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A new catalyst for organic synthesis: mercuric triflate†

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Herein, we describe $Hg(OTf)_2$ as a new catalytic system for organic synthesis, which can achieve the hydration of alkynes, C–C bond forming cyclizations, heterocycle synthesis and cyclization initiated by allylic alcohols at very high catalytic turnovers under mild conditions. The first solid-supported mercuric salt, silaphenylmercuric triflate, was also developed and found to act as a powerful catalyst for most $Hg(OTf)_2$-catalyzed reactions.

Introduction

In early 1980, one of the authors (M. N.) encountered a delicious fruit called "duku" (*Lansium domesticum*, Meliaceae) during a visit to Indonesia (Fig. 1). The major constituent of this fruit peel is lansic acid, a novel triterpene dicarboxylic acid (**1**),[1] which is extracted in large quantities by a simple procedure (Scheme 1). Lansic acid was found to display significant hair restoration activity.[2] Several years later a hair restoration agent called Kanebo Shidenkai Lansic, containing lansic acid as the active ingredient, appeared in the market. Meanwhile, we started work towards the synthesis of **1**. In order to achieve the transformation of **2** into **3**, we developed mercuric trifluoromethanesulfonate $[Hg(OTf)_2]$[3] by modifying $Hg(OCOCF_3)_2$, a known mercury reagent,[4] as a

Fig. 1 *Lansium domesticum* (Duku) and Kanebo Sidenkai, Lansic, a hair restoration agent.

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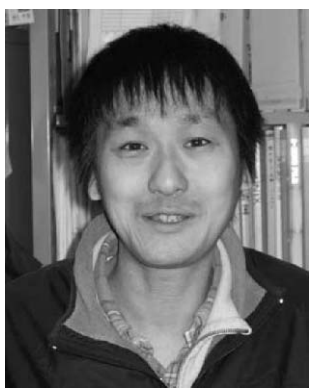
† Dedicated to Professor Paul A. Grieco on the occasion of his 65th birthday.

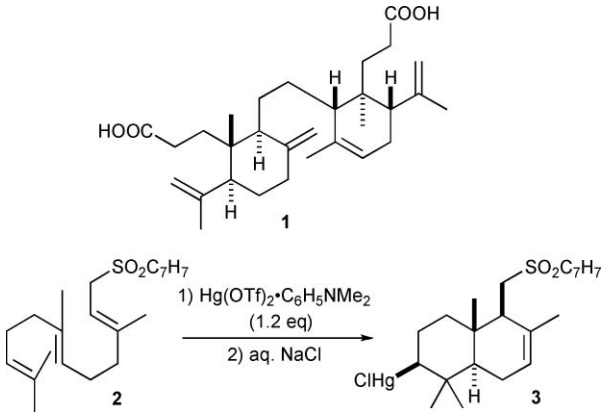
Mugio Nishizawa

Professor Mugio Nishizawa received a Dr. Sci. degree in 1975 under the guidance of Professor Takeo Sakan at Osaka City University of Japan. He then moved to USA and spent two years as a postdoctoral fellow in the research group of Professor Paul A. Grieco at the University of Pittsburgh. In 1977 he returned to Japan and was appointed as an instructor in the research group of Professor Ryoji Noyori of Nagoya University. In 1980, he moved to Osaka City University as an instructor and started his own research group by collaboration with Professor Yuji Hayashi. In 1986 he moved to the Faculty of Pharmaceutical Sciences, Tokushima Bunri University as a full Professor. He received The Chemical Society of Japan Award for Young Chemist in 1980, Tokushima Press Award in 2000, and The Pharmaceutical Society of Japan Award in 2010. His research interests include $Hg(OTf)_2$-catalyzed reactions, approach into the mystery of steroid biosynthesis by organic synthesis, and development of an intensive immune system stimulating compound named vizantine.

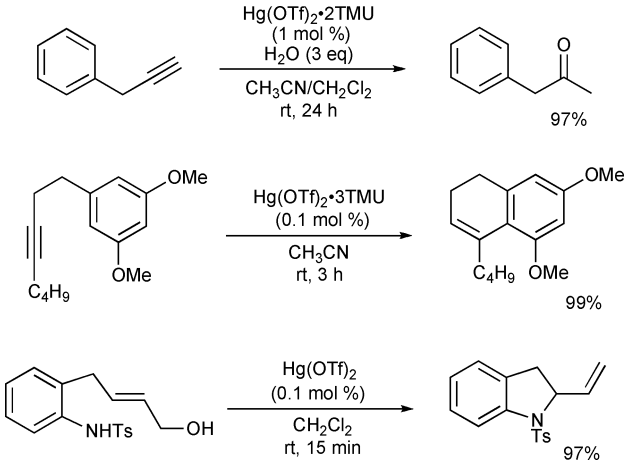


Hiroshi Imagawa

Professor Hiroshi Imagawa received his PhD in 1995 under the guidance of Professor Mugio Nishizawa at Tokushima Bunri University. He was appointed as an instructor in the research group of Professor Nishizawa. In 1995, he moved to USA and spent one year as a postdoctoral fellow in the research group of Professor Chi-Huey Wong of the Scripps Research Institute. In 2000 he returned to Japan and was promoted to assistant Professor in Nishizawa's group. In 2005, he was promoted to Associate Professor. In 2007, he received The Young Chemist Award from The Society of Synthetic Organic Chemistry Japan, Chugoku-Shikoku Branch. His interests include the total synthesis of bioactive natural products and development of synthetic methodologies.



Scheme 1 Lansic acid and $Hg(OTf)_2$-induced biomimetic olefin cyclization.



Scheme 2 Typical $Hg(OTf)_2$-catalyzed reactions.

new biomimetic olefin cyclization agent. Because $Hg(OTf)_2$ is an excellent reagent for the biomimetic olefin cyclization, a number of polycyclic terpenoids have been synthesized by using $Hg(OTf)_2$-induced cyclization as the key step.[5]

In 2002, after 20 years of development, we noticed the remarkable catalytic activity of $Hg(OTf)_2$ by achieving the hydration of terminal alkynes to give methyl ketones with high catalytic turnover.[6] Since then, a variety of $Hg(OTf)_2$-catalyzed reactions such as hydroxylative enone synthesis, *E*-selective conjugate ester synthesis, hydroxylative enyne cyclization, arylyne cyclization, biomimetic tandem cyclization, indole synthesis, furan synthesis, cyclic carbonate synthesis, glycosylation, S_N2 reaction, furanoyne cyclization, aryl allyl alcohol cyclization and *N*-allyl alcohol cyclization have been developed (Scheme 2).[7] Indeed, the development of these catalytic reactions with high turnover can significantly reduce the effect of mercury into the environment. Recently, the first solid-supported mercuric salt, silaphenylmercuric triflate, was developed and it was found to act as a powerful catalyst for most $Hg(OTf)_2$-catalyzed reactions.[8] Thus, the utilization of highly active and reusable solid mercury salts as catalysts for practical organic synthesis is close to being realised.[9]

Hirofumi Yamamoto

Professor Hirofumi Yamamoto received his PhD in 2007 under the guidance of Professor Mugio Nishizawa at Tokushima Bunri University, and was appointed as an Assistant Professor of Professor Mugio Nishizawa's research group. In 2007, he received Best Presentation Award from 47th Symposium on the Chemistry of Natural Products. His research interests include mercuric salt-catalyzed reactions and synthesis of intensive immune system stimulating compounds in drug discovery.

Mercury: a historical view

Though Qín Shǐ Huáng (259–210 BC) of the Qín dynasty sent a mission to the eastern islands country (probably today's Japan) to collect an elixir of life of higher quality that is cinnabar (HgS), he himself did not elongate his life by taking an overdose of mercury. For more than 2000 years, Chinese medicine has employed mercury compounds, including for internal use.[10] More than 1300 years ago, mercury was very important also in Japan for the gold plating of an image of Buddha. It was also important to paint temples and shrines using a red substance known as 'aoniyoshi' ('ao' is blue due to $CuCO_3$ and 'ni' is red due to HgS; an ideal antiseptic dye). Although the original color has disappeared, 1000 year old wooden buildings painted with HgS can be seen even today in Kyoto and Nara.[11] Until very recently, mothers painted their children's body red using mercurochrome (**4**) in order to protect against serious infection (Fig. 2).[12a] PhHgOAc (**5**) was an important agrichemical that helped to prevent the spread of rice blast in Japan shortly after the end of World War II.[12b] The demand for mercury is significant even today for use in fluorescent lights, thermometers, barometers, sensors and the amalgam used in dental fillings. Therefore, the toxicity of mercury is perhaps not as serious as sometimes reported in the press.[13] Nevertheless, Japan suffered a tragedy of methylmercury intoxication (so-called Minamata disease) in the 1950s. Methylmercuric chloride (hereafter CH_3HgCl) is a natural product and widely distributed in nature, particularly in fish meat. However, the CH_3HgCl readily passes through the blood–brain barrier, giving rise to serious neurotoxicity once the concentration reaches a certain threshold.[14] Thus, it is very important to distinguish between the highly toxic CH_3HgCl and most other safe mercury compounds.

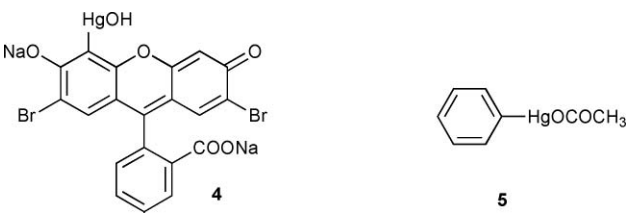
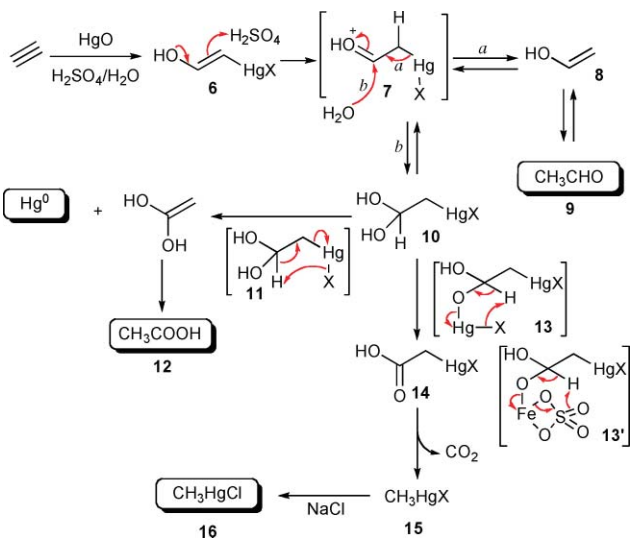


Fig. 2 Mercurochrome and phenylmercuric acetate.

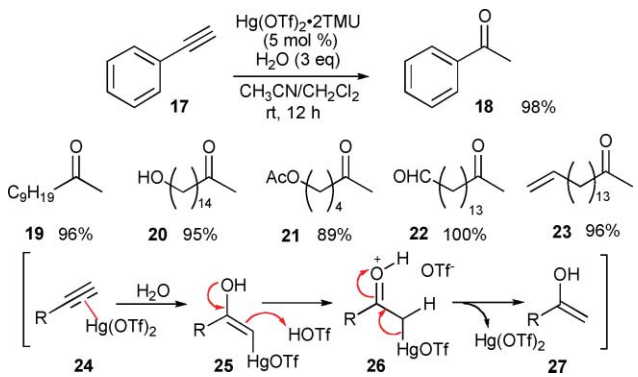
In 1952, a neurological disorder appeared due to CH_3HgCl exhausted from the Chisso Corporation chemical factory into Minamata bay.[14] However, the link with the Chisso chemical factory was not immediately apparent because the company had launched the acetaldehyde production plant in 1932 using a well-established procedure involving hydration of acetylene. Indeed, a similar process had been operated without incident at various locations around the world. Nishimura and Okamoto investigated why Minamata disease occurred specifically at Minamata (the second Minamata disease occurred in 1965 at Niigata).[15] They found that the tragedy coincided with a change in the oxidation promoter from MnO_2 to HNO_3 in order to oxidize Fe^{2+} to Fe^{3+}, and the Fe^{3+} oxidizes Hg^0 to Hg^{2+}.[14] This change in the process increased the generation of a side product, CH_3HgCl, by almost ten-fold. Unfortunately, the scale of the disaster was exacerbated by the geographic circumstances around the Minamata bay, which resulted in an extraordinarily efficient biological concentration of CH_3HgCl in the fish. Nishimura also investigated the process that had been carried out in the reaction vessel of Chisso. Acetylene, HgO, sulfuric acid and H_2O had been mixed and heated to nearly 100 °C.[14] It is useful to understand the background chemistry of this process. Oxymercuration of acetylene should lead to the formation of **6** (Scheme 3). Sulfuric acid then protonates **6** to generate the oxonium ion **7**. Demercuration of **7** takes place to regenerate Hg^{2+} and results in the formation of acetaldehyde (**9**) as the major reaction product (pass *a*) *via* enol **8**. In addition, the oxonium cation **7** may also be attacked by H_2O to form the *gem* diol **10** (pass *b*). When the intramolecular oxidation/reduction sequence takes place as seen in **11**, acetic acid (**12**) is produced along with Hg^0 as the side-product (irreversible process). Indeed, the floor of the Chisso factory was reported to be entirely covered by Hg^0, which had to be oxidized to Hg^{2+} for re-use. The conversion of **7** to **9** is in equilibrium, so that acetaldehyde is also converted to diol **10** unless removed from the reaction vessel. As an alternate process, intermolecular oxidation/reduction sequence of the diol **10** with HgX_2 is possible, thereby generating mercurioacetic acid **14** *via* **13** irreversibly. The extra oxidizing agent such as $Fe_2(SO_4)_3$ for the oxidation of Hg^0 should result in an accelerated formation of **14** *via* **13′**, for instance. Although the chemistry is not fully understood, it is surmised that the decarboxylation of **14** takes place under some conditions to lead to the formation of CH_3HgX (**15**).[14] Contact with seawater finally generates CH_3HgCl (**16**).



Scheme 3 Possible mechanism of CH_3HgCl formation.

$Hg(OTf)_2$-catalyzed hydration of alkynes

During the mechanistic considerations for the hydration of acetylenes, we reasoned that $Hg(OTf)_2$ was likely to be an ideal catalyst for the hydration of terminal alkynes. The hydration of alkynes in the presence of mercuric salt was first reported by Kutscheroff in 1881.[16,17] The procedure reported by Thomas in 1938,[18] using HgO and H_2SO_4 under heating conditions, is currently accepted as standard by registration in *Org. Synth.*[19] We first examined the reaction of phenylacetylene (**17**) with 3 eq. of H_2O in the presence of neutral $Hg(OTf)_2{\cdot}2TMU$ (tetramethylurea) complex (5 mol%) as the catalyst in 3 : 1 CH_3CN–CH_2Cl_2 without using any acid (Scheme 4).[6] After stirring for 12 h at room temperature, acetophenone (**18**) was obtained in quantitative yield. The formation of dimeric Hg–acetylide reduces the catalytic efficiency of $Hg(OTf)_2$ in the absence of TMU. Nevertheless, the presence of a long alkyl chain, hydroxy, acetoxy, aldehyde and double bond on the substrate does not interfere with the reaction. Indeed, ketones **19–23** were obtained in excellent yields under similar conditions. The reaction is presumably initiated from the alkyne–Hg complex **24**. Nucleophilic attack of H_2O leads to the generation of the hydroxymercuration product **25**. Protonation of **25** by the *in situ* formed TfOH generates the oxonium ion **26**, which undergoes a smooth elimination of the catalyst $Hg(OTf)_2$ to produce the enol **27**. The protonation of **25** by the super acid TfOH to form **26** is recognized as the rate determining step. Although a large number of catalysts have been developed for the hydration of alkynes, most reactions require elevated temperatures. However, the $Hg(OTf)_2$-catalyzed reactions were mostly achieved at room temperature, reflecting its extremely high reactivity.[20] It is very important to express that $Hg(OTf)_2$ always behaves as a divalent species throughout the catalytic cycle due to its pronounced cationic character without falling into the irreversible oxidation/reduction sequence. This behaviour avoids the formation of CH_3HgCl if applied to the hydration of acetylene.

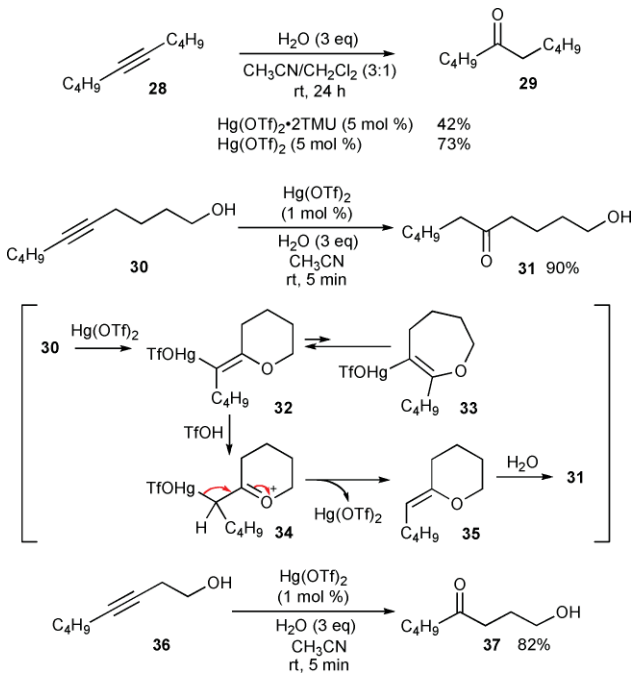


Scheme 4 $Hg(OTf)_2$-catalyzed hydration of terminal alkyne.

$Hg(OTf)_2$-catalyzed hydration of internal alkynes

We also examined the hydration of internal alkynes, such as dec-5-yne (**28**), using 3 eq. of H_2O in the presence of 5 mol%

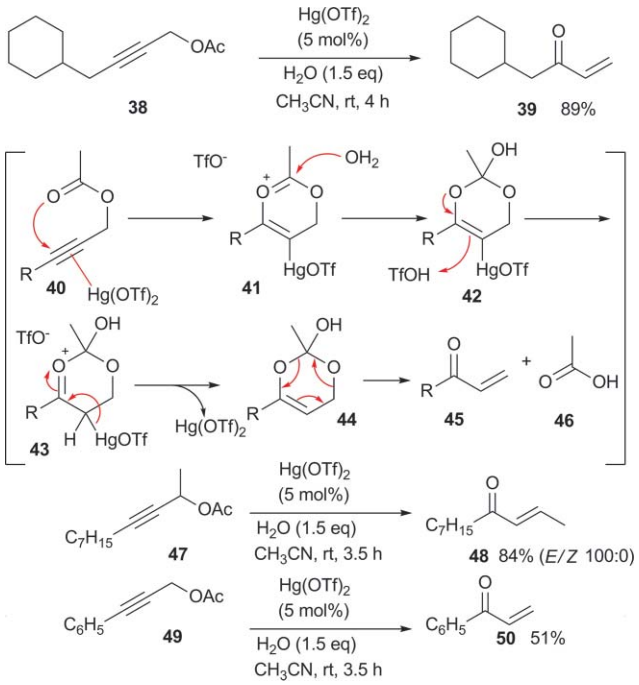
of $Hg(OTf)_2 \cdot 2TMU$ complex under the reaction conditions described above (Scheme 5). The reaction was very slow and the ketone **29** was obtained in only 42% yield after 24 h. Although $Hg(OTf)_2$ itself showed higher reactivity (Hg–acetylide formation does not take place from the internal alkyne), a yield of only 73% was obtained after 24 h. In contrast, the reaction of a δ-hydroxy internal alkyne, dec-5-yn-1-ol (**30**), was completed almost instantaneously, even using 1 mol% of $Hg(OTf)_2$ at room temperature, leading to the selective generation of **31** in 90% yield.[21] The reaction should involve a rapid equilibrium between the *exo*-cyclization leading to **32** and the *endo*-cyclization leading to **33**, with the favoured **32** producing the cation **34** *via* the rate determining protonation by the *in situ* generated TfOH. Subsequent demercuration to form **35** and hydration results in the selective formation of **31**. The hydration of β-hydroxyl internal alkyne, oct-3-yn-1-ol (**36**), is also completed within 5 min to selectively give 1-hydroxyoctan-4-one (**37**) in 82% yield *via* a five membered ring intermediate.[21] Uchimoto has reported the hydration of hydroxy-substituted internal alkynes to give hydroxy ketones using $PdCl_2$.[22]



Scheme 5 $Hg(OTf)_2$-catalyzed hydration of internal alkynes.

$Hg(OTf)_2$-catalyzed hydration of propargyl acetates

$Hg(OTf)_2$-catalyzed hydration of the propargyl acetate **38** by the reaction with 1.5 eq. of H_2O in CH_3CN at room temperature selectively produces the enone **39** (Scheme 6).[23] Acid-catalyzed rearrangement of propargyl alcohols (not hydration) to give α,β-unsaturated ketones is known as the Meyer–Schuster reaction.[24] This reaction is usually carried out under extreme conditions and it is applicable only to *tert*-alcohols. Engel has recently reported a Au-catalyzed Meyer–Schuster rearrangement of aryl-substituted *tert*-propargyl alcohols.[25] Our process corresponds to the Meyer–Schuster rearrangement applicable to the primary propargyl system. The $Hg(OTf)_2$ complex **40** generates the oxonium ion **41**,



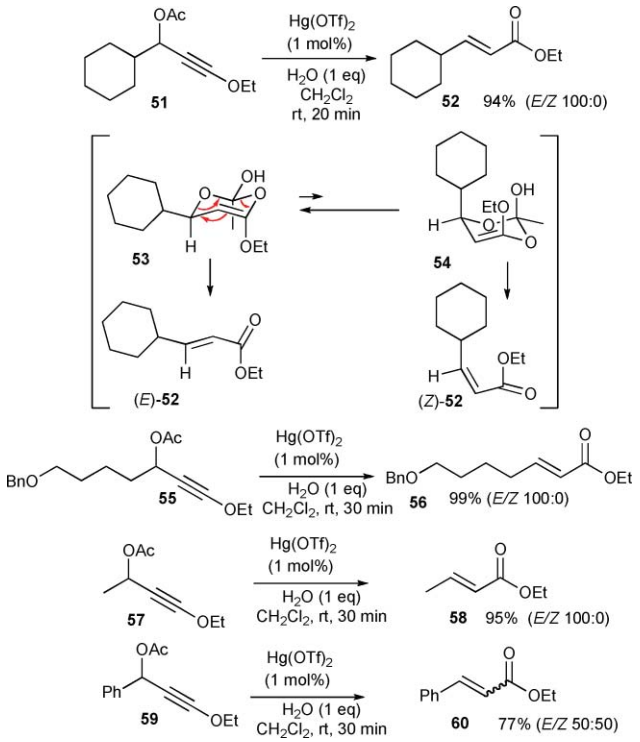
Scheme 6 $Hg(OTf)_2$-catalyzed hydration of propargyl acetate.

which is attacked by H_2O to produce the intermediate **42** and TfOH is liberated. Protonation of **42** by TfOH forms the alternate oxonium ion **43** which undergoes demercuration to produce yet another intermediate **44** and the catalyst $Hg(OTf)_2$ is regenerated. A 6π electrocyclic reaction of **44** should yield the enone **45** and acetic acid (**46**). The procedure is applicable to a variety of propargyl acetates. The secondary acetate **47** selectively provides the *E*-enone **48** in good yield. However, the aryl-substituted alkyne **49** affords the enone **50** in only a moderate yield.

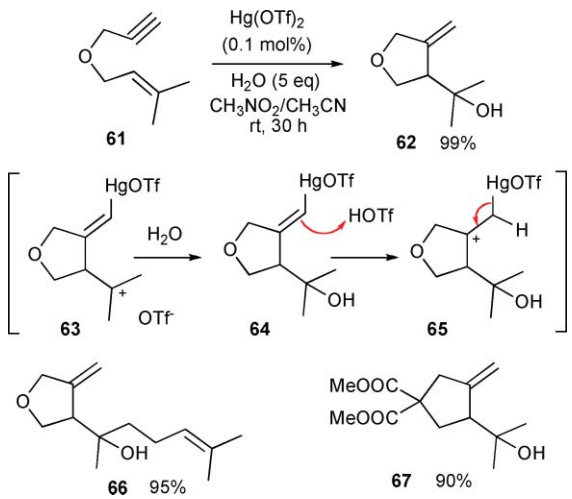
Hydration of the ethoxy-substituted propargyl acetate **51** affords the conjugated ester **52** with complete *E*-selectivity (Scheme 7). The orthoester-type intermediate **53** (corresponding to **44**), which is favoured over **54**, leads selectively to (*E*)-**52**.[26] A variety of alkyl-substituted conjugated esters were prepared by this procedure. The long alkyl chain-substituted acetate **55** gave **56** quantitatively with complete *E*-selectivity. Even the smallest methyl-substituted propargyl acetate **57** affords **58** with complete *E*-selectivity. However, the aryl-substituted propargyl acetate **59** gave a 1 : 1 mixture of *E*-**60** and *Z*-**60**, probably *via* a stable propargylic/benzylic cation without the involvement of the neighboring acetoxyl group (*e.g.*, **41**). Engel has reported a non-stereoselective Au-catalyzed rearrangement of ethoxy-substituted propargyl alcohols to give conjugated esters.[25,27]

C–C bond-forming cyclization of alkynes

When a nucleophilic double bond is located near the alkyne, one can expect C–C bond formation prior to the hydration (*i.e.*, enyne cyclization).[28] Slow addition of $Hg(OTf)_2$ to a mixture of **61** and 5 eq. of H_2O in CH_3NO_2 at room temperature afforded **62** quantitatively with a catalytic turnover of 1000 (Scheme 8).[29] However, a high yield was not obtained when the reaction was carried out in CH_3CN due to the formation of a Ritter-type by-product. The cationic intermediate **63** is hydrated to generate the



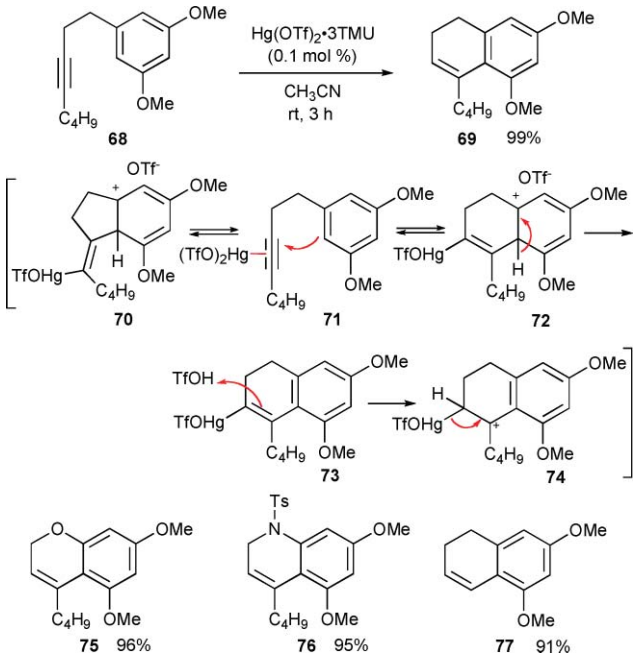
Scheme 7 $Hg(OTf)_2$-catalyzed hydration of ethoxy propargyl acetate.



Scheme 8 $Hg(OTf)_2$-catalyzed hydroxylative enyne cyclization.

vinyl mercuric intermediate **64**, which is then protonated to form the *tert*-cation **65**. Smooth demercuration produces **62** and the catalyst $Hg(OTf)_2$ is regenerated. The geraniol derivative **66** (20 : 1 diastereomeric mixture) and the malonate derivative **67** were also prepared by this procedure in high yields.

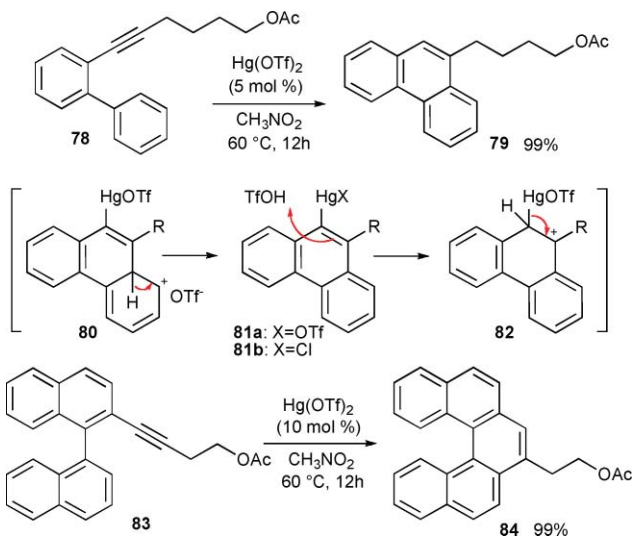
When a nucleophilic aryl group is located near the alkyne, Friedel–Crafts-type arylyne cyclization takes place. Among the numerous catalysts that have been used for arylyne cycloisomerization,[30] $Hg(OTf)_2$ seems likely to show one of the highest catalytic activities. The alkyne **68** was transformed into dihydronaphthalene **69** quantitatively with a catalytic turnover of 1000 by using $Hg(OTf)_2 \cdot 3TMU$ complex in CH_3CN at room temperature (Scheme 9). $Hg(OTf)_2$ was too reactive for this reaction and led to the polymerization of the unstable product



Scheme 9 $Hg(OTf)_2$-catalyzed arylyne cycloisomerization.

69.[31] The Hg complex **71** exists in an equilibrium between **70** and **72**. The reaction takes place from the more stable **72** by forming the intermediate **73**. Protonation of **73** by the *in situ*-formed TfOH generates **74**, which meets a facile demercuration to produce **69** and the catalyst. Alkynyl phenol and aniline derivatives gave **75** and **76**, respectively, in excellent yields. Moreover, even a terminal alkyne afforded only the *endo*-cyclization product **77** in 91% yield. A similar reaction has been achieved by Murai using Pd and Rh salts as the catalysts with the catalytic turnover approaching 100.[32]

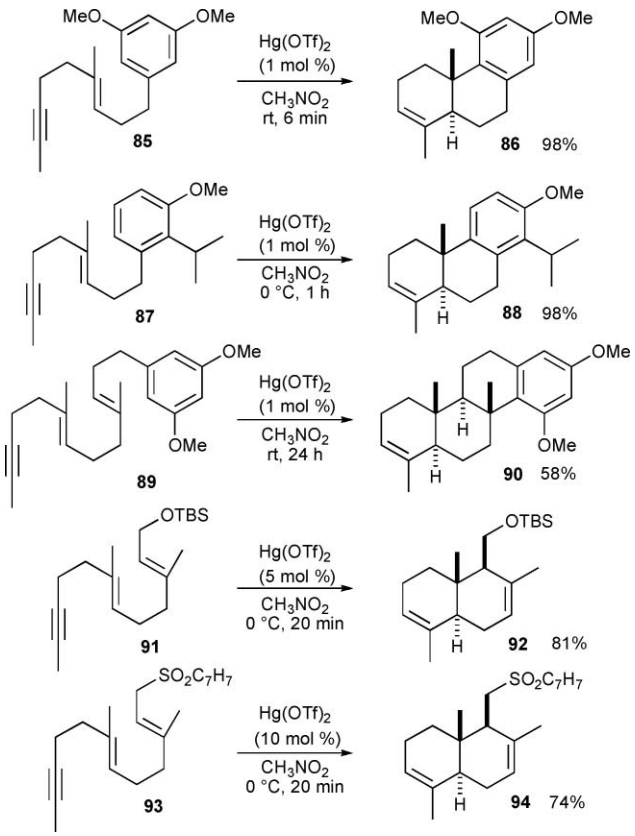
However, arylyne cyclization of the alkynyl biphenyl derivative **78** required elevated temperatures, up to 60 °C, using 5 mol% $Hg(OTf)_2$ in CH_3NO_2 to give **79** in 99% yield (Scheme 10).[33] The reaction at room temperature stopped with the formation of **81a** (isolable as chloride **81b** after treatment with aq. NaCl).



Scheme 10 $Hg(OTf)_2$-catalyzed cyclization of alkynyl biphenyl and binaphthyl.

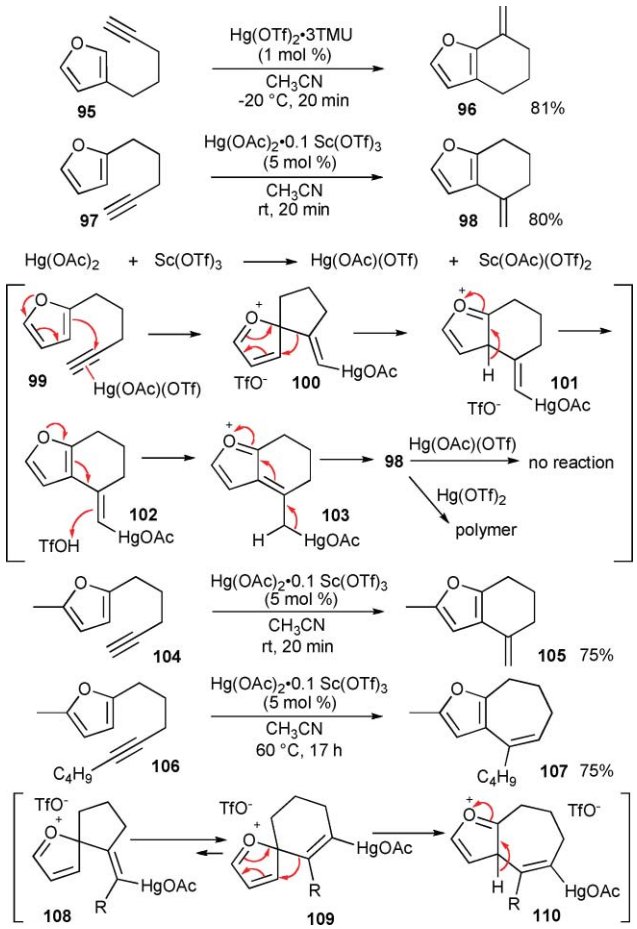
Protonation of **81a** with TfOH to generate the cation **82** requires 60 °C to overcome the energy barrier for dearomatization. When the reaction was applied to the binaphthyl derivative **83**, the substituted [5]helicene **84** was obtained quantitatively. Fürstner has reported catalytic phenanthrene synthesis using a variety of metal salts.[30c,34]

$Hg(OTf)_2$-catalyzed reaction of an arylenyne, such as **85**, was expected to give a polycarbocycle. CH_3NO_2 was the solvent of choice to give the tricyclic **86** in 98% yield by the reaction with 1 mol% $Hg(OTf)_2$ at room temperature for 6 min (Scheme 11).[35] Diterpenoid-like compound **88** was also obtained in 98% yield with a catalytic turnover of 100. The tetracyclic compound **90** was obtained in 58% yield.[36] Alkynyl dienes **91** and **93** were cyclized to give **92** and **94**, respectively, in acceptable yields under mild conditions. These are the first examples of Hg salt-catalyzed biomimetic tandem cyclization.



Scheme 11 $Hg(OTf)_2$-catalyzed biomimetic tandem cyclization.

The cycloisomerization of alkynyl furans in Friedel–Crafts mode is not yet fully understood. This is due to the instability of the product. Only the Pt- and Au-catalyzed phenol syntheses *via* the Diels–Alder mode of cyclization of alkynyl furans are reported.[37] Although the reaction of 3-(4-pentynyl)furan (**95**) with $Hg(OTf)_2$ afforded **96** in low yield, a satisfactory result was achieved by using the milder $Hg(OTf)_2 \cdot 3TMU$ complex at –20 °C in CH_3CN (Scheme 12).[38] The reaction of 2-(4-pentynyl)furan (**97**) is more difficult, and even $Hg(OTf)_2 \cdot 3TMU$ complex did not give **98** in good yield. After careful screening, we found a 10 : 1 mixed reagent of $Hg(OAc)_2$ and $Sc(OTf)_3$ to give **98** in high yield.[38] The real catalytic species is presumed to be Hg(OAc)(OTf), which

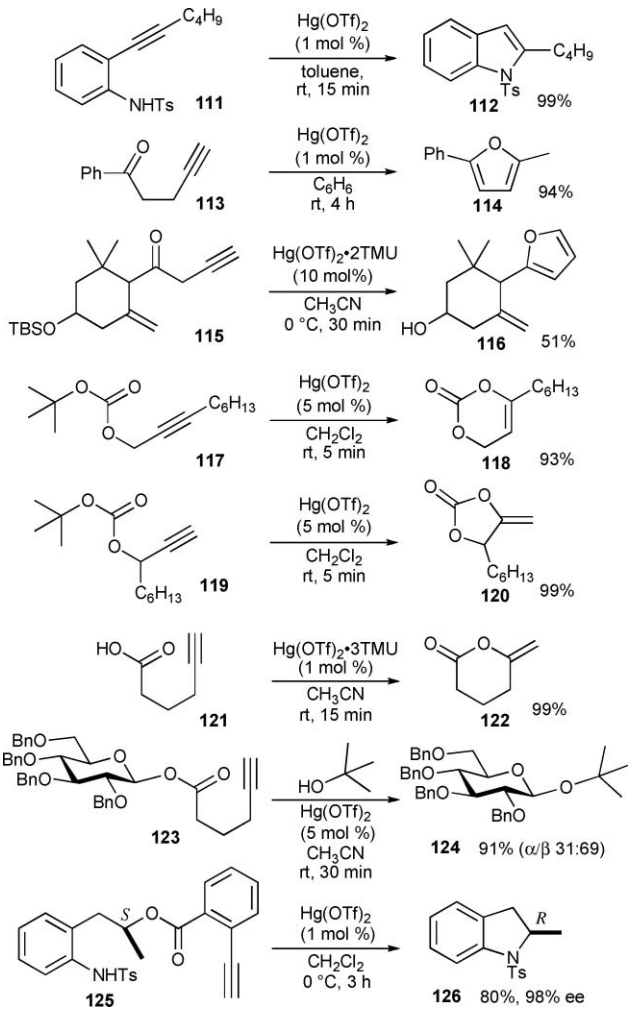


Scheme 12 $Hg(OTf)_2$-catalyzed furanoyne cyclization.

is generated *in situ* upon mixing the two reagents. The reaction is likely to be initiated from the Hg-complex **99**. The cyclized oxonium ion **101**, which is probably generated *via* the spirocyclic cation **100**, then produces the vinylmercury intermediate **102** on deprotonation. The alternative oxonium ion **103**, which is generated *via* protonation of **102** by the *in situ*-formed TfOH, facilitates demercuration to regenerate the catalyst Hg(OAc)(OTf) and affords the product **98**. Although Hg(OAc)(OTf) is inert against **98**, reactive $Hg(OTf)_2$ decomposes **98** to produce some polymer. The methyl-substituted terminal alkynyl furan **104** also provided the *exo*-mode cyclization product **105** in good yield on reaction with Hg(OAc)(OTf). However, the reaction of the internal alkyne **106** generated only the *endo*-mode cyclization product **107**, which strongly supports the initial spirocyclization mechanism. The latter reaction involves an equilibrium between **108** and **109**, and the favoured **109** selectively generates the intermediate cation **110**.

Heterocycle synthesis

$Hg(OTf)_2$ shows highly effective catalytic activity, not only for C–C bond forming cyclizations, but also for heterocycle synthesis by forming C–O and C–N bonds. The reaction of the alkynyl aniline derivative **111** with 1 mol% $Hg(OTf)_2$ in toluene afforded the indole **112** in quantitative yield almost instantaneously at room temperature (Scheme 13).[39] A variety of 2-substituted indoles have



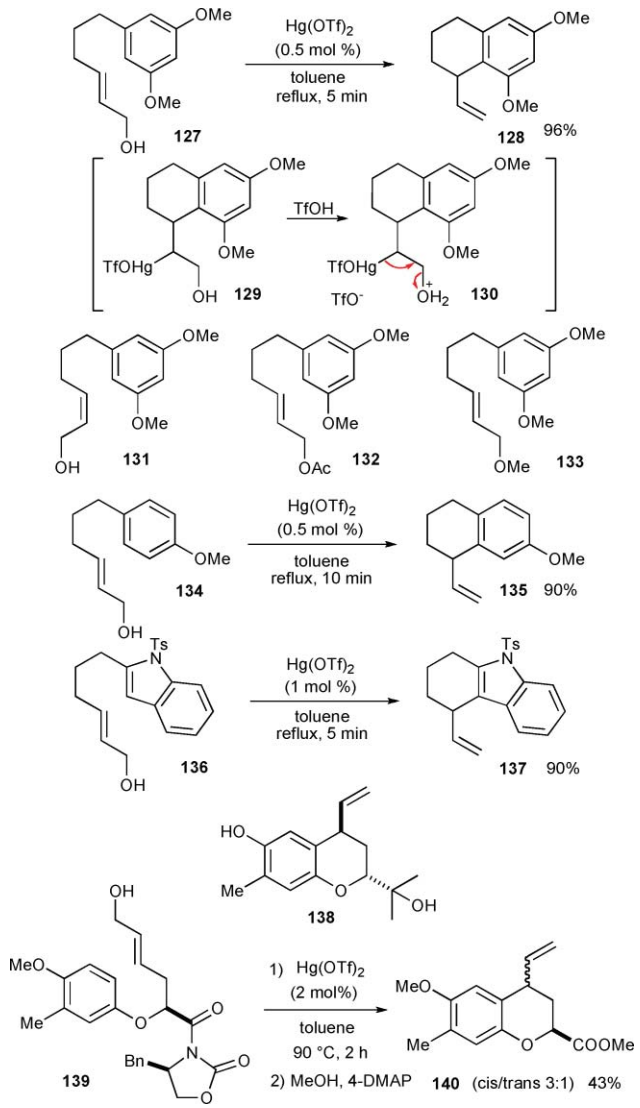
Scheme 13 $Hg(OTf)_2$-catalyzed synthesis of heterocycles.

been prepared by this procedure. Although a number of catalysts have been reported for the cycloisomerization of alkynyl aniline derivatives to indoles,[40] the catalytic activity of $Hg(OTf)_2$ appears to be the highest. Among the protecting groups on the nitrogen examined (Ac, Boc, *o*- and *p*-nosyl, and H), the tosyl group afforded the best result. Furan synthesis by the cyclization of a γ-alkynyl ketone is also efficiently catalyzed by $Hg(OTf)_2$. The reaction of **113** with 1 mol% of $Hg(OTf)_2$ in benzene at room temperature afforded 2-methylfuran **114** in 94% yield.[41] A variety of 2-methylfurans were prepared by this procedure in high yields. The methyl group originates from the terminal alkynyl carbon *via exo*-mode cyclization following protodemercuration and isomerization. Gosselin has reported an alternative $Hg(OTf)_2 \cdot 2TMU$-catalyzed furan synthesis from the β-alkynyl ketone **115** to give the furan **116** *via endo*-mode cyclization.[42] The reaction of the propargyl *tert*-butyl carbonate **117** with 5 mol% $Hg(OTf)_2$ took place smoothly to afford a novel six-membered ring carbonate **118** in 93% yield *via* a selective *endo*-mode cyclization.[43] The Boc-protected terminal propargyl alcohol **119** provided only the *exo*-mode cyclization product **120** in quantitative yield. Au salt-catalyzed cyclization of propargyl carbonates is reported to give only the *exo*-mode cyclization product, even from the reaction of an internal alkyne after complicated rearrangement.[44] These results reflect the pure cationic character of $Hg(OTf)_2$-catalyzed reactions. The Au complex contains some carbenoid character. For the catalytic cyclization of ω-alkynoic acids, $Hg(OTf)_2$ is too reactive to control the reaction to form ω-exomethylene-ω-lactone. However, the milder reagent $Hg(OTf)_2 \cdot 3TMU$ complex efficiently catalyzes the reaction of **121** to give **122** at room temperature.[45] Because the reaction of **121** and $Hg(OTf)_2$ takes place very quickly accompanying the isomerization of the double bond to a more stable isomer, we thought we could utilize the alkynoic acid residue as the leaving group for glycosylation. The reaction of **123** and *tert*-butyl alcohol in the presence of 5 mol% $Hg(OTf)_2$ in CH_3CN at room temperature afforded the glycoside **124** in 91% yield with a moderate β-selectivity.[46] Because the glycosylation is a typical S_N1 reaction, we were interested in applying $Hg(OTf)_2$ to an S_N2 reaction. Thus, the optically pure (*S*)-alkynoate **125** was treated with 1 mol% of $Hg(OTf)_2$ at 0 °C in CH_2Cl_2 to obtain the inverted (*R*)-indoline **126** in 80% yield with 98% ee. This is the first catalytic activation of a leaving group in a S_N2 reaction.[47]

$Hg(OTf)_2$-catalyzed cyclization of alkenes

The reaction of $Hg(OTf)_2$ with alkynes, such as **17**[19] and **68**[31] (Scheme 4 and 9), generates vinylmercuric intermediates *i.e.*, **25** and **73**, respectively. These intermediates are protonated by *in situ*-formed TfOH, producing stable cations **26** and **74**, and leading to smooth demercuration to give the product **18** or **69**, respectively, and regenerate the catalyst $Hg(OTf)_2$, thereby establishing the catalytic cycle. However, the reaction of the olefin **2** with $Hg(OTf)_2$ produces organomercuric product **3** having a stable sp^3-carbon–Hg bond, and is essentially a stoichiometric reaction (Scheme 1).[3] To achieve catalytic arylene cyclization, we tried to introduce an oxygen-based functional group into the allylic position for the protonation site, thereby triggering smooth demercuration. We found that the reaction of the (*E*)-6-(3,5-dimethoxyphenyl)hex-2-en-1-ol (**127**) with 0.5 mol% of $Hg(OTf)_2$ in toluene at reflux for 5 min was sufficient to afford cyclization product **128** in 96% yield (Scheme 14).[48] The organomercuric intermediate **129** is protonated to form the oxonium ion **130**, thereby facilitating smooth demercuration to give **128** and the regeneration of the catalyst. In this case, the first nucleophilic cyclization, rather than protonation, is the most likely rate limiting step in the reaction. Thus, the reaction requires a reflux temperature for toluene. The corresponding *Z*-isomer **131** also afforded **128** in similar yield. The reactions of the acetoxy derivative **132** and the methoxy derivative **133** were slow, and afforded **128** in 63 and 73% yields, respectively, after 1 h reflux in toluene. The *p*-methoxy derivative **134** and the indole derivative **136** also reacted well to give **135** and **137**, respectively. The alkenyl functional group maintained in the product should be useful for further molecular modifications such as hydroboration, ozonolysis and metathesis. Shishido has efficiently employed this process for a total synthesis of the irregular sesquiterpenoid heliannuol **138** by achieving the reaction of **139** to **140** in 43% yield by using 2 mol% $Hg(OTf)_2$.[49]

The $Hg(OTf)_2$-catalyzed cyclization of aryl allyl alcohol is effectively extended to the reaction of the aniline derivative **141** to afford indoline derivative **142** in excellent yield with nearly 1000 catalytic turnover at room temperature in CH_2Cl_2 (Scheme 15).[50] Pd-catalyzed cyclization of aminoallylic alcohol has been intensively studied by Hirai.[51] Both *E*- and *Z*-trisubstituted

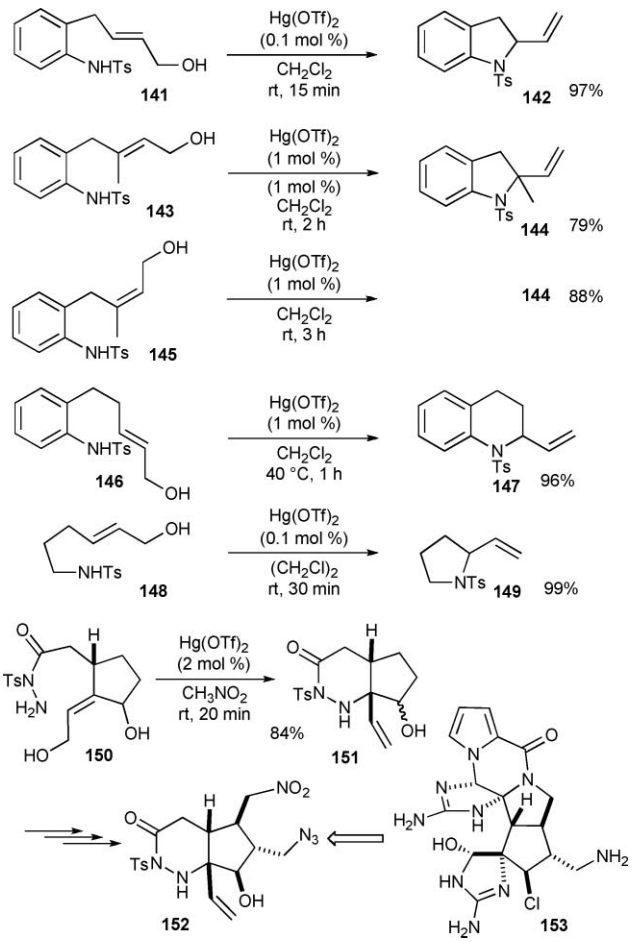


Scheme 14 $Hg(OTf)_2$-catalyzed aryl allyl alcohol cyclization.

olefins **143** and **145** also reacted with $Hg(OTf)_2$ catalytically to generate **144** that contains a quaternary carbon center in good yield. The piperidine derivative **147** was prepared in excellent yield under a slightly higher temperature condition by the reaction of **146**. The reaction of aminoallylic alcohol derivative **148** gave 2-vinylpyrrolidine **149** in quantitative yield with 1000 catalytic turnover. When the procedure was applied to the hydrazide alcohol **150** using 2 mol% of $Hg(OTf)_2$, clean cyclization took place to give the *cis*-fused *N*-cyclization product **151**, which also contains a quaternary carbon center, in 84% yield. The product **151** was converted to a fully substituted cyclopentyl triamine derivative **152**, which corresponds to the cyclopentane core of marine natural product palau'amine (**153**).[52]

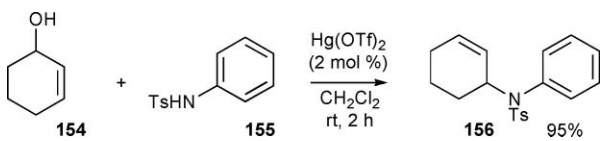
$Hg(OTf)_2$-catalyzed intermolecular sulfonamidation

Because $Hg(OTf)_2$ is extraordinarily active against sulfonamide allyl alcohols such as **141** and **148** (Scheme 15), the procedure was applied to an intermolecular sulfonamidation reaction. Treatment of 2-cyclohexen-1-ol (**154**) with 1.5 eq. of aniline derivative **155** in



Scheme 15 $Hg(OTf)_2$-catalyzed sulfonamide allyl alcohol cyclization.

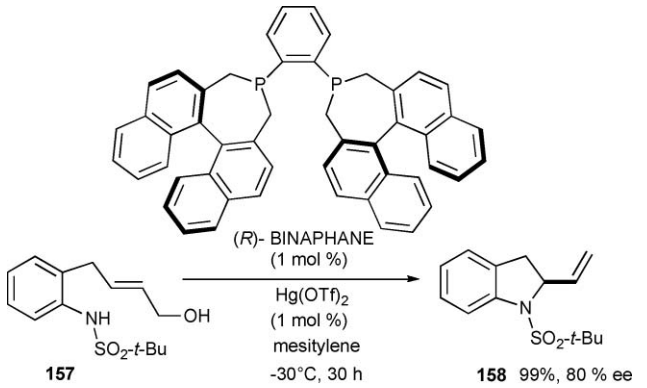
the presence of 2 mol% $Hg(OTf)_2$ in CH_2Cl_2 at room temperature for 2 h afforded 3-*N*-tosylanilino-1-cyclohexene (**156**) in 95% yield (Scheme 16).[53] Although the yield is not optimized, the procedure is applicable to a wide variety of substrates. This reaction constitutes the first intermolecular $Hg(OTf)_2$-catalyzed reaction to be described.



Scheme 16 $Hg(OTf)_2$-catalyzed intermolecular sulfonamidation of allyl alcohol.

$Hg(OTf)_2$-catalyzed enantioselective cyclization

Based on the exceptionally high reactivity of the sulfonamide allyl alcohol **141** creating a new chiral center, we were interested in the reaction together with a chiral auxiliary. BINAPHANE[54] was found to be the chiral modifier of choice. (*S*)-Indoline **158** with 80% ee was obtained on reaction of **157** with 1 mol% $Hg(OTf)_2$ in the presence of 1 mol% (*R*)-BINAPHANE in mesitylene at –30 °C (Scheme 17).[55]



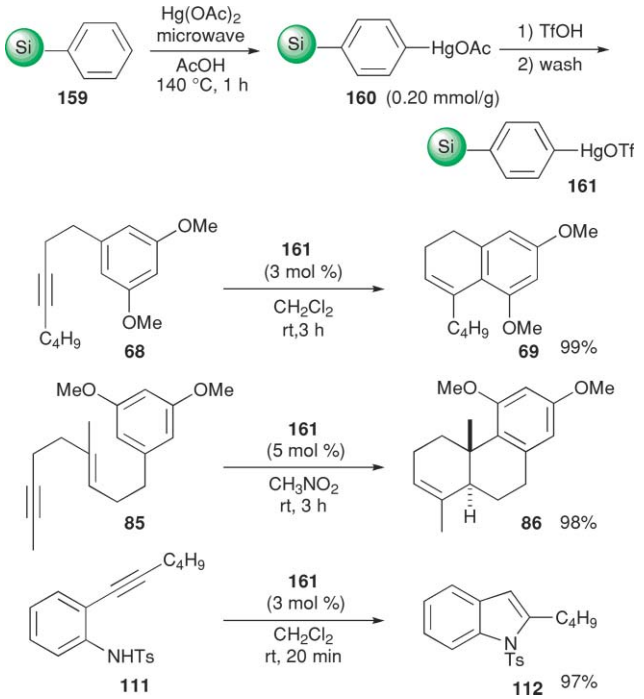
Scheme 17 $Hg(OTf)_2$-catalyzed enantioselective cyclization of sulfonamide allyl alcohol to give indoline.

Solid-supported catalyst, silaphenylmercuric triflate

When the cycloisomerization of alkynyl furan **97** (Scheme 12) was examined, $Hg(OTf)_2$ and its TMU complex were too reactive, resulting in the formation of polymers. Nevertheless, the expected product **98** was obtained in good yield when **97** was treated with Hg(OAc)(OTf) prepared by mixing $Hg(OAc)_2$ and $Sc(OTf)_3$ in a 10 : 1 ratio.[38] This finding suggests that a single OTf group is enough for the catalytic cycle. Furthermore, the reaction of the alkynyl aniline derivative **111** with 5 mol% of phenylmercuric triflate (prepared *in situ* by mixing PhHgOAc and an equimolar amount of TfOH) to give the indole derivative **112** was completed in 97% yield within 15 min at room temperature (Scheme 13).[56] Thus, we have attempted to prepare the first solid-supported mercuric salt catalyst. The development of reusable heterogeneous catalysts is an attractive and valuable target in regard to green chemistry.[57] Silaphenylmercuric triflate **161** was prepared from Silia*Bond*® Phenyl **159** (Silicycle, 230-400 mesh, loading 1.62 mmol g^{-1}) by heating to 140 °C with an equimolar amount of $Hg(OAc)_2$ in acetic acid and using microwave irradiation to give silaphenylmercuric acetate (**160**) followed by treatment with TfOH (Scheme 18). The filtered residue was washed and dried to give **161**.[8] The average diameter of the solid particles was determined to be 50–80 μm from the optical microscope image using Image-Pro software (Media Cybernetics) (Fig. 3).[8]

The solid-supported mercury complex **161** showed a remarkable catalytic activity for the reaction of the aryl alkyne **68** to give the dihydronaphthalene **69** in quantitative yield using 3 mol% (based on Hg loading; 0.2 mmol g^{-1}) at room temperature (Scheme 18). The biomimetic tandem cyclization of **85** to the tricyclic species **86** and the anilinoalkyne cyclization of **111** to the indole **112** were also efficiently catalyzed by **161** at room temperature. The procedure is operationally very simple as it involves stirring the reaction mixture with the solid catalyst followed by mere filtration to remove the catalyst.[8]

Silia*Bond*® Phenyl (**159**) is commercially available as a stationary phase for reverse phase column chromatography. Thus, we next examined the reaction in a flow system by simply charging a 2 : 3 mixture of **161** and ordinary silica gel into a glass column fitted with a cotton wool plug. When 0.2 M solution of **111** (40 μmol) in CH_2Cl_2 was eluted through the column at room temperature, indole **112** was obtained in quantitative yield (Scheme 19). The



Scheme 18 Preparation and reaction of solid supported mercuric triflate catalyst.

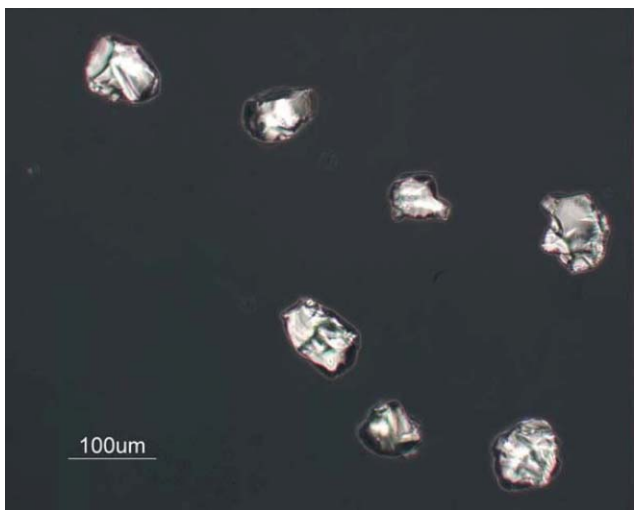
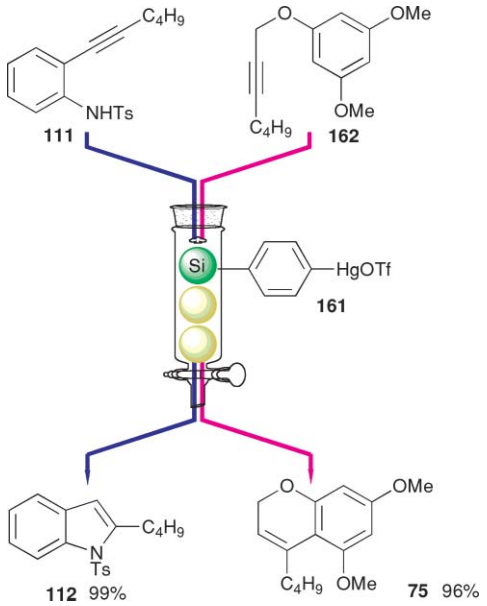


Fig. 3 Optical microscope image of SiC_6H_4HgOTf (**157**)using Image-pro software (Media Cybernetics).

reaction was repeated 20 times, and the yields were always quantitative. Then, a 0.02 M solution of the arylyne **162** (40 μmol) was eluted through this column and the isomerized **75** was obtained in 96% yield. Mercury leakage was also determined. Each run leached 0.014 to 0.028% of Hg, corresponding to 0.21 to 0.37 ppm. Because 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 or production of Hg^0 species after oxidation/reduction sequence.[8] Therefore, appearance of highly active reusable solid



Scheme 19 Flow reaction using silaphenyl mercuric triflate.

mercuric salts should be close to be utilized in practical organic synthesis.

Conclusions

Here, we have introduced $Hg(OTf)_2$ as a new catalyst for organic synthesis based on its very high activity. In particular, the high affinity of mercury for the alkyne moiety led us to develop a variety of reactions initiated from alkynes. Hydration, C–C bond-forming cyclization and heterocycle synthesis have been achieved in very high catalytic efficiency. The reaction of alkynes produces vinyl mercury intermediates along with the super acid TfOH. Protonation of the olefinic bond by the *in situ*-generated TfOH produces a cationic intermediate that leads to product formation *via* a smooth demercuration step to regenerate the catalyst. In contrast, the reaction of a double bond with $Hg(OTf)_2$ produces a stable sp^3 C–Hg bond and, hence, it is a fundamentally stoichiometric reaction. However, introduction of an allylic hydroxyl group at the protonation site made possible the first mercuric salt-catalyzed olefin cyclization, such as aryl allyl alcohol cyclization and sulfonamide allyl alcohol cyclization. Based on the high reactivity of sulfonamide allyl alcohols, the procedure was extended to an intermolecular sulfonamidation. This observation will lead to the development of the next version of $Hg(OTf)_2$-catalyzed reactions. Because the sulfonamide allyl alcohol cyclization generates a new chiral center, catalytic asymmetric sulfonamidation was also examined and some positive preliminary results were obtained. Furthermore, on the basis of our finding that a single OTf group is sufficient for the catalytic cycle, we prepared the first solid-supported mercuric salt, silaphenylmercuric triflate. Silaphenylmercuric triflate also acts as a powerful catalyst for most $Hg(OTf)_2$-catalyzed reactions. Should the Hg-leakage be brought to nil or even reduced considerably further from the present level by preparing modified solid-supported merciric triflate catalyst, the highly active mercury salt is ideally suited as a catalyst for industrial organic synthesis.

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