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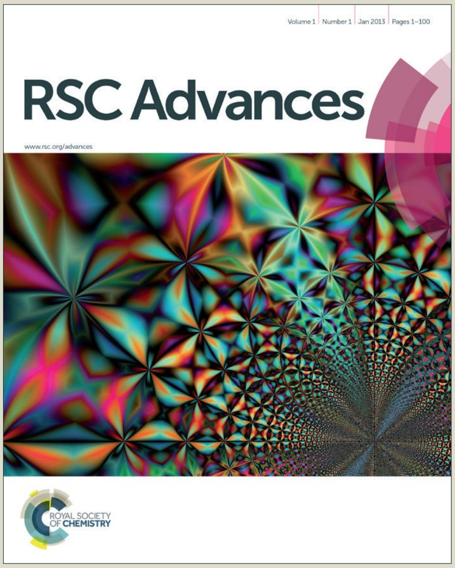

ROYAL SOCIETY
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Journal Name

ARTICLE

A Heterogeneous Mercury Salt Catalyst Stabilized by *m*-Carbaborane

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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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*-carboranylmercury (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.

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 $HgSO_4$, $Hg(OAc)_2$, $Hg(OTf)_2$ 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. Figure 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 (Figures 1B and 1C). The entirely decomposed sample of **2** was identified using HPLC-ICPMS analysis with authentic samples of **1**, **2**, $HgCl_2$, and $Hg(OTf)_2$ (Figure 1D).[6] Because the peak pattern and retention time of decomposed **2** are in accord with that of authentic $HgCl_2$ 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 – one that can be completely recovered without leaching the metal. Additionally, based on an *in vivo* study with ICR mice, the median lethal dose (LD_{50}) of **1**

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization for all new compounds. See DOI: 10.1039/x0xx00000x

was found to be more than 300 mg/kg (Table S1),[9] which indicates incredibly low toxicity compared with that of $HgCl_2$ (LD_{50} = 6.00 mg/kg)[10a] and phenylmercury acetate (13.25 mg/kg),[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.

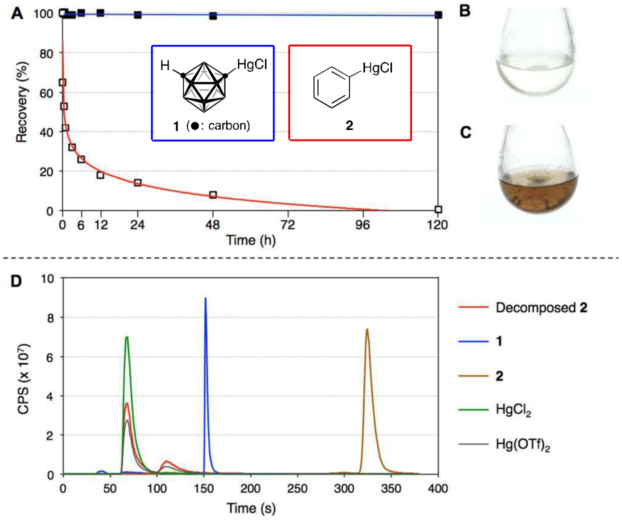
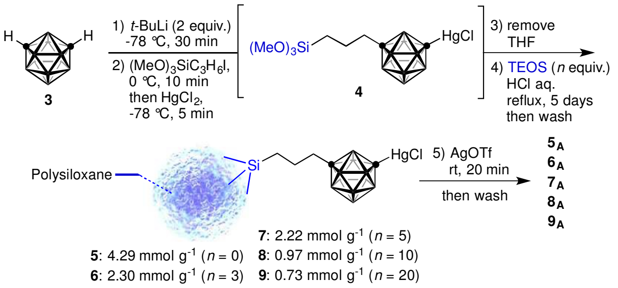


Fig 1. (A) Kinetic study of the decomposition of **1** and **2**. Reactions performed on a 0.1 mmol scale using 1 equiv of HOTf at room temperature. Recovery rates of **1** (■) and **2** (□) were determined by ^{1}H-NMR analysis using $CHBr_3$ as an internal standard. (B) At 48 h in the reaction of **1** 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). Elemental ^{202}Hg was detected.

Results and discussion

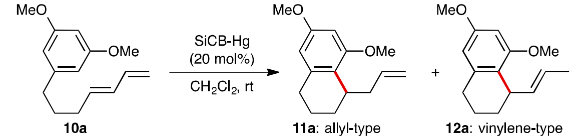
To prepare an insoluble, polymer-linked version of **1**, *m*-carbaborane (**3**) was first converted to **4**, the trialkyloxysilane moiety of which was condensed using a Brønsted acid, as follows (Scheme 1). Two equivalents of *tert*-butyl lithium were slowly added to a THF solution of *m*-carbaborane at -78 °C to generate the dianion intermediate, which was treated with 3-iodopropyltrimethoxysilane and $HgCl_2$ 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 H_2O and MeOH. The load of mercury in **5** was estimated to be 4.29 mmol/g based on the 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 **5A**.) 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 **5A**.



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

Table 1 shows the activities of SiCB-Hg salts **5** and **5A**-**9A** 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 1. Cyclization of **10a** using SiCB-Hg catalyst.[a]



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 ^{1}H-NMR spectroscopy. [h] Residual catalyst in filtrate. Determined using AAS with reductive vaporization method.

Activated **5A** 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 **6A**-**9A** was even better than **5A**, 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 (Figures 2A and 2B). 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** (Figure 2C). The EDX analysis of **7_A** clearly indicates the presence of elemental fluorine (0.68 keV; derived from trifluoromethly sulfonyl group) along with signals from mercury, carbon, oxygen and silicon (Figure 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.

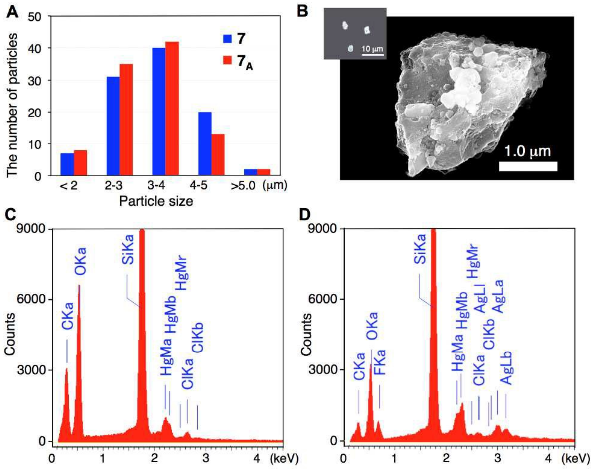
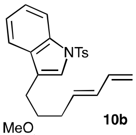
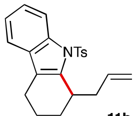
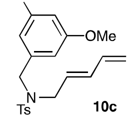
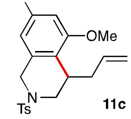
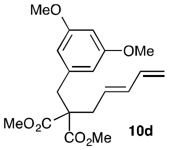
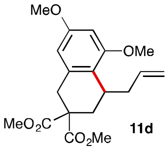
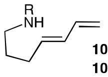
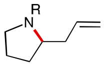
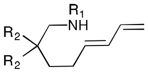
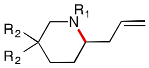
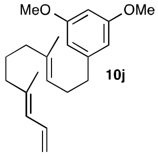
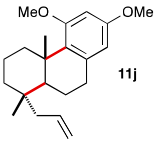


Fig 2. A) The mean particle sizes of **7** and **7_A** were determined using image analysis software. B) Picture and SEM image of **7**. C) EDX analysis of **7**. D) EDX analysis of **7_A**.

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 diastereoselectivelly, although a vinylene-type minor product was also encountered. In all cases, the catalysts used were completely recovered without significant leaching of the metal.

Table 2. Regioselective cyclization of 1,3-dienes.[a]

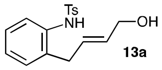
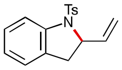
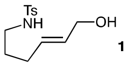
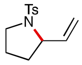
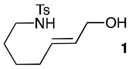
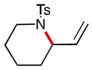
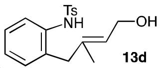
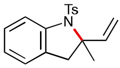
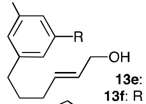
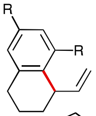
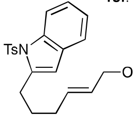
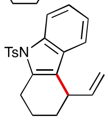
Entry	Substrate	Product	
1[b]	 **10b**	 **11b**	15 h, 92%[c] (**11**:**12** ratio) = (>99:-)[d] <0.001%[e]
2	 **10c**	 **11c**	14 h, 86%[c] (>99:-)[d] <0.001%[e]
3	 **10d**	 **11d**	24 h, 88%[c] (>99:-)[d] 0.001%[e]
4	 **10e**: R = Ts **10f**: R = Mts		**11e**: 24 h, 93%[c] (>99:-)[d] <0.001%[e] **11f**: 18 h, 90%[c] (>99:-)[d] <0.001%[e]
5	 **10g**: R_1 = Ts, R_2 = Me **10i**: R_1 = Mts, R_2 = Me **10h**: R_1 = Mts, R_2 = H		**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]	 **10j**	 **11j**	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 ^{1}H-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.

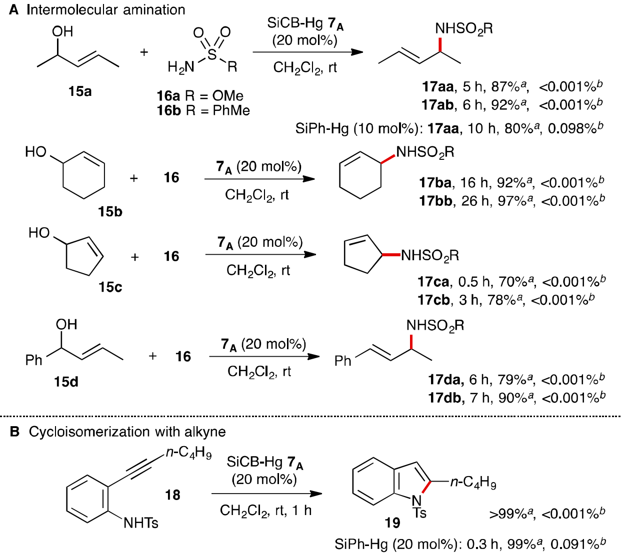
Interestingly, it was found that **7_A** worked extremely well with allyl alcohols (Table 3).[16] 20 mol% of **7_A** smoothly promoted the C-N bond-forming cyclization of **13a** to afford vinyl-substituted **14a** quantitatively within 8 h. The double coordination of **7_A** toward the hydroxyl group and the C-C double bond in **13a** 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**$_\mathrm{A}$ was virtually nonexistent in the synthesis of indole derivative **19**.

Table 3. Cyclization of allyl alcohols.[a]

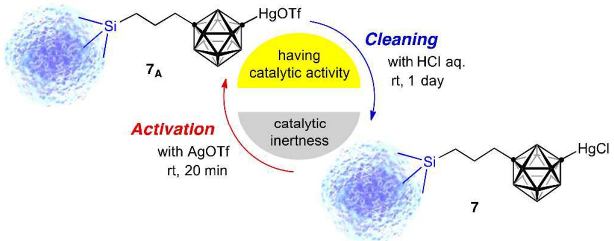
Entry	Substrate	Product	
1	 **13a**	 **14a**	rt[b], 8 h[c], >99%[d] <0.001%[e]
2	 **13b**	 **14b**	rt[b], 10 h[c], 93%[d] <0.001%[e]
3	 **13c**	 **14c**	rt[b], 24 h[c], 71%[d] 0.001%[e]
4	 **13d**	 **14d**	rt[b], 16 h[c], 83%[d] <0.001%[e]
5	 **13e**: R = OMe **13f**: R = H,OMe		**14e**: reflux[b], 6 h[c], 89%[d] <0.001%[e] **14f**: reflux[b], 12 h[c], 70%[f] 0.001%[e]
6	 **13g**	 **14g**	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**$_\mathrm{A}$ in CH_2Cl_2. [b] Reaction temperature. [c] Reaction time, [d]Isolated yield. [e] Residual **7**$_\mathrm{A}$ 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**$_\mathrm{A}$ in filtrate. Determined using AAS.

The reuse performance of **7**$_\mathrm{A}$ was confirmed by using it multiple times for the synthesis of **14a** (Table 4). For the best performance, 50 mol% of **7**$_\mathrm{A}$ 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**$_\mathrm{A}$. 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 2). Because the signal pattern of aqueous HCl-washed **7**$_\mathrm{A}$ 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**$_\mathrm{A}$ is probably converted to normal **7** again (Fig. S3). Thus, reactivation with AgOTf was carried out. The resuscitated **7**$_\mathrm{A}$ demonstrated the same level of activity as that of fresh **7**$_\mathrm{A}$, giving product **13a** within 3 h (21st-23rd runs). Clearly, the catalyst was available for further reaction.



Scheme 2. Reactivating cycle of **7**$_\mathrm{A}$

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**$_\mathrm{A}$ 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.

Table 4. Reuse of activated polymer catalyst $\mathbf{7_A}$ for the synthesis of **14a**.[a]

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[d] (3)[e]	3[e]	3[e]
Yield (%)[b]	99	>99	>99	>99	99	>99	>99	>99	>99	>99	>99	>99	>99	>99	>99[d,e]	>99[e]	>99[e]
Residual $\mathbf{7_A}$ (%)[c]	<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[d,e]	<0.001[e]	<0.001[e]

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%. [a] Reactions performed on 0.2 mmol scale at room temperature. [b] Isolated yield. [c] Determined using AAS. [d] Reaction performed on 0.09 mmol scale using dried $\mathbf{7_A}$. [e] Reaction performed on 0.1 mmol scale using reactivated $\mathbf{7_A}$.

Acknowledgements

Dedicated to the late Professor Mugio Nishizawa. We are grateful to Dr. Yasuko Okamoto (analysis center in Tokushima Bunri University) for determining the HRMS. This study was financially supported by a Grant-in-Aid (No. 23790034) from the MEXT (Ministry of Education, Culture, Sports, Science, and Technology) of the Japanese Government.

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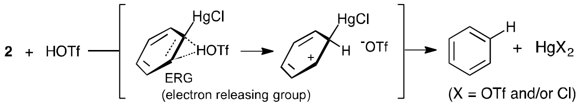

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