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A Carbaboranylmercuric Salt Catalyzed Reaction; Highly Regioselective Cycloisomerization of 1,3-Dienes

Hirofumi Yamamoto,* Ikuo Sasaki, Shinya Shiomi, Naoto Yamasaki, and Hiroshi Imagawa

Faculty of Pharmaceutical Science, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

hirofumi@ph.bunri-u.ac.jp

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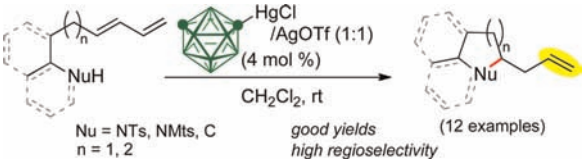
ABSTRACT



The combination of carbaboranylmercuric chloride (new type of bulky Lewis acid) and silver triflate efficiently catalyzes cycloisomerization of 1,3-dienes at room temperature. The catalytic system gives allyl-substituted azacycles and cycloalkanes in excellent yields with high to complete regioselectivity.

Catalytic hydroamination is an atom-ecomomical and pivotal transformation for the synthesis of organonitrogen molecules.[1] In recent years, especially, the development of a method for the hydroamination of conjugated dienes (diene-hydroaminations) has attracted a great deal of attention[2,3] because the olefinic functionality maintained in the product is useful for subsequent molecular modifications (such as ozonolysis, hydroboration, metathesis, etc.). Most recently, Toste and co-workers reported the asymmetric hydroamination of *p*-methoxy benzenesulfonyl (Mbs)-protected amino-1,3-dienes using catalytic amounts of the (*R*)-DTBM-SEGPHOS(AuCl)$_2$ complex and $AgBF_4$ in the presence of (−)-menthol.[4] Although high enantioselectivity as well as good reactivity was observed with that catalytic system, a regioisomeric mixture of olefinic moieties was obtained in most cases. The formation of such untoward regioisomers are no exception in diene-hydroaminations, and efficient methods which afford a single isomer are still limited. We recently reported the Hg(OTf)$_2$-catalyzed cyclization of *p*-toluenesulfonyl (Ts)-protected amino dienes **1** leading to 2-propenyl azacycles **3** (vinylene-type products) as single *E*-isomers (Scheme 1).[5] In the hydroaminations, the Hg(OTf)$_2$ activated the internal olefin of the conjugated diene to regulate the position of the nascent double bond in the products via demercuration of the mercuric intermediate **2**. Therefore,

(1) (a) Harder, S. *Chem. Rev.* **2010**, *110*, 3852–3876. (b) Müller, T. E.; Hultzsch, K. C.; Yus, M; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (c) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114. (d) Molander, G. A.; Romero, J. C. *Chem. Rev.* **2002**, *102*, 2161–2185. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703.

(2) For selected recent examples of intramoleculer reactions: (a) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245–249. (b) Aillaud, I.; Olier, C.; Chapurina, Y.; Collin, J.; Schulz, E.; Guillot, R.; Hannedouche, J.; Trifonov, A. *Organometallics* **2011**, *30*, 3378–3385. (c) Ramachary, D. B.; Narayana, V. V. *Eur. J. Org. Chem.* **2011**, 3514–3522. (d) Baeza, A.; Nájera, C. *Synlett* **2011**, 631–634. (e) Deschamp, J.; Collin, J.; Hannedouche, J.; Schulz, E. *Eur. J. Org. Chem.* **2011**, 3329–3338. (f) Yeh, M.-C. P.; Pai, H.-F.; Lin, Z.-J.; Lee, B.-R. *Tetrahedron* **2009**, *65*, 4789–4794. (g) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878–15892. (h) Hong, S.; Marks, T. J. *J. Am. Chem. Soc.* **2002**, *124*, 7886–7887. (i) Flubacher, D.; Helmchen, G. *Tetrahedron Lett.* **1999**, *40*, 3867–3868.

(3) For selected recent examples of intermoleculer reactions: (a) Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 2193–2207. (b) Giner, X.; Nájera, C.; Kovács, G.; Lledós, A.; Ujaque, G. *Adv. Synth. Catal.* **2011**, *353*, 3451–3466. (c) Giner, X.; Nájera, C. *Synlett* **2009**, 3211–3213. (d) Giner, X.; Nájera, C. *Org. Lett.* **2008**, *10*, 2919–2922. (e) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839. (f) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611–1614.

(4) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9919–9922.

(5) Yamamoto, H.; Shiomi, S.; Odate, D.; Sasaki, I.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem. Lett.* **2010**, *39*, 830–831.

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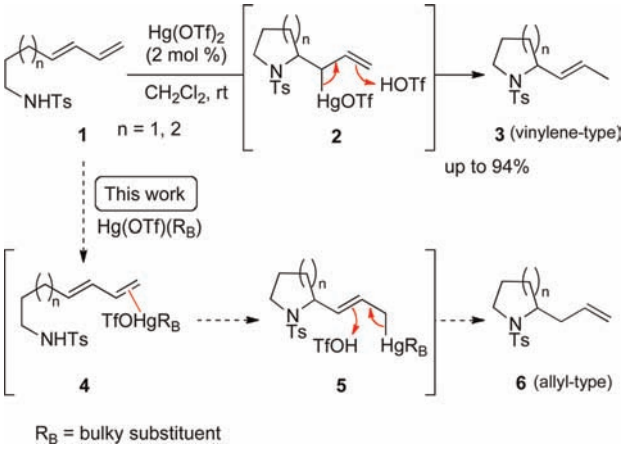
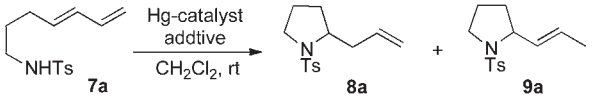
we reasoned that if the terminal olefin moiety could be preferentially activated using a bulky mercuric reagent which avoids a crowded internal olefin, the allyl-substituted **6** (allyl-type product) might be constructed from the identical **1**. Herein, a new method for regioselective synthesis of allyl-substituted compounds from 1,3-dienes is demonstrated, using a 1:1 combination of a novel carbaboranylmercuric chloride and AgOTf. The efficient synthesis of such allylic compounds using diene-hydroamination is seldom described in the literature, with the $(CGC)Th(NMe_2)_2$-catalyzed hydroamination reported by the Marks group being the sole example.[6]

Scheme 1. $Hg(OTf)_2$-Catalyzed Cycloisomerization of 1,3-Diene **1** and Synthetic Approach to Allyl-Substituted Azacycle



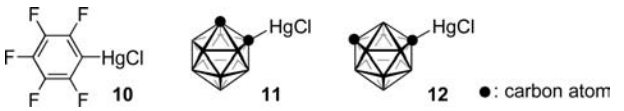
In the process of developing the $Hg(OTf)_2$-catalyzed cycloisomerization of 1,3-dienes, we found that a regioisomeric mixture of **8a** and **9a** was produced, when **7a** was treated with 5 mol % of PhHgOTf,[7] which was prepared by *in situ* mixing of PhHgOAc and HOTf in a 1:1 ratio (Table 1, entry 1).[8] Thus, our initial study focused on screening various combinations[9] of phenylmercuric salts and additives with the aim of achieving the synthesis of allyl-substituted **8a** with high regioselectivity. However, as shown in entries 2−5, the selective synthesis of **8a** is very difficult, as regioisomeric mixtures were produced in all cases. A better result was obtained by changing the mercuric reagent from phenylmercuric chloride to pentafluorophenylmercuric chloride (**10**), but the ratio of **8a** and **9a** was still 54:46 (entry 6). Therefore, we needed to design a bulkier reagent to improve the selectivity. Carbaboranes ($C_2B_{10}H_{12}$),[10] in which two of the BH^- units of the dodecaborane dianion ($B_{12}H_{12}^{2-}$) are replaced with two CH vertices, are charge-neutral, stable, and icosahedral-bulky clusters. Moreover, chemical modification of the two carbon atoms in the clusters is easy to perform via a carbanion intermediate (generated by treatment with alkyl lithium reagents).[11] Because of the properties of the material, we hypothesized that carbaboranes would be ideal bulky substituents on the mercury center. While attempts to catalyze the reaction of **7a** using only 5 mol % of *o*-carbaborane-linked mercuric chloride **11** did not produce appreciable amounts of pyrrolidine (entry 7), it was found that the addition of AgOTf induced production of **8a** with high regioselectivity in very high yield (entry 8). For *m*-carbaborane-linked **12**, the regioselectivity was increased further, giving only **8a** quantitatively (entry 9). It is particularly noteworthy that the carbaborane-linked reagents were highly reactive and that a catalyst loading of 4 mol % was enough to complete the reaction within a short period of time (entry 10).

Table 1. Investigation of the Catalysts Leading to 2-Allylpyrrolidine **8a**[a]



entry	Hg-catalyst (mol %)	addtive (mol %)	time	yield[b] (**8a**:**9a**)[c]
1	PhHgOAc (5)	HOTf (5)	72 h	97% (49:51)[d]
2	PhHgOAc (5)	$HNTf_2$ (5)	18 h	35% (13:87)
3	PhHgCl (5)	AgOTf (5)	72 h	96% (48:52)
4	PhHgCl (5)	$AgNTf_2$ (5)	72 h	83% (19:81)
5	PhHgCl (5)	$AgSbF_6$ (5)	72 h	86% (4:96)
6	**10** (5)	AgOTf (5)	48 h	95% (54:46)
7	**11** (5)	-	24 h	0%[e] -
8	**11** (5)	AgOTf (5)	40 min	94% (97:3)
9[f]	**12** (5)	AgOTf (5)	40 min	>99% (>99:-)[d]
10[f]	**12** (4)	AgOTf (4)	70 min	>99% (>99:-)[d]
11	**12** (3)	AgOTf (3)	5.5 h	98% (>99:-)[d]
12	-	AgOTf (5)	24 h	0%[g] -

[a] Reactions were conducted with **7a** (0.1 mmol). [b] Combined yield of isolated **8a** and **9a**. [c] Determined by ^1H NMR spectroscopy. [d] Determined by ^1H NMR spectroscopy and HPLC analysis. [e] The starting material **7a** was recovered in >99% yield. [f] Reactions were conducted with **7a** (5.0 mmol). [g] The starting material **7a** was recovered in 95% yield.



(6) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253–4271.

(7) Yamamoto, H.; Sasaki, I.; Hirai, Y.; Namba, K.; Imagawa, H.; Nishizawa, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1244–1247.

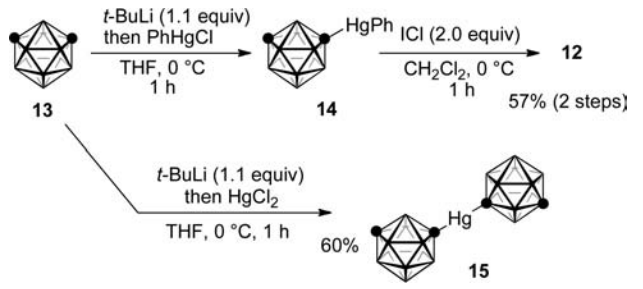
(8) Yamamoto, H.; Sasaki, I.; Shiomi, S.; Imagawa, H. Unpublished result.

(9) (a) Yamamoto, H.; Sasaki, I.; Namba, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2007**, *9*, 1399–1402. (b) Yamamoto, H.; Sasaki, I.; Mitsutake, M.; Karasudani, A.; Imagawa, H.; Nishizawa, M. *Synlett* **2011**, 2815–2818.

(10) (a) Scholz, M.; Hey-Hawkins, E. *Chem. Rev.* **2011**, *111*, 7035–7062. (b) Hawthorne, M. F.; Maderna, A. *Chem. Rev.* **1999**, *99*, 3421–3434.

As shown in Scheme 2, *m*-carbaborane-linked **12**, which showed the best result, can be prepared easily by treatment of **14** with iodine monochloride (ICl) in CH_2Cl_2 at 0 °C. The direct mercuration of *m*-carbaborane (**13**) with $HgCl_2$ led to overreaction, giving dimerized **15** as the major product.[12]

Scheme 2. Preparation of *m*-Carbaboranylmercuric Chloride



The molecular structure[13] of **12** was confirmed by an X-ray diffraction study (Figure 1).[14] The C−Hg distance of **12** is 2.07 Å, which is equivalent to that of **11**.[15] Therefore, the exact substituent effect of *m*-carbaborane, which induces higher regioselectivity than *o*-carbaborane, is unclear. More detailed investigation is required for full elucidation of the role of the substituent in the activity.

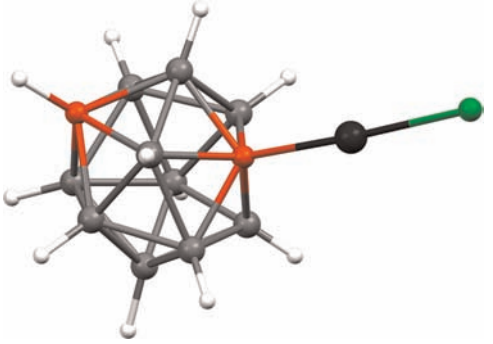
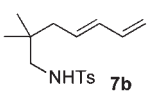
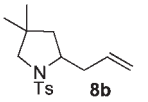
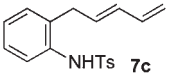
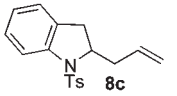
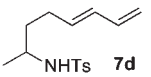
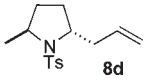
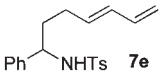
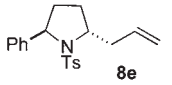
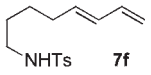
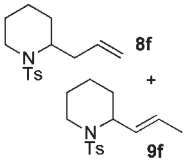
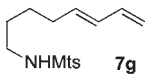
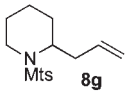
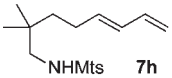
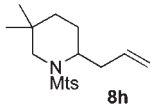
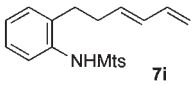
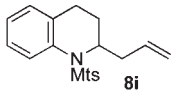
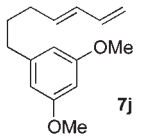
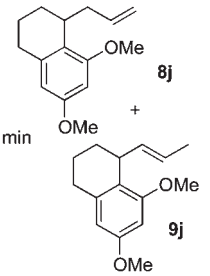
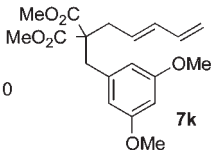
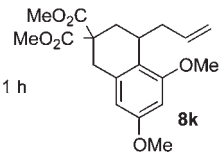
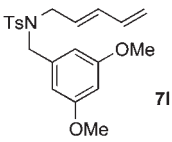
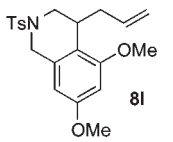


Figure 1. X-ray structure of **12**.

Table 2 shows the results for the reactions of a 1:1 combination of **12** and AgOTf with a variety of 1,3-dienes.

Table 2. Reaction of 1,3-Dienes **7b**–**l** with 4 mol % of **12** and AgOTf (1:1) in CH_2Cl_2 at Room Temperature[a]

entry	substrate	time	product	yield[b] (**8**:**9** ratio)[c]
1	 **7b**	10 min	 **8b**	>99% (>99:-)
2[d]	 **7c**	30 min	 **8c**	94% (>99:-)
3	 **7d**	15 min	 **8d**	95% (>99:-)
4	 **7e**	1 h	 **8e**	94% (>99:-)
5	 **7f**	1 h	 **8f** + **9f**	>99% (91:9)
6	 **7g**	1 h	 **8g**	98% (>99:-)
7	 **7h**	5 min	 **8h**	>99% (>99:-)
8[e]	 **7i**	1 h	 **8i**	97% (>99:-)
9	 **7j**	5 min	 **8j** + **9j**	>99% (93:7)
10	 **7k**	1 h	 **8k**	97% (>99:-)
11	 **7l**	30 min	 **8l**	98% (>99:-)

[a] Reactions were conducted with substrate (0.1–0.5 mmol). [b] Combined yield of isolated **8** and **9**. [c] Determined by ^{1}H NMR spectroscopy. [d] Substrate **7c** was *E*/*Z* (4:1) mixture. [e] Substrate **7i** was *E*/*Z* (10:1) mixture.

(11) (a) Kiran, B.; Anoop, A.; Jemmis, E. D. *J. Am. Chem. Soc.* **2002**, *124*, 4402–4407. (b) Jemmis, E. D.; Kiran, B. *J. Am. Chem. Soc.* **1997**, *119*, 4076–4077.

(12) (a) Yang, X.; Zheng, Z.; Knobler, C. B.; Hawthome, M. F. *J. Am. Chem. Soc.* **1993**, *115*, 193–195. (b) Schöberl, U.; Magnera, T. F.; Harrison, R. M.; Fleischer, F.; Pflug, J. L.; Schwab, P. F. H.; Meng, X.; Lipiak, D.; Noll, B. C.; Allured, V. S.; Rudalevige, T.; Lee, S.; Michl, J. *J. Am. Chem. Soc.* **1997**, *119*, 3907–3917.

(13) The single crystal of **12** was obtained from AcOEt at room temperature.

(14) CCDC 862695 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

(15) C−Hg distances of **11** and **12** were calculated using crystal analysis software (Mercury), which is available as a free download from the CCDC via www.ccdc.cam.ac.uk/.

Introduction of a dimethyl group at the β-position of the diene does not affect the course of reaction, and the 2-allylpyrrolidine derivative **8b** formed quantitatively (entry 1). An anilinoic derivative **7c** also completely reacted, giving 2-allylindoline **8c** as a single isomer (entry 2). Even with *sec*-alkyl amino derivatives **7d** and **7e** as substrates (entries 3 and 4), good reactivity and high regioselectivity (as well as diastereoselectivity[16]) were observed in the formation of the 2,5-*trans*-disubstituted pyrrolidines **8d** and **8e**, respectively. However, an elongation of the methylene unit in **7a** decreased the regioselectivity to give a 91:9 mixture of **8f** and **9f** (entry 5). To attain complete regioselectivity in the cyclization of **7f**, the effect of the protecting group on the nitrogen was investigated with several sulfonamide derivatives. The bulkiness of the *N*-protecting group contributed to the regioselectivity,[17] and the reaction of 2,4,6-trimethylbenzenesulfonyl (Mts)-protected **7g** was found to give **8g** as the sole product in 98% yield (entry 6). This procedure was similarly applicable to the reaction of **7h** and **7i**, giving the corresponding 2-allylpiperidine derivatives **8h** and **8i** in excellent yields with complete regioselectivity (entries 7 and 8). Furthermore, an attempt was made to find the utility of the present catalytic system in C−C bond forming reactions. The Friedel−Crafts-like cyclization of **7j** with 4 mol % of **12** and AgOTf was carried out at room temperature to afford the desired allyl-substituted product **8j** in good yield with high regioselectivity (entry 9). Introduction of a substituent into the **7j** core exerted no negative influence on the selectivity, as the diester **7k** and sulfonamide derivative **7l** gave the corresponding **8k** and **8l** in excellent yields with complete selectivity (entries 10 and 11).

In conclusion, we have developed a carbaboranyl mercuric chloride and have shown that the combination of *m*-carbaborane-linked **12** and AgOTf achieves intramolecular cyclization of 1,3-dienes with excellent reactivity and regioselectivity.[18] Both sulfonamide and aromatic functionalities can be used as nucleophiles. To the best of our knowledge, **12** is the first example employing carbaborane as a bulky substituent. These results will help facilitate the synthesis of a variety of allyl cyclic compounds, which function as potentially important synthons for the synthesis of natural products and pharmaceuticals.

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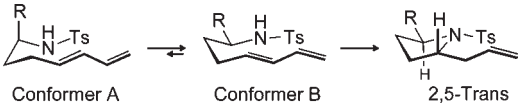
Supporting Information Available. Experimental procedures and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) 2,5-Cis-isomers were not detected. Cycloisomerizations of **7d** and **7e** proceed through the conformer B which offers minimal 1,3-diaxial interactions, consistent with the observed diastereoselectivity.



(17) When using the methylsulfonamide derivative, a mixture of allyl-type **8** and vinylene-type **9** was obtained in a 55:45 ratio.

(18) The mixture of **12** and AgOTf in CH_2Cl_2 can be stored at room temperature at least for several days.

The authors declare no competing financial interest.