Supported Catalysts

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Silaphenylmercuric Triflate Catalyzed Reactions: Synthesis of a Solid-Supported Mercuric Salt Catalyst**

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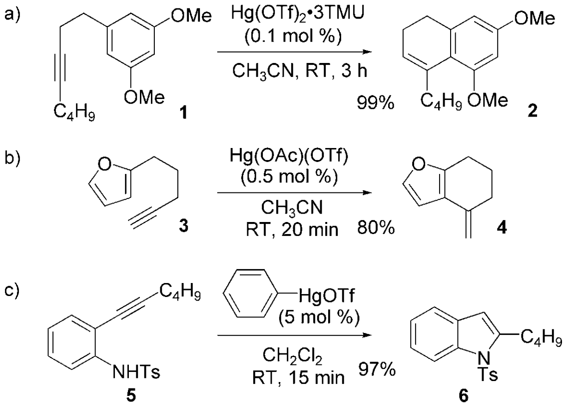
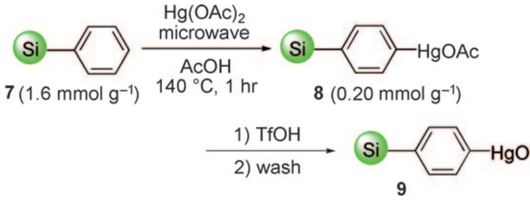
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

For many years considerable effort has been directed towards the immobilization of transition-metal catalysts used in organic syntheses.[1] There are several important benefits associated with immobilization, including easier separation of materials, straightforward recycling of the catalyst, and simplification in handling, and in most cases the metals are coordinated to polymer-supported ligands.[2] We designed a novel σ-bonded metal salt polymer, silaphenylmercuric triflate, which shows efficient catalytic activity for a variety of mercury(II) trifluoromethanesulfonate [$Hg(OTf)_2$]-catalyzed reactions.[3] Recently we reported the highly efficient catalytic activity of the $Hg(OTf)_2$·tris(tetramethylurea) (TMU) complex for arylyne cyclizations of **1** leading to carbocycle **2** with up to 1000 times catalytic turnover under mild conditions (Scheme 1 a).[4] $Hg(OTf)_2$ itself is too reactive for the cyclization of **1**, resulting in a low product yield because of side reactions such as polymerization of the product. When the cycloisomerization of alkynyl furan **3** was examined the use of $Hg(OTf)_2$ and TMU also proved to be too reactive. However, the expected product **4** was obtained when **3** was treated with Hg(OAc)(OTf) (Scheme 1 b), which was prepared by mixing $Hg(OAc)_2$ and $Sc(OTf)_3$ in a 10:1 ratio.[5] This finding suggests that a single OTf is sufficient for the catalytic cycle. Futhermore the reaction of alkynyl aniline derivative **5** with 5 mol% of phenylmercuric triflate (prepared in situ by mixing PhHgOAc and an equimolar amount of TfOH) to give an indole derivative **6** was complete after 15 minutes at room temperature to give a 97% yield of **6** (Scheme 1 c).[6] We have attempted to prepare silaphenylmercuric triflate, the first solid-supported mercuric salt catalyst, and describe herein the preparation of solid-supported silaphenylmercuric triflate (**9**) and several examples of silaphenylmercuric triflate-catalyzed reactions such as indole synthesis, furanoyne cyclization, arylyne cyclization, and tandem carbocyclizations. The starting polymer, Silia*Bond* Phenyl, is a silica gel used for column chromatography[7] which led us to establish a flow reaction system. Although the mercury center and the aromatic carbon atom are connected by a σ bond, a small amount of Hg leaching was nevertheless detected (i.e., up to $\delta = 0.37$ ppm).



Scheme 1. Mercury-catalyzed cyclization of alkynes. Ts = *p*-toluenesulfonyl.

Silaphenylmercuric triflate (**9**) was prepared by initially heating Silia*Bond* Phenyl (**7**; Silicycle, 230–400 mesh, loading 1.62 mmol g^{-1})[7] at 140°C for one hour with an equimolar amount of $Hg(OAc)_2$ in acetic acid by using microwave radiation (Scheme 2).[8] Silaphenylmercuric acetate (**8**) was isolated after filtration of the reaction mixture and washing the residue. The loading of the phenylmercuric acetate group on dried **8** was estimated to be 0.20 mmol g^{-1} based on the quantity of consumed $Hg(OAc)_2$ as determined by using atomic absorption spectrometry with the reductive vapor-



Scheme 2. Preparation of silaphenylmercuric triflate (**9**).

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ization method.[9,10] A suspension of **8** in CH_3CN was stirred with two equivalents of TfOH at room temperature for 10 minutes, and then the filtered residue was washed and dried to give **9**. The average diameter of the solid particles was determined to be 50 to 80 μm by using Image-Pro software (Media Cybernetics).[11]

First we examined the reaction of alkynyl aniline **5** with solid-supported **9** at room temperature. Dichloromethane was found to be the solvent of choice as because it led to indole **6** in a 99% yield within three hours by using 3 mol% of **9** (Table 1, entries 1–4).[3i] The reaction time decreased when the quantity of catalyst used was increased; the reaction was complete within 20 minutes when 20 mol% of **9** was employed (Table 1, entry 7), and almost instantaneously complete upon using 50 mol% of **9** (Table 1, entry 8). In contrast, silaphenylmercuric acetate (**8**) did not promote the reaction with **5** even when 50 mol% was used (Table 1, entry 9).

Table 1: Optimization of reaction conditions for the synthesis of indole **6** from **5** using catalyst **9** (see Scheme 1).

Entry	**9** (mol%)	Solvent	*t* [min]	Yield[a] [%]
1	3	CH_3CN	1440	0
2	3	CH_3NO_2	1440	16
3	3	$C_6H_5CH_3$	240	98
4	3	CH_2Cl_2	180	99
5	5	CH_2Cl_2	90	99
6	10	CH_2Cl_2	30	99
7	20	CH_2Cl_2	20	99
8	50	CH_2Cl_2	5	99
9	50[b]	CH_2Cl_2	90	0

[a] Yield of isolated product. [b] Reaction using **8** as the catalyst.

The ability to recycle the catalyst was also investigated by analyzing the reaction of **5** to give indole **6**. As seen in Table 2, the filtered catalyst displayed 100% catalytic activity until the fifth round of recycling. A longer reaction time was required for the sixth round of recycling, and the seventh recycle did not demonstrate the same level of activity relative to that of the first round reaction. The observed deterioration in catalytic activity is probably because of the limited mechanical durability of this polymer upon stirring.

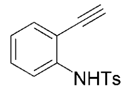
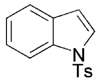
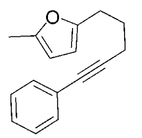
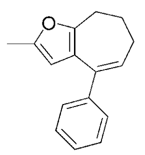
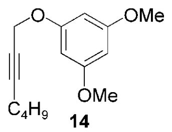
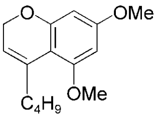
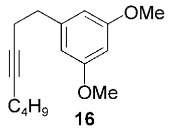
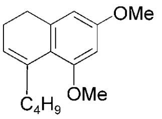
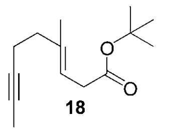
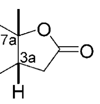
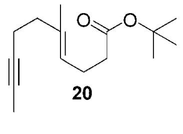
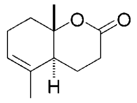
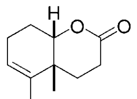
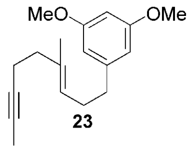
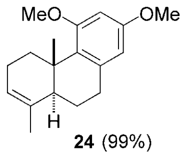
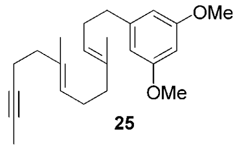
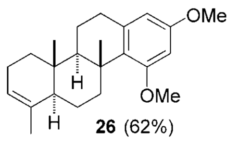
Table 2: Recycling of the catalyst **9** for the synthesis of indole **6** (see Scheme 1).

Entry	Catalyst[a]	*t*	Yield [%][b]
1	1st reaction	90 min	99
2	2nd reaction	90 min	99
3	3rd reaction	90 min	99
4	4th reaction	90 min	99
5	5th reaction	90 min	97
6	6th reaction	240 min	92
7	7th reaction	24 h	62

[a] 5 mol% of the catalyst used. [b] Yield of isolated product.

To explore the scope reaction aniline derivative **10** was reacted with 10 mol% of **9** in CH_2Cl_2 at room temperature for 60 minutes, after which *N*-tosylindole **11** was obtained in 92% yield (Table 3, entry 1).[3i] Although the Friedel–Crafts type cycloisomerization of 2-alkynlfuran is a very difficult reaction because of the instability of the product,[5] the reaction of **12** with 10 mol% of **9** in CH_3CN at 60°C was complete within

Table 3: Silaphenylmercuric triflate (**9**)-catalyzed cyclization.

Entry	Substrate	**9** (mol%) conditions	Product (yield [%])[a]
1	 **10**	(10 mol%) CH_2Cl_2 RT, 60 min	 **11** (92%)
2	 **12**	(10 mol%) CH_2Cl_2 60°C, 3 h	 **13** (81%)
3	 **14**	(5 mol%) CH_3CN RT, 90 min	 **15** (99%)
4	 **16**	(10 mol%) CH_3CN RT, 90 min	 **17** (80%)
5	 **18**	(5 mol%) CH_3NO_2 90°C, 1 h	 **19** (60%)
6	 **20**	(10 mol%) CH_3NO_2 90°C, 4 h	 **21** (72%)  **22** (24%)
7	 **23**	(10 mol%) CH_3NO_2 RT, 40 min	 **24** (99%)
8	 **25**	(20 mol%) CH_3NO_2 RT, 2 h	 **26** (62%)

[a] Yield of isolated product.

three hours to afford the seven-membered ring product **13** in 81% yield (Table 3, entry 2).[5] The $Hg(OTf)_2$-catalyzed arylyne cycloisomerization did not go to completion because of the instability of the dihydronaphthalene products to the catalyst;[4] however, the solid-supported **9** was mild enough (similar to $Hg(OTf)_2{\cdot}3TMU$) to give **15** and **17** upon reaction with **14** and **16**,[4] respectively, in satisfactory yields when the reaction was performed at room temperature. Tandem cyclizations were also achieved by using **9**. For example, the reaction of yne/ene/ester **18** with 5 mol% of **9** in CH_3NO_2 at 90°C for one hour afforded *cis*-fused bicyclic product **19** in 60% yield.[12] The reaction of yne/ene/ester **20** with **9** (10 mol%) in CH_3NO_2 at 90°C was completed within four hours to give *trans*-fused **21** in 72% yield along with rearranged *cis*-fused **22** in 24% yield. Tandem carbocyclizations were also achieved by using **9**; the reaction of yne/ene/aryl **23** with 10 mol% of **9** in CH_3NO_2 was complete within 40 minutes at room temperature, giving rise to tricyclic **24** in quantitative yield,[3d] and the reaction of **25** with 20 mol% of **9** at room temperature for two hours afforded **26** in 62% yield.[3e] The workup of these reactions was very simple, as the catalyst was recovered by filtration of the reaction mixture through ordinary filter paper. The filtrate was concentrated and the resulting crude reaction mixture was purified by column chromatography to afford analytical grade products.

Silia*Bond* Phenyl, from which **9** is made, was developed as a stationary phase for reverse phase column chromatography (Figure 1). Therefore, we next examined the inclusion of our catalyst into a flow reactor system[13] by simply combining a **9** and silica gel (60 N (Kanto)) in a 2:3 ratio in a glass column (Pasteur pipette) and sealed it with a cotton wool plug. The amount of **9** in the column corresponded to 40 μmol. A 0.2 M solution of **5** (40 μmol) in CH_2Cl_2 was eluted through the column at room temperature and indole **6** was obtained in quantitative yield. The elution was repeated 20 times and the yields were always quantitative (Table 4). A 0.02 M solution of yne/aryl **14** (40 μmol) was then eluted through the same column, and **15** was obtained in 96% yield. Mercury leakage was determined by atomic absorption spectrometry with the reductive vaporization method.[9] Each run leached 0.014 to 0.028% of Hg, corresponding to 0.21 to 0.37 ppm. Since the Hg and phenyl group are connected through a σ bond, the observed Hg leakage was presumed to take place by TfOH induced hydrolysis of O−Si bond originating from Silia*Bond* Phenyl.

Table 4: Repeated flow reaction of **5** to give **6**.

Flow	Yield [%][a]	Hg leaching	
		[%]	(ppm)
1st	99	0.019	0.25
2nd	99	0.023	0.30
3rd	99	0.020	0.27
4th	99	0.016	0.21
5th	99	0.018	0.24
6th	99	0.028	0.37
7th	99	0.023	0.30
8th	99	0.022	0.29
9th	99	0.024	0.32
10th	99	0.018	0.24
11th	99	0.015	0.20
12th	99	0.017	0.23
13th	99	0.017	0.23
14th	99	0.017	0.23
15th	99	0.022	0.29
16th	99	0.018	0.24
17th	99	0.015	0.20
18th	99	0.017	0.22
19th	99	0.022	0.29
20th	99	0.014	0.18

[a] Yield of isolated product.

In conclusion, we have developed the synthesis of solid-supported mercuric salts silaphenylmercuric acetate (**8**) and silaphenylmercuric triflate (**9**). Although **8** did not show any catalytic activity, **9** showed remarkable catalytic activity for the cycloisomerization of various alkyne derivatives.

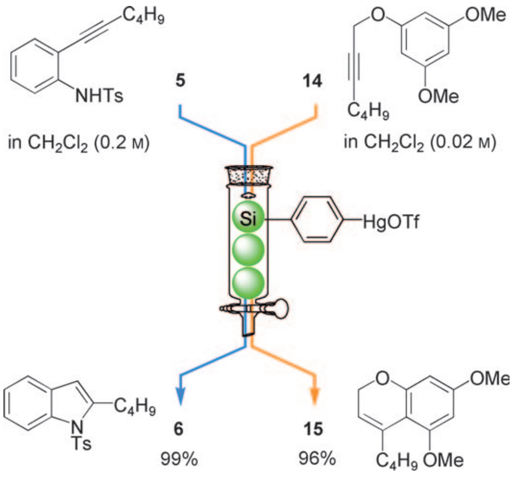


Figure 1. Flow system reaction for **5** and **14**.

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[5] H. Yamamoto, I. Sasaki, K. Namba, H. Imagawa, M. Nishizawa, *Org. Lett.* **2007**, *9*, 1399 – 1402.

[6] H. Yamamoto, Y. Hirai, K. Namba, H. Imagawa, M. Nishizawa, unpublished result (cf. supporting information).

[7] Silia*Bond* Phenyl (R34030B) is supplied by SiliCycle Inc. Canada.

[8] M. Kidwai, S. Kohli, P. Kumar, *J. Chem. Res. S* **1998**, 52 – 53.

[9] To determine the loading of mercury, combined filtrate and washed solvent was examined using a mercury analyzer.

[10] It is possible to prepare higher Hg loaded polymer, however, it showed less catalytic activity for the reaction of **5** to **6**.

[11] Typical optical microscopic image of **9** (20 x magnification) is shown in the Supporting Information.

[12] An NOE relationship was observed between the methyl group on C7a and the H atom on C3a of **19**.

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