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Aryl−Allene Cyclization via a Hg(OTf)$_2$-Catalytic Pathway

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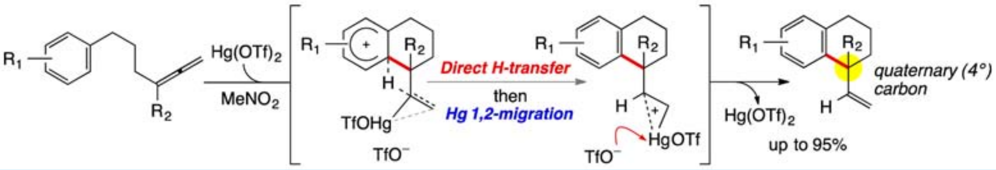
S *Supporting Information*

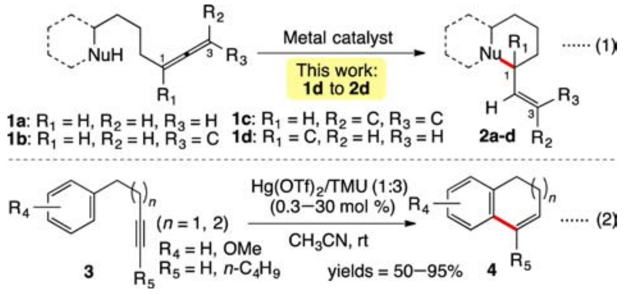


ABSTRACT: Hg(OTf)$_2$-catalyzed aryl−allene cyclization accompanied by formation of a quaternary carbon center has been realized. Deuterium-labeling experiments and computational modeling were used to propose a novel catalytic pathway involving direct H-transfer from the aromatic ring to the vinyl mercury moiety followed by mercury 1,2-migration.

The use of allene functionality to construct C−C bonds is a well-known and conventional method in the field of synthetic chemistry.[1] Recently, metal-catalyzed allene-cyclizations, such as *exo-trig*, *exo-dig*, *endo-dig*, and *endo-trig* type cyclizations, have been widely studied with the aim of synthesizing useful carbon frameworks.[2] Indeed, this strategy plays an important role in the synthesis of many natural products and bioactive compounds.[1d,3] Enantioselective cyclizations have also been developed, which facilitate easy access to some chiral inductions.[4] Most of these reactions, however, used naked **1a**, 1,3-disubstituted **1b**, and 1,3,3-trisubstituted allenes **1c** as substrates, while the cyclization of 1,1-disubstituted allenes **1d**, especially *exo-trig* cyclization of **1d** by the formation of a quaternary carbon center,[3f] has not been widely reported (eq 1, Scheme 1). We have contributed to this area through the development of a Hg(OTf)$_2$-catalyzed protocol and mechanistic studies of these reactions.

In 2003 we reported that Hg(OTf)$_2$ showed high catalytic activity for the carbocyclization of ω-arylalkyne **3** (eq 2).[5] Since that time, various Hg(OTf)$_2$-catalyzed reactions,[6] including ene−yne cyclization,[6b] aryl−allyl alcohol cyclization,[6c] and aryl−diene cyclization,[6d] have been developed on the basis of strong affinity of the mercury salt for C−C multiple bonds. In connection with this previous work we examined the corresponding Friedel−Crafts type 6-*exo-trig* cyclization of aryl 1,1-disubstituted allene derivative **1d** with the Hg(OTf)$_2$ catalyst, which leads to isochromane derivative **2d** in good yield under mild conditions. A 1,1-disubstituted allene derivative **5** was initially designed as a substrate, which was reacted with 5 mol % of Hg(OTf)$_2$ in CH_3CN at room temperature for 2 h (entry 1, Table 1). While a considerable amount of **5** was recovered, a sole product obtained in 36% yield was analyzed to be the desired isochromane derivative **6**. Although the yield was unsatisfactory, the result indicated that Hg(OTf)$_2$ acted as a catalyst to promote the desired cyclization.

Scheme 1. Allene 6-*exo-trig* Cyclizations and Hg(OTf)$_2$-Catalyzed Aryl−Yne Cyclizations



In order to make the reaction synthetically valuable, reaction conditions were optimized by investigating the effect of utilizing different solvents. Using CH_2Cl_2, the yield of **6** was improved to 75% (entry 2), whereas toluene or Et_2O did not give any products (entries 3 and 4). By contrast, CH_3NO_2 showed remarkable reactivity, giving rise to **6** in 95% yield within 1.5 h (entry 5). The comparative experiment with HOTf failed to give the desired product (entry 6). Using HOTf as an additive did not significantly change the yield of **6** (entry 7 vs 8). In light of our previous success in the cycloisomerization of 2-(4-pentynyl)furan with a combination of Hg(OAc)$_2$ and Sc(OTf)$_3$,[7] the catalytic performance of other mercuric salts and additives including Hg(OAc)$_2$/Sc(OTf)$_3$, $HgCl_2$/AgOTf, $HgCl_2$/$AgBF_4$, and $HgCl_2$/$AgNTf_2$ was examined (entries 9−12). However, all showed inferior catalytic activities compared to that of the Hg(OTf)$_2$ catalyst. The Hg(OAc)$_2$/Sc(OTf)$_3$ combination also afforded the desired product in moderate yield (entry 9). Platinum and gold catalysts (entries 13 and 15)

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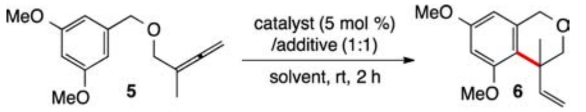
Table 1. Screening of Catalysts and Solvents[a]



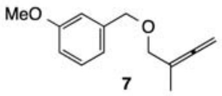
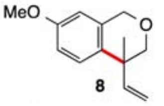
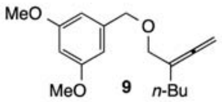
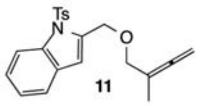
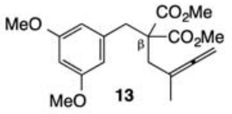
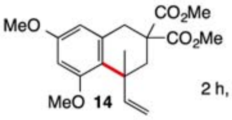
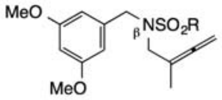
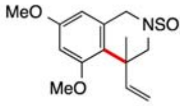
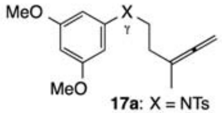
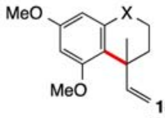
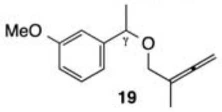
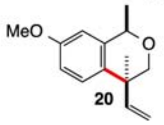
entry	catalyst	additive	solvent	yield (%)[b] 5	6
1	Hg(OTf)$_2$	–	MeCN	54	36
2	Hg(OTf)$_2$	–	CH$_2$Cl$_2$	trace	75
3	Hg(OTf)$_2$	–	PhMe	76	0
4	Hg(OTf)$_2$	–	Et$_2$O	81	0
5[c]	Hg(OTf)$_2$	–	MeNO$_2$	0	95
6	–	HOTf	MeNO$_2$	83	0
7[d]	Hg(OTf)$_2$	–	MeNO$_2$	39	55
8[d]	Hg(OTf)$_2$	HOTf	MeNO$_2$	30	51
9	Hg(OAc)$_2$	Sc(OTf)$_3$	MeNO$_2$	0	83
10	HgCl$_2$	AgOTf	MeNO$_2$	84	0
11	HgCl$_2$	AgBF$_4$	MeNO$_2$	98	0
12	HgCl$_2$	AgN(Tf)$_2$	MeNO$_2$	92	0
13	PtCl$_2$	–	MeOH	64	0
14	PtCl$_2$	AgOTf	MeOH	67	0
15	AuCl$_3$	–	CH$_2$Cl$_2$	84	0
16	AuCl$_3$	AgSbF$_6$	CH$_2$Cl$_2$	50	0
17	AuCl$_3$	AgOTf	CH$_2$Cl$_2$	56	0
18	AuCl$_3$	AgOTf	PhMe	83	0
19[e]	PPh$_3$AuCl	–	PhMe	76	0
20[e]	PPh$_3$AuCl	AgOTf	PhMe	42	22
21[e]	PPh$_3$AuCl	AgBF$_4$	PhMe	69	10

[a] Reactions conducted with 0.02 mmol of substrate **5**. [b] Isolated yield. [c] Reaction conducted with 0.1 mmol of substrate **5**, which was complete within 1.5 h. [d] 2 mol % of catalyst was used for the reaction. [e] Reaction carried out for 20 h.

in addition to other well-known combinations such as PtCl$_2$/AgOTf, AuCl$_3$/AgSbF$_6$, and AuCl$_3$/AgOTf (entries 14 and 16−18) were inefficient catalysts for the reaction. Under gold(I) catalytic conditions with PPh$_3$AuCl/AgOTf and PPh$_3$AuCl/AgBF$_4$, the desired cyclization proceeded, but the reaction rates were low i.e., 22% yield of **6** after 20 h (entries 20 and 21).

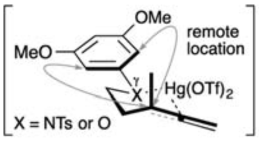
Thus, from among the several solvents and catalysts screened in our study, Hg(OTf)$_2$ in CH$_3$NO$_2$ was shown to be the most suitable combination. Hence, the scope of the reaction was examined using the optimized conditions. As shown in Table 2, the corresponding cyclic products were obtained in excellent to good yield in many cases. The reaction of mono-*m*-methoxy substituted **7** with 5 mol % of the mercury catalyst proceeded smoothly at room temperature affording **8** at the *p*-position for the methoxy group in 84% yield with complete regioselectivity (entry 1). Using *n*-butyl substituted allene **9** instead of methylallene as the substrate, the desired **10** with a quaternary carbon center was afforded in 78% yield (entry 2). Indole derivative **11** also underwent the desired reaction (entry 3). The cyclizations of dimethyl malonate derivative **13** as well as sulfonamide substrates **15a−e** gave the corresponding products **14** and **16a−e** in good yield, respectively (entries 4 and 5). However, it was found that the polar functional group at the *γ*-position affected the course of the reaction. Indeed, the cyclization of **17a**, including *p*-toluenesulfonyl (tosyl) amide at the *γ*-position, furnished no product even after 2 days (entry 6). The reactivity of ether **17b** also decreased in comparison with that of **5**, giving **18b** in 23% yield after 24 h.

Table 2. Assessment of Hg(OTf)$_2$-Catalyzed Cyclization in MeNO$_2$[a]

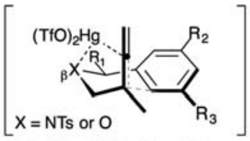
entry	substrate[b]	product[c]	
1	 **7**	 **8**	1 h, 84%
2	 **9**	 **10**	2 h, 78%
3[d]	 **11**	 **12**	1 h, 61%
4	 **13**	 **14**	2 h, 73%
5	 **15a**: R = Ph*p*-Me **15b**: R = Ph(*m*-Me)$_2$ **15c**: R = Ph*o*-NO$_2$ **15d**: R = Me **15e**: R = CH$_2$Ph	 **16a**: 3 h, 90% **16b**: 1 h, 74% **16c**: 3 h, 66% **16d**: 4 h, 91% **16e**: 4 h, 79%	
6	 **17a**: X = NTs **17b**: X = O	 **18a**: 48 h, 0%[e] **18b**: 24 h, 23%[e]	
7	 **19**	 **20**	2 h, 74%

[a] See Supporting Information for full experimental details. [b] These reactions were conducted with 0.05−0.1 mmol of substrate. [c] Isolated yield. [d] Ts = *p*-toluenesulfonyl. [e] Starting substrate was mainly recovered.

Because of the characteristics and size of the sulfonyl group at the *β*-position of **15b−e**, there was no difference in reactivity. Thus, **17a** and **17b** probably formed **21** in which Hg(OTf)$_2$ interacted with the *γ*-nitrogen atom (or *γ*-oxygen atom) as well as the allene moiety to define the location of the reactive site for the phenyl group as being set apart from the allene moiety. In contrast, the *β*-functional group produces a phenyl group close to the allene moiety through the formation of **22a**. Therefore, **19**, possessing a nonligating methyl substituent at the problem *γ*-position, reacted smoothly via **22b** giving **20** as the sole product in good yield with complete diastereoselectivity.[8]



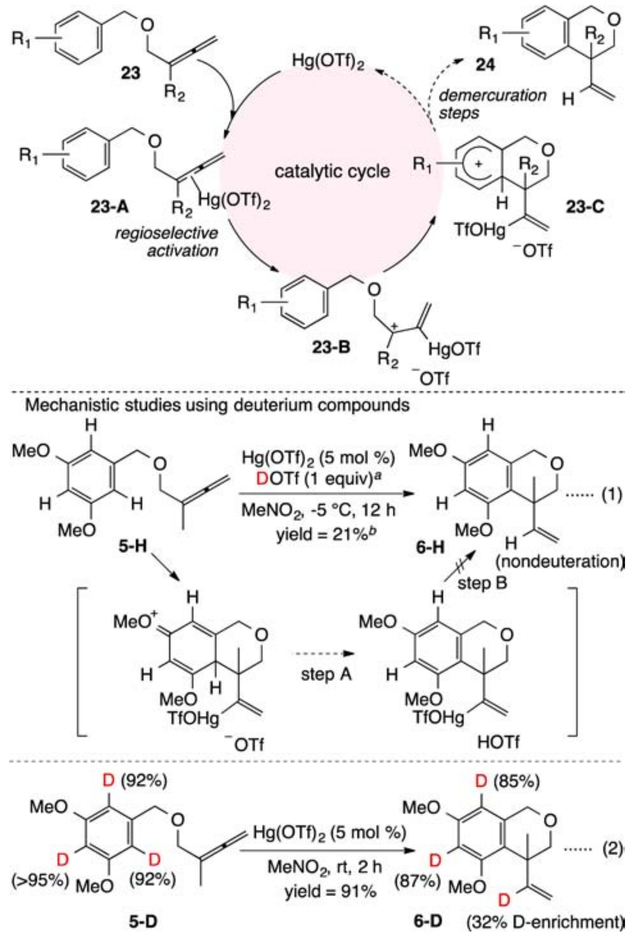
21



22a: R$_1$ = H, R$_2$,R$_3$ = OMe
22b: R$_1$ = Me, R$_2$ = OMe, R$_3$ = H

Considering the nature of the mercury salt reagent, these catalytic reactions probably begin with Hg(OTf)$_2$ activating the internal double bond of the allene group **23-A**, rather than the external double bond, due to formation of a stable tertiary carbenium intermediate species **23-B** (Scheme 2). **23-B** promotes cyclization followed by the generation of organo-Hg^{2+} intermediate **23-C**. However, the likely mechanism for the conversion of **23-C** to **24** was unclear. Thus, several deuterium-labeling experiments were performed to gain mechanistic insight into the course of the catalytic cycle. The reaction of **5-H** with Hg(OTf)$_2$ in the presence of a stoichiometric amount of DOTf resulted in the formation of normal **6-H**, where deuterium was not incorporated exclusively at the vinyl moiety (eq 1). This result suggested that if 5 mol % of HOTf was generated *in situ* through aromatization (step A), it did not promote cleavage (step B) of the vinyl-Hg bond.[9] Hence, deuterium-labeled **5-D**, which could be prepared in high purity from 3,5-dihydroxybenzoic acid in five steps,[10] was used as a substrate. The reaction of **5-D** with 5 mol % of Hg(OTf)$_2$ in CH$_3$NO$_2$ resulted in the production of 32% D-enriched **6-D** (eq 2).[11] This observation established that the deuterium atom originated from the aromatic ring and is directly used in the cleavage of the vinyl−Hg bond of **23-C**. It is known that a β-mercury atom on a carbocation exerts a stabilizing effect (i.e., the so-called β-mercury effect[13]), which would assist in the observed D-transfer reaction. DFT calculations using a simplified methoxymercury model were carried out to obtain further data regarding the reaction mechanism (Figure 1). **25-C** represents a likely cationic intermediate formed immediately upon cyclization and is equivalent to **23-C** in Scheme 2. The lowest energy pathway of the H-transfer reaction of **25-C** via a sole first-order saddle point was estimated using the B3LYP/CEP-121G method. The reaction proceeds through a transition structure **25-D** with an activation energy E_a of 19.0 kcal/mol, which involves concomitant aryl carbon−hydrogen bond cleavage (C$_{aryl}$−H; 1.42 Å) and transferal of hydrogen to vinyl carbon (H−C$_{vinyl}$; 1.51 Å). Eventually, **25-D** shifts to the secondary carbenium **25-G** via mercury 1,2-migration, which is computed by the IRC calculation as shown by the reaction path geometries of **25-F**[12] and **25-E**. The calculations revealed that the H-transfer reaction of **25-C** could proceed with a low activation barrier and suggested that Hg(OTf)$_2$ forms from **25-G** without generating HOTf. This suggestion is consistent with the experimental finding that the extrinsic addition of HOTf had no influence on the catalytic activity (entry 8, Table 1). The mercury 1,2-migration (**25-E** → **25-G**) is reasonable in terms of cationic stability. The natural bond orbitals (NBO) analysis to calculate the distribution of electron density clearly recognized the existence of the secondary carbenium species in the **25-G** state.

Scheme 2. Mechanistic Studies of Hg(OTf)$_2$-Catalyzed Cyclization



[a]20 times the amount of DOTf to generating HOTf. [b]Starting material **5-H** was recovered in 60% yield.

In summary, we have demonstrated a novel cyclization of aryl 1,1-disubstituted allenes with formation of a quaternary carbon center catalyzed by Hg(OTf)$_2$ in CH$_3$NO$_2$. The experimental and computational results indicate an interesting mechanistic pathway, which involves novel direct H-transfer from the

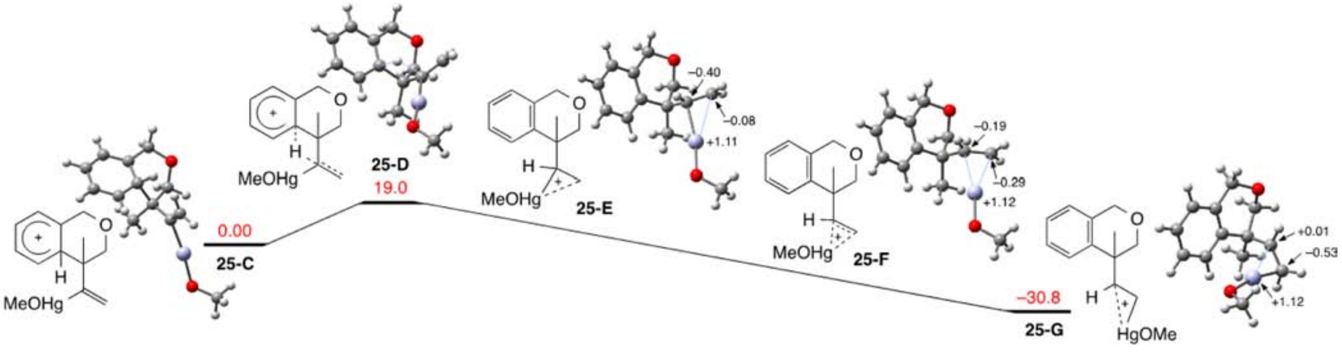


Figure 1. Transition states and energy changes for the H-transfer pathway from optimized structure **25-C**. The white, gray, blue, and red in the structures indicate hydrogen, carbon, mercury, and oxygen atoms, respectively. Energy is in kcal/mol with zero-point vibrational energy correction. The NBO charges for carbon and mercury atoms in **25-E**, **-F**, and **-G** are displayed.

aromatic ring to the vinyl mercury moiety. We also suggest that $Hg(OTf)_2$ forms as a catalytic complement from a cationic vinyl mercury intermediate **25-G** without generating HOTf.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01144.

Detailed experimental procedures and characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) See Supporting Information with regard to the preparation of deuterium-labeled **5-D**.

(11) **5-D** is moisture sensitive and gradually changes to **5-H**. Thus, 68% of the protonated **6-D** was probably generated from the cyclization of **5-D** whose *o*-deuterium converted to protons derived from the water that could not be completely removed from the $MeNO_2$ solvent. $MeNO_2$ might also act as a competitive proton source.

(12) The NBO analysis suggests that the cationic charges of the obtained geometries **25-E**, **-F**, and **-G** are delocalized by the coordination of $MeOHg^+$ to vinyl double bond, in which the electronic occupancy of the π-orbitals are ca. 1.70 (typically 1.95−2.00).

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