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A heterogeneous mercury salt catalyst stabilized by *m*-carbaborane†

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Development of reusable heterogeneous catalysts has attracted a great deal of attention for both environmental and atom-economic reasons. In particular, a considerable amount of work has focused on reusable heavy- and rare-metal catalysts in order to limit the use and/or minimize the generation of problematic metal waste upon disposal. Herein is reported the development of a new polysiloxane-linked *m*-carbaboranylmercury (SiCB–Hg) catalyst, which can be used for various mercury salt-induced reactions such as the regioselective cyclization of 1,3-dienes and allyl alcohols, the intermolecular amination of allyl alcohols with sulfamates, and the cycloisomerization of alkynes. The catalyst can be completely recovered by simple filtration, with residual mercury in the filtrate <0.001% (nearly the quantitative limit). Furthermore, the catalyst can be reactivated by treatment with aqueous HCl and then AgOTf for reuse.

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Introduction

For many years considerable effort has been directed towards the immobilization of metal reagents used in organic syntheses.^{1,2} In particular, heavy- and rare-metal reagents have attracted a great deal of attention, since there are several important benefits associated with immobilization, including easier separation of materials, simplified handling and straightforward reuse of the reagent. Mercury salt reagents such as HgSO₄, Hg(OAc)₂, Hg(OTf)₂ *etc.* show high reactivity toward unsaturated C–C bonds, and have been utilized for various transformations.³ Thus, immobilized mercury salt reagents have been developed by several groups.⁴ However, recovery and reusability have not been satisfactory in all cases, and only alkynes have been usable as reactants. Our group previously reported an operationally simple process for the cyclization of alkyne derivatives using a silica gel-supported phenylmercuric triflate (SiPh–Hg) catalyst;^{4b} however, it decomposes in the presence of trifluoromethane sulfonic acid (HOTf) which is generated *in situ* during the catalytic cycle, and hence, decomposed mercury salts were detected in the products. Therefore, the development of a versatile heterogeneous reagent that can be reused safely for various mercury salt-induced reactions without leaching the metal is challenging, but of high value in both organic synthesis and green chemistry.

In 2012, we designed *m*-carbaboranylmercuric chloride (**1**) as a new type of mercury reagent, and demonstrated that the combination of **1** and AgOTf efficiently catalyzes the cycloisomerization of 1,3-dienes, leading to allyl-substituted cyclic compounds in excellent yields with high to complete regioselectivity.^{5a} More recently, our attention has shifted to the material properties of **1**, and various experiments have been carried out. Of significant note, **1** was found to possess high acid stability. Fig. 1A shows the results of kinetic studies of the reaction of **1** and phenyl mercuric chloride (**2**) with a stoichiometric amount of HOTf at room temperature. While most of the phenyl mercuric chloride decomposes within 48 h, the *m*-carbaboranylmercuric chloride can be completely recovered from the reaction mixture (Fig. 1B and C). The entirely decomposed sample of **2** was identified using HPLC-ICPMS analysis with authentic samples of **1**, **2**, HgCl₂, and Hg(OTf)₂ (Fig. 1D).⁶ Because the peak pattern and retention time of decomposed **2** are in accord with that of authentic HgCl₂ and Hg(OTf)₂, the phenyl mercuric chloride was found to disintegrate into benzene and bivalent mercury salts in presence of HOTf. Protonation of HOTf at the α -position of **2** likely triggers the decomposition.⁷ However, *m*-carbaborane, possessing three-center two-electron bonds, acts as an electron-deficient group (EDG);⁸ and hence, the carbaborane moiety of **1** is nonresponsive to HOTf. Even when stirred for one week with a high load (10 equiv.) of the super-acid, **1** was stable, existing without cleavage of the σ -bond that connects the mercury center with the carbon vertex of carbaborane. Thus, if the covalent immobilization of **1** on an insoluble polymeric material can be achieved, it might serve as an ideal heterogeneous mercuric reagent

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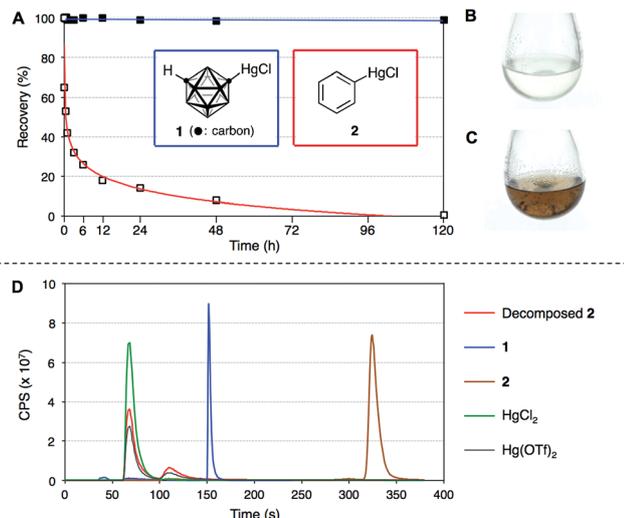
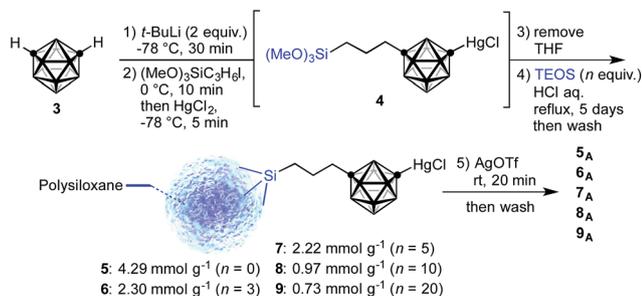


Fig. 1 (A) Kinetic study of the decomposition of 1 and 2. Reactions performed on a 0.1 mmol scale using 1 equiv. of HOTf at room temperature. Recovery rates of 1 (■) and 2 (□) were determined by ¹H-NMR analysis using CHBr₃ as an internal standard. (B) At 48 h in the reaction of 1 with HOTf. (C) At 48 h in the reaction of 2 with HOTf. (D) HPLC-ICP-MS analysis of decomposed 2 compared to 1, 2, and Hg(OTf)₂ (0.1–0.5 mg mL⁻¹). Elemental ²⁰²Hg was detected.

– one that can be completely recovered without leaching the metal. Additionally, based on an *in vivo* study with ICR mice, the median lethal dose (LD₅₀) of 1 was found to be more than 300 mg kg⁻¹ (Table S1†),⁹ which indicates incredibly low toxicity compared with that of HgCl₂ (LD₅₀ = 6.00 mg kg⁻¹)^{10a} and phenylmercury acetate (13.25 mg kg⁻¹),^{10b} as well as other mercuric compounds.^{10c} Practically, therefore, the use of 1 could also alleviate some of the anxiety involved in handling mercury-containing reagents.

Results and discussion

To prepare an insoluble, polymer-linked version of 1, *m*-carbaborane (3) was first converted to 4, the trialkoxysilane moiety of which was condensed using a Brønsted acid, as follows (Scheme 1). Two equivalents of *tert*-butyl lithium were slowly added to a THF solution of *m*-carbaborane at –78 °C to generate the dianion intermediate, which was treated with 3-



Scheme 1 Synthesis of SiCB-Hg catalyst carried out with 4.0 mmol of 3. TEOS = tetraethyl orthosilicate.

Table 1 Cyclization of 10a using SiCB-Hg catalyst^a

The reaction scheme shows the cyclization of 10a (1-methoxy-2-(3-methoxyphenyl)but-3-en-1-yl) using SiCB-Hg (20 mol%) in CH₂Cl₂ at room temperature. The reaction yields two products: 11a (allyl-type) and 12a (vinylenic-type).

Entry	SiCB-Hg	Time (h)	Yield ^b (%)	11 : 12	Hg-residue ^h (%)
1	5	120	0 ^c	—	—
2	5 _A	120	35 ^d	>99:— ^g	0.001
3 ^e	5 _A	120	60 ^f	>99:— ^g	0.001
4	6 _A	14	89	>99:— ^g	<0.001
5	7 _A	12	94	>99:— ^g	<0.001
6	8 _A	13	88	97 : 3	<0.001
7	9 _A	15	87	97 : 3	<0.001

^a Reactions performed on 0.1 mmol scale. ^b Combined yield (%) of 11 and 12. ^c Starting material was recovered in 98% yield. ^d Starting material was recovered in 50% yield. ^e 5_A (30 mol%). ^f Starting material was recovered in 22% yield. ^g Determined by ¹H-NMR spectroscopy. ^h Residual catalyst in filtrate. Determined using AAS with reductive vaporization method.

iopropyltrimethoxysilane and HgCl₂ in succession. Next, the reaction solvent was removed under vacuum at room temperature, and residual 4 (without isolation)¹¹ was immediately polymerized with aqueous HCl solution. Using TfoH as a condensing agent in ethanol, undesirable aggregation gradually occurred, generating sticky precipitates. Similar aggregates occurred using acetic acid and TFA, but aqueous HCl under reflux promoted ideal polymerization, giving white, solid particles of the polysiloxane-linked *m*-carbaboranylmercury salt (SiCB-Hg) 5. Since the average diameter of 5 thus prepared is 2.28 μm,¹² it was possible to collect the particles using ordinary filter paper and then wash them with H₂O and MeOH. The load of mercury in 5 was estimated to be 4.29 mmol g⁻¹ based on the

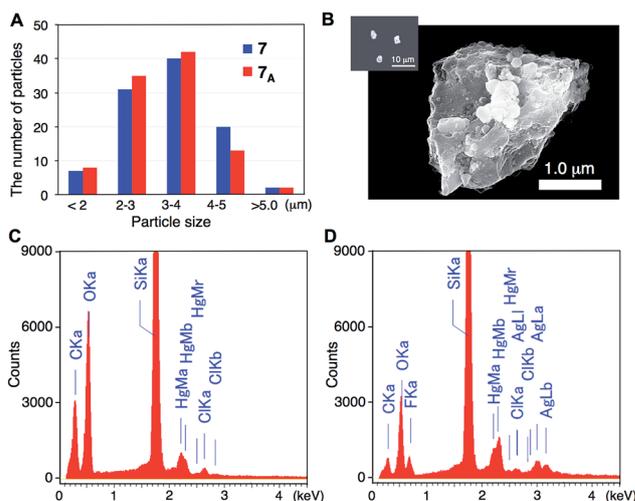


Fig. 2 (A) The mean particle sizes of 7 and 7_A were determined using image analysis software. (B) Picture and SEM image of 7. (C) EDX analysis of 7. (D) EDX analysis of 7_A.

quantity of HgCl_2 consumed, as determined using atomic absorption spectrometry (AAS) with the reductive vaporization method. In our previous study,^{5a} the mixing of AgOTf and **1** was key to inducing the catalytic activity. It is conceivable that *m*-carbaboranylmercuric triflate was generated as the true catalyst through a salt metathesis reaction between the reagents, and catalyzed cyclization of the 1,3-dienes. Thus, the isolated particles of **5** were activated with AgOTf in CH_2Cl_2 at room temperature and washed with toluene to remove excess AgOTf . (Hereafter, activated **5** is abbreviated **5_A**.) Separately, monomer **4** was co-condensed with 3, 5, 10 and 20 equivalents of tetraethyl orthosilicate to prepare **6–9**, respectively, with the aim of strengthening the polymer framework and securing additional space around the mercury center (the reactive site) of **5**.¹³ Particles of **6–9** were also activated with AgOTf and washed in the same manner as **5_A**.

Table 1 shows the activities of SiCB-Hg salts **5** and **5_A–9_A** in the cyclization of aryl 1,3-diene derivative **10a** at room temperature. Unactivated **5** did not produce appreciable amounts of product (entry 1).

Table 2 Regioselective cyclization of 1,3-dienes^a

Entry	Substrate	Product
1 ^b		 15 h, 92% ^c (11:12 ratio) = (>99:–) ^d <0.001% ^e
2		 14 h, 86% ^c (>99:–) ^d <0.001% ^e
3		 24 h, 88% ^c (>99:–) ^d 0.001% ^e
4		 11e: 24 h, 93% ^c (>99:–) ^d <0.001% ^e
		 11f: 18 h, 90% ^c (>99:–) ^d <0.001% ^e
5		 11g: 29 h, 85% ^c (>99:–) ^d <0.001% ^e
		 11h: 19 h, 92% ^c (>99:–) ^d <0.001% ^e
		 11i: 24 h, 96% ^c (>99:–) ^d <0.001% ^e
6 ^f		 38 h, 67% ^c (6:1) ^d <0.001% ^e

^a Reactions performed on 0.3–0.6 mmol scale using 20 mol% of **7_A** in CH_2Cl_2 at room temperature. ^b Substrate **10b** was *E/Z* (12 : 1) mixture. ^c Isolated yield. ^d Determined by ¹H-NMR spectroscopy. ^e Residual **7_A** in filtrate. Determined using AAS. ^f Diene group in substrate **10j** was *E/Z* (5 : 1) mixture, and the reaction performed using 30 mol% of **7_A**. Ts = *p*-toluenesulfonyl, Mts = 2,4,6-trimethylbenzenesulfonyl.

Activated **5_A** induced production of allyl-substituted **11a** as a single regioisomer, but the reaction was not complete even after 5 days with a catalyst load of 30 mol% (entries 2 and 3). However, the reactivity of **6_A–9_A** was even better than **5_A**, as a catalyst load of 20 mol% was sufficient to complete the reaction within a reasonable period of time (entries 4–7). **7_A** showed especially good performance, giving **11** within 12 h in excellent yield and with complete regioselectivity (**11** : **12** = >99:–), which is not possible with the combination of **1** and AgOTf .⁵ Furthermore, **7_A** was nearly completely recovered from the reaction mixture by simple paper-filtration (<0.001% loss). The residual mercury in the filtrate was near the quantitative limit (0.010 ppb) by AAS. In fact, for **7_A**, the exact quantity (0.016–0.047 ppb) could not be determined using AAS.¹⁴

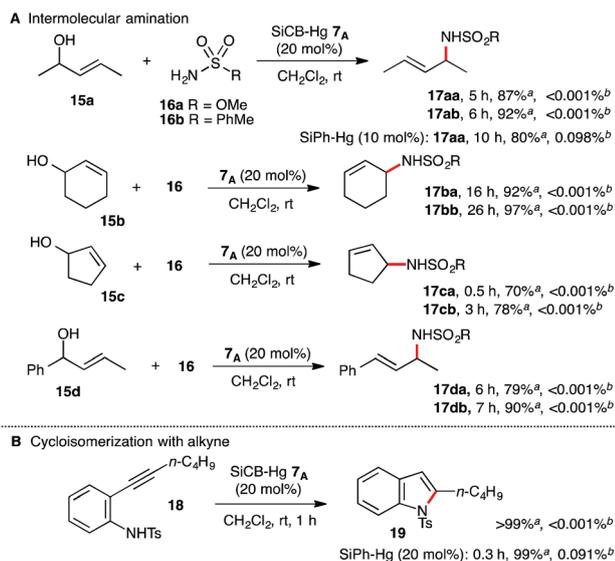
Material analyses of **7** and **7_A**

The mean particle sizes of **7_A** and **7** are 3–4 μm (Fig. 2A and B). In a point analysis by using energy dispersive X-ray spectroscopy (EDX), signals characteristic of mercury (2.20, 2.28 and 2.49 keV) and chlorine (2.62 and 2.82 keV) are clearly detected from the surface of normal **7** (Fig. 2C). The EDX analysis of **7_A** clearly indicates the presence of elemental fluorine (0.68 keV; derived from trifluoromethyl sulfonyl group) along with signals from mercury, carbon, oxygen and silicon (Fig. 2D).¹⁵ Although silver and chlorine signals were also detected from the surface of **7_A**, these elements are probably derived from a nearly insoluble AgCl salt generated *via* a salt metathesis reaction of **7** and AgOTf .

Table 3 Cyclization of allyl alcohols^a

Entry	Substrate	Product
1		 <i>rt</i> ^b , 8 h ^c , >99% ^d <0.001% ^e
2		 <i>rt</i> ^b , 10 h ^c , 93% ^d <0.001% ^e
3		 <i>rt</i> ^b , 24 h ^c , 71% ^d 0.001% ^e
4		 <i>rt</i> ^b , 16 h ^c , 83% ^d <0.001% ^e
5		 14e: reflux ^b , 6 h ^c , 89% ^d <0.001% ^e
		 14f: reflux ^b , 12 h ^c , 70% ^f 0.001% ^e
6		 reflux ^b , 18 h ^c , 88% ^d 0.001–0.002% ^e

^a Reactions performed on 0.3 mmol scale using 20 mol% of **7_A** in CH_2Cl_2 . ^b Reaction temperature. ^c Reaction time. ^d Isolated yield. ^e Residual **7_A** in filtrate. Determined using AAS. ^f Combined yield of isolated *p*-cyclization product and *o*-cyclization product (8 : 1).

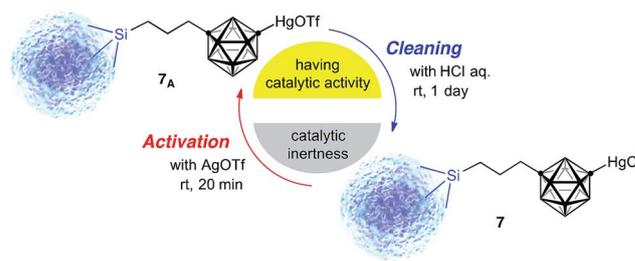


Scheme 2 (A) Intermolecular amination of allyl alcohols with methylsulfamate, and (B) cycloisomerization of an alkynyl aniline. Reactions performed on 0.3–0.5 mmol scale. ^a Isolated yield. ^b Residual 7_{A} in filtrate. Determined using AAS.

Reactions with immobilized catalyst 7_{A}

Catalyst 7_{A} could also be applied to other Friedel–Crafts-like cyclizations of 1,3-dienes (Table 2). When indole derivative **10b** and 20 mol% of 7_{A} were mixed at room temperature, the regioselective cyclization desired proceeded steadily to afford **11b** as the sole product in 92% yield. Allyl-substituted cyclic **11c** and **11d** were also obtained in good yields with excellent regioselectivity. In C–N bond forming reactions with **10e–i**, the bulkiness of the N-protecting group does not affect the cyclization, giving the corresponding azacyclic product with complete selectivity in good yield. Tandem carbocyclization was also achieved in CH_3NO_2 at room temperature; the reaction of diene/ene/aryl **10j** with 30 mol% of 7_{A} was complete within 38 h, giving tricyclic **11j** in 67% yield with high diastereoselectivity, although a vinylene-type minor product was also encountered. In all cases, the catalysts used were completely recovered without significant leaching of the metal.

Interestingly, it was found that 7_{A} worked extremely well with allyl alcohols (Table 3).¹⁶ 20 mol% of 7_{A} smoothly promoted the C–N bond-forming cyclization of **13a** to afford vinyl-substituted **14a** quantitatively within 8 h. The double coordination of 7_{A} toward the hydroxyl group and the C–C double bond in **13a**



Scheme 3 Reactivating cycle of 7_{A} .

probably contributed to the smooth ring formation, and then elimination of the alcohol. **13b** and **13c**, as well as **13d** bearing prenyl alcohol, also reacted well with 7_{A} , giving the corresponding products (**14b**, **14c**, **14d**) along with water as the sole co-product (entries 2–4). For the C–C bond-forming cyclizations (entries 5 and 6), reflux conditions were required to induce the reactions, but the products were obtained in good yields without significant mercury leakage. Furthermore, 7_{A} catalyzed the intermolecular allylic amination of allyl alcohols **15a–c** with sulfonamide derivatives **16a** and **16b** (Scheme 2A). Critically, in the reaction of **15a** with **16a**, the mercury leakage of 7_{A} was dramatically improved compared to our previous experiment with a silica gel-supported phenylmercury (SiPh–Hg) catalyst (<0.001% here, vs. 0.098% earlier).¹⁷ This tendency was also observed in the cycloisomerization of alkynyl aniline derivative **18** (Scheme 2B).^{4b,18} While the SiPh–Hg catalyst leached 0.0913% of the mercury, elution from 7_{A} was virtually nonexistent in the synthesis of indole derivative **19**.

The reuse performance of 7_{A} was confirmed by using it multiple times for the synthesis of **14a** (Table 4). For the best performance, 50 mol% of 7_{A} was used in the reaction. When the cyclization reaction of **13a** was repeated 20 times, the yield was always quantitative, and without any significant metal leaching. The gradual extension of reaction times was necessitated by the fact that the water byproduct gradually covered the surface of 7_{A} . Indeed, desiccating at 80 °C under vacuum for 3 h dramatically increased the activity of the catalyst, shortening the reaction time from 48 h to 12 h (21st run). After multiple optimization experiments it was discovered that treatment with aqueous HCl and then AgOTf was ideal for revitalization of the catalyst (Scheme 3). Because the signal pattern of aqueous HCl-washed 7_{A} was identical to that of **7** in EDX analysis, especially the signals characteristic of elemental mercury (2.20, 2.28 and 2.49 keV) and chlorine (2.62 and 2.82 keV), washed 7_{A} is

Table 4 Reuse of activated polymer catalyst 7_{A} for the synthesis of **14a**^{a,b}

Run	1st	2nd	3rd	4th	5th	6th	7th...	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd
Time (h)	2.5	2.5	2.5	2.5	4	5	6	10	12	12	12	16	24	48	12 ^e (3) ^f	3 ^f	3 ^f
Yield ^c (%)	99	>99	>99	>99	99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99 ^{e,f}	>99 ^f	>99 ^f
Residual 7_{A} ^d (%)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001 ^{e,f}	<0.001 ^f	<0.001 ^f

^a Run 8th; 6.5 h, >99%, <0.001%, run 9th; 7 h, >99%, <0.001%, run 10th; 7.5 h, >99%, <0.001%, run 11th; 7.5 h, >99%, <0.001%, run 12th; 8 h, >99%, <0.001%. Run 13th; 9 h, >99%, <0.001%. ^b Reactions performed on 0.2 mmol scale at room temperature. ^c Isolated yield. ^d Determined using AAS. ^e Reaction performed on 0.09 mmol scale using dried 7_{A} . ^f Reaction performed on 0.1 mmol scale using reactivated 7_{A} .

probably converted to normal **7** again (Fig. S3†). Thus, reactivation with AgOTf was carried out. The resuscitated **7_A** demonstrated the same level of activity as that of fresh **7_A**, giving product **13a** within 3 h (21st–23rd runs). Clearly, the catalyst was available for further reaction.

Conclusions

In summary, we have developed a novel mercury salt polymer catalyst stabilized by *m*-carbaborane which has been applied to the regioselective synthesis of allyl- and vinyl-substituted cyclic compounds and allyl amine derivatives from a wide range of 1,3-dienes and allyl alcohols. The catalyst precursor **7** can be easily prepared in a one-pot process from *m*-carbaborane, and it has high durability under acidic conditions. Catalyst **7_A** can be recovered without mercury leakage, and revitalization is possible by simple treatment with aqueous HCl and AgOTf when catalytic activity decreases through repeated use. To the best of our knowledge, the present catalyst is the first utilizing *m*-carbaborane to safely concatenate a heavy metal and a polymer material. It has distinctive reactivity (towards 1,3-dienes), and its reactivity constitutes a reasonable alternative to existing mercury salt reagents. We firmly believe that it will be proved quite useful in organic syntheses from utility, safety and green chemistry perspectives.

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