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Hg(OTf)₂ Catalyzed Intramolecular 1,4-Addition of Donor–Acceptor Cyclopropenes to Arenes

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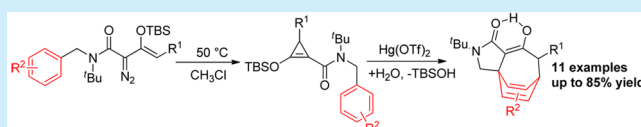
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S Supporting Information

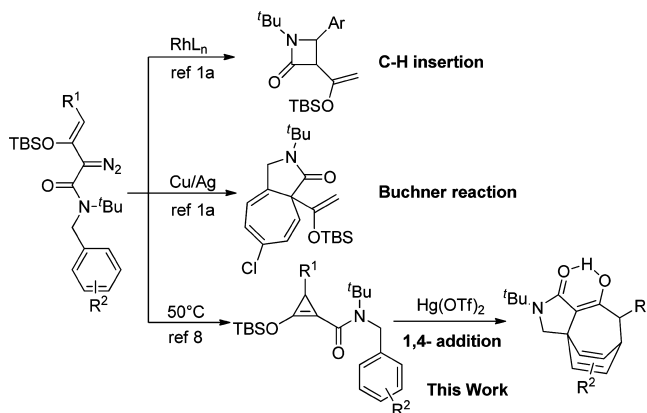
ABSTRACT: A Hg(OTf)₂ catalyzed intramolecular arene 1,4-addition reaction of *N*-benzyl donor–acceptor cyclopropenecarboxamides was developed to synthesize a series of [3.2.2]nonatriene derivatives. This novel reaction is also observed with silver(I) catalysts known to form metal carbene intermediates in competition with the Buchner reaction.



In our efforts to broaden the scope of transition metal complexes suitable for catalysis in metal carbene reactions of diazo compounds, we have investigated and compared reactivities and selectivities of transition metal complexes, especially those of dirhodium(II), copper, and silver, capable of forming metal carbene intermediates from diazoesters.¹ These efforts have prompted us to investigate reactions with diazo compounds of those transition metals having limited evidence for the formation of metal carbene intermediates. Mercury(II) is one such candidate having both a rich history as a π -acceptor electrophilic catalyst² and recent developments in metal-NHC chemistry,³ but limited evidence for the intermediate formation of a reactive mercury-carbene intermediate.^{4,5} The most relevant indicator for a mercury carbene in reactions of a diazo compound is that of mercury(II) catalyzed cyclopropanation reactions of diazooxindoles which was reported in this journal by Zhou and co-workers.⁵ We have recently described intramolecular C–H insertion reactions of *N*-benzyl-enoldiazoacetamides at the benzyl C–H bond to form β -lactams that occur in competition with the Buchner reaction at the aromatic ring of the benzyl group;^{1a} since these reactions occur in high yields with dirhodium(II), copper, and silver catalysts, we thought that C–H insertion/aromatic cycloaddition of *N*-benzyl-enoldiazoacetamides could be a good indicator for the involvement of metal carbene intermediates. However, the use of highly electrophilic mercury(II) compounds with *N*-benzyl-enoldiazoacetamides has surprised us with its complexity and has led us to a novel Hg(OTf)₂ catalyzed intramolecular 1,4-addition reaction across the benzyl aromatic ring to form bicyclononatriene derivatives in high yield (Scheme 1).

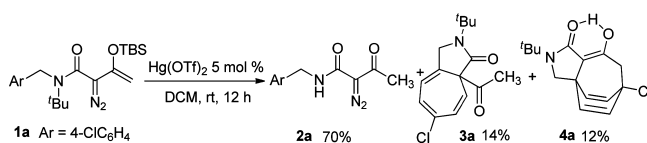
In our initial survey to evaluate mercury(II) activity, we selected reactions of *N*-*tert*-butyl-*N*-(4-chlorobenzyl)enoldiazoacetamide **1a** and expected products from either C–H insertion or aromatic cycloaddition.^{1a} However, the highly electrophilic mercuric triflate catalyzed dinitrogen loss with the formation of

Scheme 1. Divergent Pathways for Intramolecular Reactions of Enoldiazoacetamide and Donor–Acceptor Cyclopropenes



a product mixture dominated by the enol-silyl ether hydrolysis product **2a** (Scheme 2). Enol-silyl ether hydrolysis products were also dominant in Hg(OTf)₂ catalyzed reactions with other enoldiazoacetamides and enoldiazoacetates. Neither the careful drying of reagents and solvents nor the use of molecular sieves could substantially reduce interference from this reaction. However, thorough examination of the reaction mixture from

Scheme 2. Hg(OTf)₂ Catalyzed Reaction of *N*-*tert*-Butyl-*N*-(4-chlorobenzyl)enoldiazoacetamide **1a**



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the reaction of **1a** with mercuric triflate in dichloromethane following exposure to water for hydrolysis provided evidence for two reaction products formed with the loss of dinitrogen. One was the product expected from the Buchner reaction⁶ following hydrolysis of the vinyl-OTBS group (**3a**), and the other one was bicyclo[3.2.2]nonatriene **4a** which formally results from 1,4-addition across the benzene ring of the *N*-benzyl group. The β -lactam C–H functionalization product was not detected (Scheme 2). The structure of bicyclo[3.2.2]nonatriene **4a** was confirmed by single-crystal X-ray diffraction (Figure 1).⁷

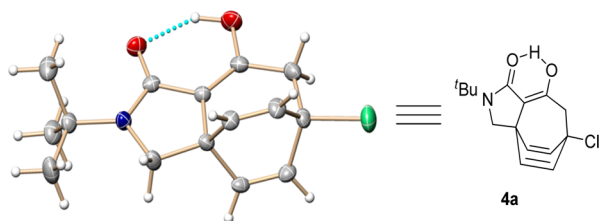
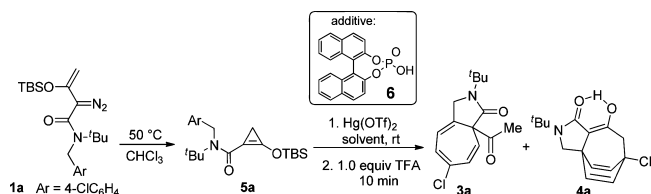


Figure 1. X-ray crystal structure of 2-(*tert*-butyl)-6-chloro-8-hydroxy-2,3,6,7-tetrahydro-1*H*-3a,6-ethenocyclohepta[*c*]pyrrol-1-one **4a**.

To avoid the dominant hydrolysis observed in $\text{Hg}(\text{OTf})_2$ -catalyzed reactions of enoldiazoacetamides, we considered that their corresponding donor–acceptor cyclopropenes might be suitable alternatives that minimized this side reaction. Donor–acceptor cyclopropenes can be thermally generated from enoldiazoacetates and enoldiazoacetamides in quantitative yield⁸ and are known to be capable of metal carbene formation in catalytic reactions.^{1a,b,9} When cyclopropene **5a** was used in place of **1a** in the $\text{Hg}(\text{OTf})_2$ -catalyzed reaction, the combined yield of the 1,4-addition product **4a** and the Buchner reaction product **3a** was improved to 58% (entry 1, Table 1). Since some hydrolysis of the initially formed silyl ether products was observed, trifluoroacetic acid was added to produce a more

Table 1. Optimization of Reaction Conditions^a



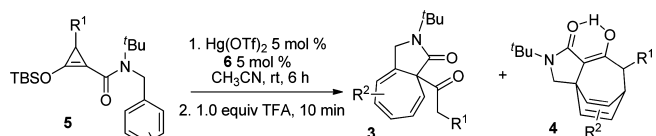
entry	catalyst	solvent	time/h	3a:4a ^b	yield ^c / % 3a+4a
1	$\text{Hg}(\text{OTf})_2$	DCM	12	52:48	58
2	$\text{Hg}(\text{OTf})_2$	CHCl_3	8	58:42	65
3	$\text{Hg}(\text{OTf})_2$	DCE	12	56:44	61
4	$\text{Hg}(\text{OTf})_2$	toluene	24	66:33	55
5	$\text{Hg}(\text{OTf})_2$	1,4-dioxane	24	55:45	40
6	$\text{Hg}(\text{OTf})_2$	hexanes	12	80:20	31
7	$\text{Hg}(\text{OTf})_2$	CH_3CN	8	38:62	69
8	HgCl_2	CH_3CN	16	42:58	39
9	$\text{Hg}(\text{OAc})_2$	CH_3CN	16	40:60	50
10 ^d	$\text{Hg}(\text{OTf})_2/6$	CH_3CN	6	30:70	85

^aReactions were performed on a 0.2 mmol scale: 0.2 mmol of **5a** was quantitatively generated from **1a** using the reported procedure;⁶ 0.2 mmol of **5a**, 5 mol % Hg catalyst, in 2 mL of solvent. ^bThe ratios of **3a** to **4a** were determined by ^1H NMR analysis of the reaction mixture before treatment with TFA. ^cIsolated yield. ^d5 mol % **6** was added with 5 mol % $\text{Hg}(\text{OTf})_2$.

homogeneous mixture. The reaction solvent was varied to further increase the combined yield of **3a** and **4a** and, perhaps, to influence their product ratio; this study revealed that acetonitrile solvent significantly increased product yield and the **4a**:**3a** product ratio (entry 7). The uses of HgCl_2 or $\text{Hg}(\text{OAc})_2$ were also examined as catalysts in acetonitrile; however, lower product yields were obtained with these mercury(II) compounds. Further improvement of yield and chemoselectivity was achieved when BINOL-derived phosphoric acid **6** was added as an additive to the reaction. The combination of a metal catalyst and BINOL-derived phosphoric acids has been exploited in organic transformations to enhance activity/selectivity.¹⁰ An NMR study of the combination of $\text{Hg}(\text{OTf})_2$ and **6** indicated a possible association between the Hg salt and the phosphoric acid (see Supporting Information), but their precise role in this transformation remains unknown.

The scope of intramolecular 1,4-addition reactions of enoldiazoacetamides was then investigated with $\text{Hg}(\text{OTf})_2$ catalysis under the optimized conditions established for **5a** (Table 1, entry 10). As indicated in Table 2, the substituent on

Table 2. Substrate Scope^a



entry	5	R ¹	R ²	3:4 ^b	yield ^c / % 3 + 4
1	5a	H	4-Cl	30:70	85
2	5b	H	3-Cl	37:63	59
3	5c	H	4-Br	46:54	71
4	5d	H	2-Cl	<5:95	83
5	5e	H	2-Br	<5:95	68
6	5f	H	2-CH ₃	<5:95	81
7	5g	H	2,3-benzo	<5:95	66
8	5h	H	H	<5:95	75
9	5i	H	4-CH ₃	<5:95	61
10	5j	CH ₃	2-Cl	<5:95	53
11	5k	C ₂ H ₅	2-Cl	<5:95	38

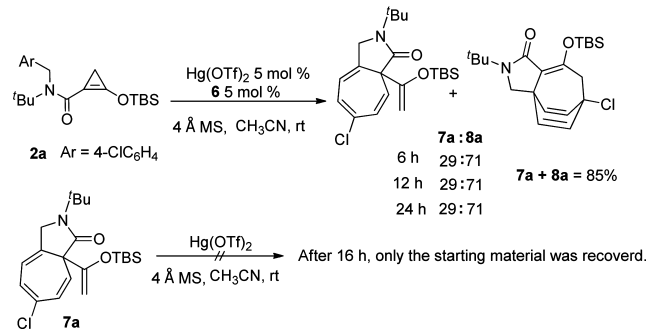
^aReactions were performed on a 0.3 mmol scale: 0.3 mmol of **5a**, 5 mol % $\text{Hg}(\text{OTf})_2$, 5 mol % **6**, in 2 mL of acetonitrile. ^bThe ratios of **3** to **4** were determined by ^1H NMR analysis of reaction mixture before treatment with 1.0 equiv of TFA. ^cIsolated yield after treatment with TFA.

the aromatic ring and its placement are the primary determinants of the observed selectivity. With chloride at either the *meta* or *para* positions, cogeneration of Buchner and 1,4-addition products occurs in 30:70 and 37:63 ratios (Table 2, entries 1 and 2). However, with chloride in the *ortho* position (**5d**) only the 1,4-addition product **3d** was obtained (entry 4). *Ortho*-substitution of the benzyl group in cyclopropene reactants produced only the 1,4-addition reaction product in good yields (entries 5–7), but so did the unsubstituted **5h** and the *p*-methyl substituted **5i** (entries 8 and 9), indicating the electronic influence of substituents on the 3:4 ratio. With the *p*-MeO substituent, however, decomposition of the cyclopropene reactant occurred without formation of either **3** or **4**. The steric effect of R¹ was also examined. As indicated by the reactions of **5j** (R¹ = Me) and **5k** (R¹ = Et), formation of the 1,4-addition product remained the sole process but in lower yields reflecting the size of R¹ (entries 10 and 11). However, no product was

obtained from the electron-withdrawing 4-nitroaryl substituted cyclopropene reactant ($R^2 = \text{NO}_2$).

Recently bicyclo[3.2.2]nonatriene derivatives were reported to be formed from benzyl enoldiazoacetates via a dirhodium(II) catalyzed Buchner reaction and subsequent Cope rearrangement.¹¹ Initially, we thought that the 1,4-addition product in the $\text{Hg}(\text{OTf})_2$ -catalyzed reactions also originated from the Buchner product after Cope rearrangement, but the influence of the *ortho*-substituted aryl group in forming only the product from 1,4-addition led us to question this interpretation. We predicted that *ortho*-halide substitution would inhibit the Buchner reaction but would have little or no influence on a subsequent Cope rearrangement.¹² Furthermore, the Buchner reaction product formed from benzyl enoldiazoacetates undergoes Cope rearrangement only at elevated temperatures, whereas 1,4-addition products formed in the $\text{Hg}(\text{OTf})_2$ -catalyzed reactions are generated at room temperature. In order to examine if the Buchner reaction and subsequent Cope rearrangement was the cause for the formation of compound **4** in this $\text{Hg}(\text{OTf})_2$ catalyzed process, reaction of **5a** was performed in the presence of molecular sieves for prolonged reaction times. As shown in Scheme 3, the silyl ether conserved

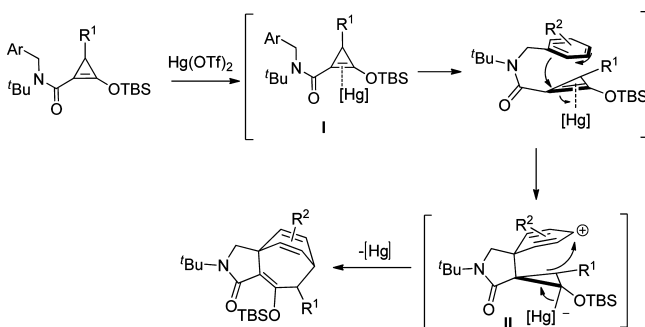
Scheme 3. Control Experiments to Determine if Cope Rearrangement Accompanied the Buchner Reaction



products **7a** and **8a** were obtained with the same selectivity as were the desilylated products from the reaction reported in Table 2. Furthermore, under prolonged reaction times up to 24 h, no conversion between **7a** and **8a** was observed. Additionally, no 1,4-addition product **8a** was detected from the isolated Buchner reaction product **7a** under the optimized reaction conditions obtained using molecular sieves to inhibit hydrolysis. These results exclude the Buchner reaction/Cope rearrangement pathway to bicyclo[3.2.2]nonatriene compounds in the $\text{Hg}(\text{OTf})_2$ catalyzed reaction of donor–acceptor cyclopropenes.

$\text{Hg}(\text{OTf})_2$ has been developed as a powerful catalyst in organic transformations including hydration of terminal alkynes and the cyclization of enyne, arylyne, and yne-en-aryl substrates, utilizing its ability to associate with olefins and alkynes.² Based on this knowledge and on our experimental observations, a plausible mechanism for this $\text{Hg}(\text{OTf})_2$ catalyzed 1,4-addition reaction is proposed in Scheme 4. Intermediate **I** is generated by π -complexation of $\text{Hg}(\text{OTf})_2$ with the cyclopropene, and this coordination occurs on the side opposite to R^1 . The bulky *tert*-butyl attachment to the amide nitrogen facilitates the proper orientation of the amide to realize nucleophilic attack by the aromatic ring to the $\text{Hg}(\text{OTf})_2$ -activated cyclopropene. Consistent with our experimental results (Table 2, entries 10 and 11), bulkier substituted

Scheme 4. Plausible Mechanism of $\text{Hg}(\text{OTf})_2$ Catalyzed 1,4-Addition Reaction of Donor–Acceptor Cyclopropenes



groups R^1 hinder the intramolecular reaction (**I** \rightarrow **II**) due to their steric conflict with the aromatic ring with the result that lower yields of 1,4-addition products are obtained (entries 10 and 11, Table 2). The bicyclo[3.2.2]nonatriene product is obtained following intramolecular nucleophilic addition to the *para* position of the aromatic ring that occurs with the release of the $\text{Hg}(\text{II})$ catalyst. The formation of the formal Buchner reaction product can also be explained with this mechanism by nucleophilic addition to the *ortho* position of the aromatic ring.

We wondered if this 1,4-addition reaction also existed in other well-studied metal catalyzed transformations, such as with Ag, Cu, and Rh catalysts. With this aim in mind, a catalyst screening was performed with donor–acceptor cyclopropene **5c**, and the results are shown in Table 3. The 1,4-addition

Table 3. Catalyst Screening^a

entry	catalyst	time/h	7c/% ^b	8c/% ^b	9c/% ^b
1	AgSbF_6	4	62	6	<5
2	AgBF_4	12	67	14	<5
3	AgClO_4	12	57	11	<5
4	AgOTf	12	68	6	<5
5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	6	8	<5	69
6	$\text{Cu}(\text{MeCN})_4\text{BF}_4$	8	18	<5	51
7	$\text{Cu}(\text{OTf})_2$	12	15	<5	38
8	$\text{Rh}_2(\text{OAc})_4$ ^c	6	<5	<5	82
9	$\text{Sc}(\text{OTf})_3$	12	<5	<5	<5
10	$\text{La}(\text{OTf})_3$	12	<5	<5	<5
11	$\text{In}(\text{OTf})_3$	12	<5	<5	<5

^aReactions were performed on a 0.2 mmol scale: 0.2 mmol of **2c**, 5 mol % catalyst, in 2 mL of acetonitrile at room temperature. ^bThe yields of **7c**, **8c**, and **9** were determined by ¹H NMR analysis of reaction mixture using an internal standard. ^c2 mol % $\text{Rh}_2(\text{OAc})_4$ was used.

product **8c** was obtained, albeit as a minor product, from various Ag catalyzed reactions (Table 3, entries 1–4), but not with the other catalysts surveyed. Both Cu and Rh catalysts produced β -lactam **9c**, but this C–H insertion product was not observed in Ag(I)-catalyzed reactions, and the Buchner addition product **7c** was a minor product in copper catalyzed reactions. No reaction occurred with Lewis acid catalysts $\text{Sc}(\text{OTf})_3$, $\text{La}(\text{OTf})_3$, and $\text{In}(\text{OTf})_3$. The 1,4-addition process found with $\text{Hg}(\text{II})$ and Ag(I) catalysts may be more broadly

applicable, but the pathway for its formation which is also linked to 1,2-addition suggests that Buchner addition products may not always be derived from a metal carbene process involving aromatic cycloaddition.

In summary, an intramolecular Hg(OTf)₂ catalyzed arene 1,4-addition reaction of donor–acceptor cyclopropenes generated from enoldiazoacetamides has been developed. Through the 1,4-addition reaction, a series of novel bicyclo[3.2.2]nonatriene compounds have been synthesized. Additionally, the 1,4-addition reaction is not unique to Hg(OTf)₂ but is also observed in silver(I) catalyzed reactions, and the general features of these mercury(II) and silver(I) reactions with donor–acceptor cyclopropenes open new synthetic approaches to multicyclic structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02129.

General experimental procedures, the X-ray structure of **4a**, and spectroscopic data for all new compounds (PDF)
Crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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