Formation of Five- and Seven-Membered Rings Enabled by the Triisopropylsilyl Auxiliary Group
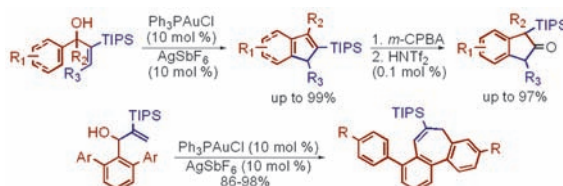
Dmitry L. Usanov and Hisashi Yamamoto*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

**yamamoto@uchicago.edu*

ABSTRACT

A highly convenient synthetic pathway to 2-indanones from aldehydes was established. The introduction of a triisopropylsilyl group greatly facilitated Meinwald rearrangement of the intermediate epoxides and alleviated the necessity of polysubstitution for the clean formation of indenes and cyclopentadienes via cyclodehydration of allylic alcohols; unprecedented freedom with respect to the product structure was thus achieved. The developed methodology could also be applicable to the formation of seven-membered rings leading to dibenzo[7]annulenes and dibenzosuberones.

Cyclodehydration of aryl-substituted allylic alcohols represents an established route toward construction of the indene scaffold. However, the existing protocols require multiple aryl/alkyl stabilizing groups in the substrates,[1] which results in a substantially narrowed scope of the available annulation products. Indeed, when we subjected α-vinylbenzyl alcohol (**1a**) to 10 mol % of boron trifluoride etherate in CH_2Cl_2, only a complex mixture of products could be detected (Scheme 1). We considered suppression of the numerous side pathways by the introduction of the sole silyl group adjacent to the alcohol moiety (Scheme 1). The reactivity of the

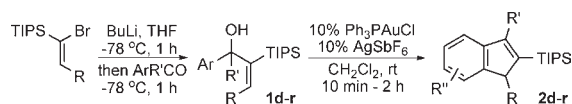**Scheme 1.** Au^I-Mediated Cyclization/Epoxidation/Meinwald Rearrangement Sequence for Allylic Alcohols
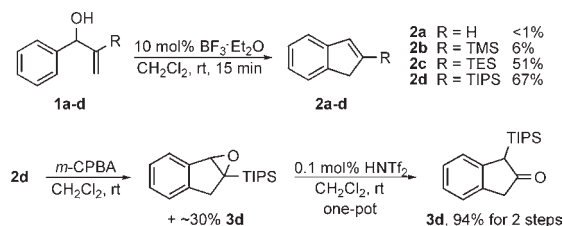
intermediate cationic species was expected to be controlled by both steric and electronic factors (β-silicon effect),[2] thereby enabling aromatic electrophilic substitution to proceed in a clean fashion; this concept was thus supposed to allow the use of unsubstituted substrates.

(1) (a) Goldschmidt, S.; Acksteiner, B. *Chem. Ber.* **1958**, *91*, 502. (b) Deno, N. C.; Pittman, C.; Turner, J. O. *J. Am. Chem. Soc.* **1965**, *87*, 2153. (c) Parham, W. E.; Egberg, D. C. *J. Org. Chem.* **1972**, *37*, 1545. (d) Miller, W.; Pittman, C. *J. Org. Chem.* **1974**, *39*, 1955. (e) Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744. (f) Pittman, C.; Miller, W. G. *J. Am. Chem. Soc.* **1973**, *95*, 2947. (g) Gassman, P. G.; Ray, J. A.; Wenthold, P. G.; Mickelson, J. W. *J. Org. Chem.* **1991**, *56*, 5143. (h) Jeong, I. H.; Park, Y. S.; Kim, M. S.; Oh, S. T. *Bull. Korean Chem. Soc.* **2001**, *22*, 1173. (i) Basavaiah, D.; Bakthadoss, M.; Reddy., G. J. *Synthesis* **2001**, 919. (j) Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2003**, *68*, 1252. (k) Radix-Large, S.; Kucharski, S.; Langlois, B. R. *Synthesis* **2004**, 456. (l) Zhou, X.; Zhang, H.; Xie, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 3958. (m) Guo, S.; Liu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2064. (n) Wang, J.; Zhang, L.; Jing, Y.; Huang, W.; Zhou, X. *Tetrahedron Lett.* **2009**, *50*, 4978. (o) Cordier, P.; Aubert, C.; Malacria, M.; Lacôte, E.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8757. (p) Smith, C. D.; Rosocha, G.; Mui, L.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 4716.

(2) Reviews on β-silicon effect: (a) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (b) White, J. M. *Aust. J. Chem.* **1995**, *48*, 1227.

Table 1. Substrate Screening for Au[I]-Mediated Indene Synthesis

entry	1	yield (%)[a]	2	yield (%)[a]
d		90		92
e		93		99
f		99		87
g		92		97
h	1h: G = Me	96	2h: 5-/7- = 1.7:1	92
i	1i: G = Br	72	2i: 5-/7- = 3.3:1	70
j		92		91
k		95		84
l		69		91
m		75[b]		82[c]
n		97		99
o		77		94
p		99		90[c]
q		73		99

[a] Isolated yields after column chromatography. [b] Prepared via transmetalation with 2LiCl•CeCl₃. [c] Carried out at 0 °C.

superiority of the system consisting of chloro(triphenylphosphine) gold(I)[3] and silver hexafluoroantimonate(V) in dichloromethane: to our delight, the product yield could be increased to 92% yield.[4]

With these results in hand, we considered the possibility of indanone synthesis via Meinwald rearrangement of epoxides[5] (Scheme 1). The use of *m*-CPBA with indene **2d** allowed clean formation of the corresponding epoxide along with the product **3d**; as low as 0.1 mol % of triflimide appeared to be sufficient for the clean and regioselective conversion to **3d** with 94% overall yield.

We then tested the Ph₃PAuCl/AgSbF₆ catalytic system (10 mol %) on a range of TIPS-substituted allylic alcohols **1d−q** (Table 1), which can easily be synthesized via organolithium species formed from (1-bromovinyl)triisopropylsilane, which in turn can be conveniently prepared on a large scale in 3 steps from inexpensive

Introduction of a TMS-substituent did render the reaction cleaner; however, the isolated yield of indene **2b** appeared to be unacceptably low (Scheme 1). The Triethylsilyl group provided a considerable increase in yield of the product **2c**. A triisopropyl-substituted alcohol **1d** furnished the desired indene **2d** with the highest yield in the series (67%). Screening of other Brønsted and Lewis acids as a catalyst for the synthesis of **2d** demonstrated the

(3) For selected reviews on gold-catalyzed reactions, see: (a) Arcadi, A.; Giuseppe, S. D. *Curr. Org. Chem.* **2004**, *8*, 795. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (f) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (g) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776. (h) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (i) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (j) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (k) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (l) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (m) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (n) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (o) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 657. (p) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675. (q) Nolan, S. P. *Acc. Chem. Res.* **2011**, *44*, 91. For discussions on the nature of the intermediates in Au-catalyzed reactions, see the following publications and references therein: (r) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (s) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030. (t) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (u) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510. (v) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482. (w) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232.

(4) The use of Ph₃PAuCl/AgSbF₆ demonstrated the same trend as BF₃: increasing the size of the silyl group led to improved yields. For substrates **1a−d** the corresponding indenes were obtained in < 1%, 5%, 56%, and 92% yields respectively.
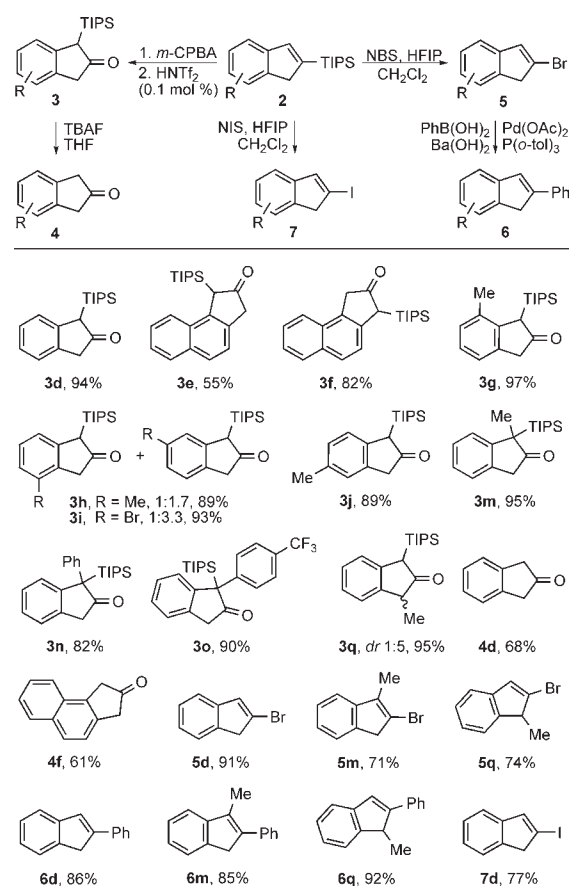
(5) Contrary to our approach, the overwhelming majority of methods on Meinwald rearrangement are based on the use of Lewis acids: Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3; Chapter 3.3, p 733 and references therein. For more recent studies, see: (a) Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3303. (b) Maruoka, K.; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3663. (c) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1995**, 721. (d) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1997**, *62*, 6547. (e) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212. (f) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Tetrahedron Lett.* **1999**, *40*, 7243. (g) Anderson, A. M.; Blazek, J. M.; Garg, P.; Payne, B. J.; Mohan, R. S. *Tetrahedron Lett.* **2000**, *41*, 1527. (h) Martínez, F.; del Campo, C.; Llama, E. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1749. (i) Bhatia, K. A.; Eash, K. J.; Leonard, N. M.; Oswald, M. C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129. (j) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917. (k) Karamé, I.; Tommasino, M. L.; Lemaire, M. *Tetrahedron Lett.* **2003**, *44*, 7687. (l) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554. (m) Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Sindona, G.; Tagarelli, A. *Synlett* **2004**, 2633. (n) Lee, S.-H.; Lee, J.-C.; Li, M.-X.; Kim, N.-S. *Bull. Korean Chem. Soc.* **2005**, *26*, 221. (o) Deng, X.-M.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6537. (p) Robinson, M. W. C.; Pillinger, K. S.; Graham, A. E. *Tetrahedron Lett.* **2006**, *47*, 5919. (q) Ko, N. H.; Kim, H. S.; Kang, S. O.; Cheong, M. *Bull. Korean Chem. Soc.* **2008**, *29*, 682. (r) Donald, J. R.; Taylor, R. J. K. *Synlett* **2009**, 59. (s) Suda, K.; Nakajima, S.; Satoh, Y.; Takanami, T. *Chem. Commun.* **2009**, 1255. (t) Ertür, E.; Göllü, M.; Demir, A. S. *Tetrahedron* **2010**, *66*, 2373. (u) Robinson, M. W. C.; Pillinger, K. S.; Mabbett, I.; Timms, D. A.; Graham, A. E. *Tetrahedron* **2010**, *66*, 8377.

starting materials (82% overall, only one purification step required). The acetophenone-derived substrate **1n** could be prepared via transmetalation with the 2LiCl•CeCl$_3$ complex to suppress undesired enolization. Notably, a catalyst loading lower than 10 mol % could also be used for efficient cyclodehydration as was exemplified for substrate **1e**: the use of 5 mol % of the Ph$_3$PAuCl/AgSbF$_6$ system still furnished the indene product with an excellent outcome (99% yield); a further decrease of the gold content to 1 mol % was also possible, although a lower yield was detected (82%). The use of 10 mol % of the gold(I) catalyst was chosen for the substrate screening experiments since it generally provided somewhat higher yields compared to the lower catalyst loadings.[6]

Excellent results were obtained for the Au[I]-mediated cyclodehydration of the substrates derived from benzaldehyde (**1d**), 1-naphthaldehyde (**1e**), 2-naphthaldehyde (**1f**, the angular tricyclic product **2f** was formed exclusively), and *o*- as well as *p*-tolualdehydes (**1g**/**1j**). The *m*-tolualdehyde derivative **1h** furnished a mixture of isomers in a 1.7:1 ratio with the less sterically congested 5-substituted product being predominant. The isomer ratio could be increased to 3.3:1 for a bromo-analogue **1i**, which is presumably due to the combination of steric and inductive effects. A thiophene-2-carboxaldehyde-derived substrate appeared to be too reactive for a clean catalysis outcome; however, the reactivity could be successfully tuned via introduction of benzannulation allowing clean formation of tricyclic product **2k**. An indole analogue **1l** could be subjected to cyclodehydration, although reactivity tuning was also necessary (*N*-tosyl moiety). Ketone derivatives **1m**−**p** were successfully employed; notably, for substrates **1m** and **1p** a substantial loss of the silyl moiety was detected when the reactions were run at room temperature; this could be easily avoided by carrying out the catalysis at 0 °C. Indeed, a complete regioselectivity of annulation was observed in the benzophenone-derived substrate **1o** with one of the aryl moieties being deactivated. Functionalization of position 1 in the indene product was possible by the use of a terminally alkylated substrate **1q**.

A number of silylated 2-indanones **3** were then prepared from indenes **2** via the one-pot epoxidation/rearrangement sequence with generally good to excellent yields (Scheme 2).[8] The 1-methylated indene **2q** furnished the corresponding *syn*- and *anti*-indanones **3q** in a 1:5 ratio. The versatile nature of the auxiliary TIPS group was demonstrated in the examples of desilylation, iodination,[9a] and a bromination[9b]/Suzuki coupling sequence (products **4**−**7**). The latter transformation is notable for the isomeric indenes **2m** and **2q**: no scrambling of the double bond was observed on

(6) The indene synthesis could also be accomplished using 5−10 mol % of AuCl$_3$ in CH$_2$Cl$_2$ for 0.5−1 h. However, the yields obtained were usually somewhat lower than those provided by the Au[I] system. For the data on other gold catalysts see Supporting Information.

(7) Abbreviations: HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; NIS = *N*-iodosuccinimide; *o*-tol = *ortho*-tolyl.

(8) Silyl indanones **3** are generally robust; however, for storage over extended periods of time fridge/freezer temperatures are recommended.

(9) (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727. (b) Carried out using the procedure analogous to iodination.[9a]

Scheme 2. 2-Indanones **3** Obtained from Indenes **2** and Derivatives thereof (**4**−**7**)[7]

either stage, allowing clean preparation of isomeric couples **5m**/**5q** and **6m**/**6q**.

We then considered expansion of the developed methodology on the silylated allylic alcohols derived from α,β-unsaturated aldehydes. To our delight, cyclopentadiene synthesis proceeded smoothly for substrates **1r**−**u** with good to excellent yields (Table 2).

The importance of the α-substituent in the parent aldehyde was postulated: only a complex mixture of products was obtained when a (*E*)-cinnamaldehyde derivative was used. However, the presence of an α-methyl group in **1r** was already sufficient for the necessary level of intermediate stabilization (provided the β-substituent was aryl). Increasing the size of the α-substitution was beneficial for the reaction yield as exemplified by **8r** and **8s**; both products were prepared as virtually single isomers shown in Table 2. On the contrary, the isomers with all the possible positions of the double bonds were present in the reaction mixture involving α-aryl,β-alkyl derivatives **1t**

(10) (a) Garner, C. M.; Prince, M. E. *Tetrahedron Lett.* **1994**, *35*, 2463. (b) Threlkel, R. S.; Bercaw, J. E.; Seidler, P. F.; Stryker, J. M.; Bergman, R. G. *Org. Synth.* **1987**, *65*, 42. (c) Jutzi, P.; Dahlhaus, J. *Synthesis* **1993**, 684. (d) Gassman, P. G.; Mickelson, J. W.; Sowa, J. R., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 6942. (e) Fang, H.; Song, Q.; Wang, Z.; Xi, Z. *Tetrahedron Lett.* **2004**, *45*, 5159. (f) Christie, S. D. R.; Man, K. W.; Whitby, R. J. *Organometallics* **1999**, *18*, 348. (g) Wang, Z.; Fang, H.; Xi, Z. *Tetrahedron* **2006**, *62*, 6967.

Table 2. Au^I-Mediated Cyclopentadiene Synthesis

entry	1	yield (%)[a]	8	yield (%)[a]
r		89		73[b]
s		94		91[b]
t		90		89[c]
u		89		96[c]

[a] Isolated yields after column chromatography. [b] >90% of the shown isomer. [c] A mixture of isomers was obtained.

and **1u**; excellent overall yields were still obtained. The presence of an aryl group, in either the α- or β-position of the parent aldehyde, was crucial for efficient catalysis; inferior results were obtained with dialkyl analogues. Only a few examples on cyclodehydration of bis-allylic alcohols have been published;[10] indeed, polyalkyl/polyaryl substitution in the substrates was required. In this context it is notable that our method provides access to trisubstituted cyclopentadienes, which were beyond the scope of previous cyclodehydration procedures.

We have also considered the possibility of building seven-membered cycles employing the developed methodology. Gratifyingly, terphenylcarbaldehyde-derived alcohols **1v−x** could be easily converted to dibenzo[7] annulenes **9v−x** with excellent yields (Scheme 3).[11] The constructed 6,7,6-tricyclic system is particularly interesting in light of its presence in allocolchicinoids, the class of compounds of great importance in cancer chemotherapy.[12]

(11) On the evidence of the formation of dibenzo[7]annulene scaffold see Supporting Information.

(12) The members of this family, e.g. allocolchicine, *N*-acetylcolchicinol methyl ether, *N*-acetylcolchicinol, and ZD 6126, have received much attention in the context of antitumor activity. For the most recent synthetic works and further details, see the following publications and references therein: (a) Boyer, F.-D.; Le Goff, X.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163. (b) Boyer, F.-D.; Hanna, I. *Eur. J. Org. Chem.* **2008**, *29*, 4938. (c) Nicolaus, N.; Zapke, J.; Riesterer, P.; Neudörfl, J.-M.; Prokop, A.; Oschkinat, H.; Schmalz, H.-G. *ChemMedChem* **2010**, *5*, 661. (d) Boyer, F.-D.; Dubois, J.; Thoret, S.; Tran Huu Dau, M.-E.; Hanna, I. *Bioorg. Chem.* **2010**, *38*, 149. (e) Djurdjevic, S.; Yang, F.; Green, J. R. *J. Org. Chem.* **2010**, *75*, 8241. (f) Nicolaus, N.; Reball, J.; Sitnikov, N.; Velder, J.; Termath, A.; Fedorov, A. Yu.; Schmalz, H.-G. *Heterocycles* **2011**, *82*, 1585.

Notably, when an *ortho,ortho*-dimethyl analogue **1y** was used, a 1,2-shift of the alkyl group was observed to furnish rearranged product **2y** (Scheme 3).

Scheme 3. Formation of 7-Membered Rings via Au^I-Catalysis
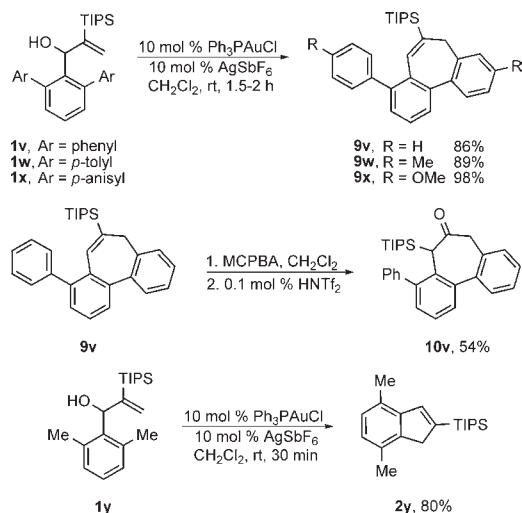
In summary, we have discovered the crucial effect of the TIPS moiety in aryl-substituted allylic alcohols in the context of gold(I)-mediated annulation, which resulted in the development of a mild, operationally simple and high-yielding three-step conversion of aromatic aldehydes into corresponding α-silyl-2-indanones. The methodology provided a route to a range of unsubstituted derivatives which were previously inaccessible via the cyclodehydration pathway. The concept could also be expanded to cyclopentadiene synthesis. Finally, the first example of an intramolecular electrophilic cyclization leading to a dibenzo[7]annulene system was successfully accomplished.

Supporting Information Available. Complete experimental procedures, characterization data of the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Current affiliation: University of Rochester.