] and Ikuya Shibata^{*[a]}

Abstract: A diastereoselective synthesis of spiro[2.3]hexane catalyzed by Sn and Mg halides was developed from a combination of methylenecyclopropane and cyanoalkene bearing an ester group. The selectivity was affected by the size of the halogen in the catalyst and by an electron deficiency in the alkene. Once synthesized only with a Pd catalyst, the spirocarbocycle was easily transformed into cyclopentene under transition metal-free conditions.

Introduction

Spiro[2.3]hexane, a bicyclocarbocycle with three- and fourmembered rings connected by one carbon center, has recently shown a degree of bioactivity¹ and is expected to be a conformationally rigid cyclopropane analogue of GABAs.4g Although demand for investigations into the potential of the spiro ring are mounting, research into its physical or pharmaceutical character is unexpectedly sluggish probably because there continues to be few practical methods that can be used to produce the ring system.^{2,3,4} Among them, a thermal [2+2] annulation of methylenecyclopropane (MCP) with alkenes² has been accepted as a reliable synthetic method since the first preparation of the spiro[2.3]hexane was accomplished by Anderson in 1962.^{2g} On the other hand, the catalytic annulation of MCP with alkenes has been less developed and only a transition metal catalyst has been exploited.³ During the course of our research project on the preparation of hetero- or carbocycles catalyzed by the tin-ate complex made from Bu₂SnX₂ and Li or Mg halides,⁵ we found that the MCP coupled with dicyanoalkenes gave the spiro[2.3]hexane in a high yield.^{5a} The spiro ring was preferred when the reaction was carried out with $Bu_2SnCl_2+MgCl_2$ as a catalyst in CH₂Cl₂. Herein, we report the diastereoselective annulation of MCP with cyanoalkenes substituted with ester groups to give the spiro rings.

[a]	Dr. I. Suzuki, JY. Shimazu, Prof. S. Tsunoi, Prof. I. Shibata* Research Center for Environmental Preservation, Osaka University
	2-4, Yamadaoka, Suita, Osaka 565-0871, Japan
	E-mail: shibata@epc.osaka-u.ac.jp
	http://www.chem.eng.osaka-u.ac.jp/shibataken/
[b]	JY. Shimazu
	Division of Applied Chemistry
	Graduate School of Engineering, Osaka University
	2-1, Yamadaoka, Suita, Osaka 565-0871, Japan

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))



Scheme 1. Tin-ate complex catalysed synthesis of spirohexanes.

Results and Discussion

We initiated optimization of the reaction conditions with MCP 1 and cyanoalkene 2a. The results are shown in Table 1. The spirocarbocycle 3a was given in a low yield when the previously optimized conditions were applied (entry 1).^{5a} The yield was improved in 1,2-dichloroethane at 80 °C for 2 h, though diastereoselectivity was not observed (entry 2). Bu₂SnCl₂ did not catalyze the coupling but MgCl₂ worked as a catalyst for the coupling (entries 4 and 5). The heavier a halogen atom of the catalyst was, the better the diastereoselectivity was, though more of the undesired cyclopentane 4a was produced, which was previously found to be mainly formed by the Bu₂SnBr₂+MgI₂ catalyst^{5a,6} and difficult to separate from the reaction mixture (entry 6). Finally, the Bu₂SnBr₂+MgCl₂ system was chosen as optimal. Each diastereomer structure was defined via X-ray crystallography using cyanoalkene 2b (Scheme 2, CCDC: 1906464, 1820470).

Table 1. Optimization of the conditions with MCP 1 and cyanoalkene 2a.^a



 a Reaction conditions: 1 (0.75 mmol), 2a (0.50 mmol), catalyst (0.050 mmol) and solvent (1 mL). b 1H NMR yield. c at 25 oC in CH_2Cl_2 for 24 h. DCE = dichloroethane

WILEY-VCH

COMMUNICATION



Scheme 2. Investigation on the scope of cyanoalkene 2^a.

The optimized conditions were then applied to investigate the scope of the cyanoalkenes 2 (Scheme 2). The electron donating groups on the phenyl ring diminished the yields somewhat (2c and 2d), but the electron-withdrawing groups tended to afford the corresponding products 3e-3k in high yields (2e-2k). Other aromatic rings such as 1- or 2-naphthyl and 2-furyl were applicable to this coupling that formed the spiro rings (3I-3n), although the bulky ester moiety of the cyanoalkene affected the yields (2o and 2p).

A plausible reaction mechanism is shown in Scheme 3. First, the tin-ate complex bearing a nucleophilic Sn-X bond opens MCP 1 to give vinylogous dienolate 5.7 Then, a conjugate γ addition of the enolate 5 to cyanoalkene 2 takes place to form ketenimine 6. Next, an intramolecular conjugate addition proceeds to provide the intermediate 7 followed by a further ring closure to afford the spirocarbocycle 3. The side product 4 is generated if the ketenimine attacks the C-X bond of the intermediate 6, which is likely to happen when X is Br or I.^{5a}



 $(Bu_2SnX_2$ $MgX_2)$ EtO₂C EtO₂C EtO₂C Вι MgX 3 NĆ CO2E Βı Bu₂SnX₂ OEt .0 XMq EtC EtO₂C EtO₂C 5 Х NĆ CO₂F 7 OE MgX₂ Мģ ĊO₂R EtO₂C ĆO₂R MaX 2 CN EtO₂C OEt ×. 6 . CO₂R

Scheme 3. Plausible reaction mechanism.

CO₂E

One possibility for how the diastereoselectivity is determined is proposed in Scheme 4. It could be elucidated by a steric hindrance that may exist between the ketenimine moiety and the C-X bond in the reaction of intermediate 6. In the case of X=Cl, there is so little steric repulsion in the intermediate 6_{right} that the ketenimine moiety can rotate to adopt both conformations 6_{left} and 6_{right}, which ends up forming 3-syn and 3-anti, respectively. In the case of X=Br or I, the conformation of the intermediate 6 is restricted to 6left by effective repulsion that preferentially forms an the diastereomer **3-syn**. To our surprise, however, the diastereoselectivity was inverted when electron-deficient alkenes such as 2g, 2j, and 2l were employed under the Bu₂SnCl₂-MgCl₂ catalyst system (Table 3). The results implied that the selectivity was controlled not only by the steric hindrance but also by electronic factors. At this time, we are unsure why the selectivity was changed so we are now carrying out DFT calculations to clarify the precise conformation model of the reaction with intermediate 6.



COMMUNICATION

Table 3. Inversion of the diastereoselectivity of 3.



Finally, the transformation of the spiro[2.3]hexane **3f** was carried out under heating conditions (Scheme 5).⁸ We expected to have its methoxy carbonyl moiety removed by means of Krapcho decarboxylation even though diethyl ester groups were contained in the product.⁹ Actually, not only the removal but also a rearrangement reaction¹⁰ took place to give the cyclopentene ring **8**, which probably followed the pathway shown in Scheme 6. After the decarboxylation occurred, the ring opening led to methylene cyclopentane **8'** followed by isomerization of the double bond to form the product **8**.¹¹ This is the first example of preparing the same cyclopentanoids without the use of a precious transition-metal catalyst.¹²

Conclusion

A diastereoselective coupling of MCP **1** and cyanoalkene **2** succeeded in the formation of spiro[2.3]hexane **3**. The selectivity depended on the size of the halogen derived from the $Bu_2SnX_2+MgX_2$ catalyst, which can be explained by considering the steric hindrance in the reaction with intermediate **6**. The spiro[2.3]hexane **3** was converted into cyclopentene **8** via decarbonylation and rearrangement. Further elucidation of the reaction mechanism and a transformation of spirocarbocycles **3** while maintaining their skeleton is underway.



Scheme 5. Further conversion of the spirohexane 3f by Krapcho decarboxylation.

Experimental Section

(Scheme 2) To a mixture of MgCl₂ (0.050 mmol) and Bu₂SnBr₂ (0.050 mol) in 1,2-dichloroethane (1 mL) was added MCP **1** (0.75 mmol) and cyanoalkene **2** (0.50 mmol). The reaction mixture was heated at 80 °C for 2 h and quenched with brine (10 mL). The resulting mixture was extracted with Et₂O (3 x 10 mL) and the collected organic layer was dried over MgSO₄. After filtration, the organic solvent was evaporated *in vacuo* to give crude product **3**, which was analyzed by ¹H NMR. The crude product **3**.

Acknowledgements ((optional))

We thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with collecting the spectral data.

Keywords: Methylenecyclopropane • Cyanoalkene • Tin • Ate Complex • Spirohexane

- a) H. Liu, Y. Tian, K. Lee, P. Krishnan, M. K.-M. Wang, S. Whelan, E. Mevers, V. Soloveva, B. Dedic, X. Liu, J. M. Cunningham, *J. Med. Chem.* **2018**, *61*, 6293; b) M. Packiarajan, M. Grenon, S. Zorn, A. T. Hopper, A. D. White, G. Chandrasena, X. Pu, R. M. Brodbeck, A. J. Robichaud, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4037; c) L. Bondada, G. Gumina, R. Nair, X. H. Ning, R. F. Schinazi, C. K. Chu, *Org. Lett.* **2004**, *6*, 2531.
- a) X.-Y. Zhang, S. Yang, Y. Wei, M. Shi, Org. Biomol. Chem. 2018, 16, 6399; b) K. Chen, R. Sun, Q. Xu, Y. Weib, M. Shi, Org. Biomol. Chem. 2013, 11, 3949; c) I. Nakamura, R. Nagata, T. Nemoto, M. Terada, Y. Yamamoto, T. Späth, A. Meijere, *Eur. J. Org. Chem.* 2007, 4479; d) S. Yamago, A, Takeichi, E. Nakamura, *Synthesis* 1996, 1380; e) S. Yamago, A, Takeichi, E. Nakamura, *Synthesis* 1996, 1380; e) S. Yamago, A, Takeichi, E. Nakamura, *J. Am. Chem. Soc.* 1994, 116, 1123; f) W. R. Dolbier, M. Seabury, D. Daly, B. E. Smart, *J. Org. Chem.*, 1986, 51, 974; g) B. C. Anderson, *J. Org. Chem.* 1962, 27, 2720

 [3] a) M. Gulías, A. Collado, B. Trillo, F. López, E. Oñate, M. A. Esteruelas, J. L. Mascareñas, J. Am. Chem. Soc. 2011, 133, 7660; b) P. Binger, A. Brinkmann, P. Wedemann, Chem. Ber. 1983, 116, 2920.

- [4] Other type of formation of spiro[2.3]hexane, see; a) B. Cao, Y. Wei, C. Ye, L.-Z, Wu, M. Shi, Org. Chem. Front. 2018, 5, 1890; b) P. An, Q. Lin, Org. Biomol. Chem. 2018, 16, 5241; c) B. Cao, Y. Wei, M. Shi, Chem. Commun. 2018, 54, 2870; d) N. V. Yashin, E. B. Averin, D. A. Vasilenko, Y. K. Grishin, D. I. Osolodkin, V. A. Palyulin, T. S. Kuznetsov, N. S. Zefirov, Russ, Chem. Bull. Int. Ed. 2017, 66, 1483; e) I. R. Ramazanov, R. N. Kadiova, T. P. Zosim, U. M. Dzhemilev, A. Mijere, Eur. J. Org. Chem. 2017, 7060; f) A, Kolleth, A. Lumbroso, G. Tanriver, S. Catak, S. Sulzer-Mossé, A. D Mesmaeker, Tetrahedron Lett. 2016, 57, 2697; g) N. V. Yashin, E. B. Averin, A. V. Chemagin, M. E. Zapolskii, Y. K. Grishin, T. S. Kuznetsov, N. S. Zefirov, Russ. Chem. Bull. Int. Ed. 2015, 64, 2178; h) Z. Yu, Q. Lin, J. Am. Chem. Soc. 2014, 136, 4153; i) N. V. Yashin, A. V. Chemagin, Y. K. Grishin, T. S. Kuznetsova, N. S. Zefirov, Dokl. Chem. 2013, 450, 547; j) V. A. D'yakonov, R. A. Tuktarova, O. A. Trapeznikova, L. M. Khalilov, N. R. Popod'ko, ARKIVOC 2011, 20. k) A. V. Chemagin, N. V. Yashin, Y. K. Grishin, T. S. Kuznetsova, N. S. Zefirov, Synthesis 2010, 259; I) H. Sami, O. Piva. Tetrahedron Lett. 2008, 49, 2994; m) T. Matsuda, M. Shigeno, M. Murakami, Chem. Lett. 2006, 35, 288; n) V. V. Razin, N. V. Ulin, Russ. J. Org. Chem. 2005, 41, 189; o) K. B. Wiberg, S. T. Waddell, Tetrahedron Lett. 1987, 28, 151; p) B. Emil, M. Wolfgang, Chimia, 1968, 22, 193.
- a) I. Suzuki, S. Tsunoi, I. Shibata, *Org. Lett.* 2017, *19*, 2690; b) S. Tsunoi,
 Y. Maruoka, I. Suzuki, I. Shibata, *Org. Lett.* 2015, *17*, 4010; c) H.
 Takahashi, S. Yasui, S. Tsunoi, I. Shibata, *Org. Lett.* 2014, *16*, 1192; d)

WILEY-VCH

COMMUNICATION

H. Takahashi, S. Yasui, S. Tsunoi, I. Shibata, *Eur. J. Org. Chem.* **2013**, 40.

- [6] The cyclopentane **4a** was actually formed selectively under the reaction conditions with the Bu₂Snl₂-Mgl₂ catalyst in THF.
- [7] We have already observed a fast ring opening of the MCP **1** by the tinate complex. See ref.5a.
- [8] We reported rearrangement of the spirohexane into the alkylidenecyclopentane mediated by Bu₂Snl₂-Mgl₂ under the heating conditions. See ref.5a.
- [9] a) A. P. Krapcho, G. A. Glynn, B. J. Grenon, *Tetrahedron Lett.* **1967**, *8*, 215; b) A. P. Krapcho, B. P. Mundy, *Tetrahedron*, 1**970**, *26*, 5437; c) A. P. Krepcho, A. J. Lovey, *Tetrahedron Lett.* **1973**, *14*, 957; d) A. P. Krapcho, E. G. E. Jahngen, Jr., A. J. Lovey, *Tetrahedron Lett.* **1974**, *15*, 1091; e) A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, W. P. Stephens, *J. Org. Chem.* **1978**, *43*, 138; f) H. A. Earl, D. R. Marshall, C. J. M. Stirling, *J. Chem. Soc. Chem. Commun.* **1983**, 779.
- [10] The related fission of the C-C bond of the spirocarbocycles by a Rh catalyst was reported by Murakami group. See, a) M. Murakami, K. Takahashi, H. Amii, Y. Ito, J. Am. Chem. Soc. 1997, 119, 9307; b) T. Matsuda, T. Tsuboi, M. Murakami, J. Am. Chem. Soc. 2007, 129, 12596.
- [11] A previously synthesized spirohexane which have a cyano group instead of a methoxy carbonyl group of 3a transformed into the corresponding cyclopentane 4a under the Krapcho decarboxylation conditions.
- The same type of the ring was prepared with a Pd catalyst. See, a) P. Binger, U. Schuchardt, *Chem. Ber.* **1981**, *14*, 3313; b) B. M. Trost, D. M. T. Chan, *J. Am. Chem. Soc.* **1983**, *105*, 2315; c) I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.*, **1984**, *25*, 5183.

Accepted Manuscril

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



Diastereselective Synthesis of Spirohexanes

Spirohexanes were synthesized via thermal annulation of methylenecyclopropanes with cyanoaokenes substituted with ester groups catalysed by a Sn and Mg ate complex. The diastereoselectivity was affected by the halogen of the catalyst and electron-withdrawing groups on the cyanoalkene. The transformation of the spirohexane was carried out to afford a cyclopentanoid which has been prepared only by a transition metal catalyst.

Key Topic: Tin-catalyzed Annulation

Itaru Suzuki, Jun-ya Shimazu, Shinji Tsunoi and Ikuya Shibata*

Page No. – Page No.

Diastereoselective Synthesis of Spiro[2.3]hexanes from Methylenecyclopropane and Cyanoalkenes Catalyzed by a Tin-ate Complex