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Silver(I)-Catalyzed Ring-Contractive Rearrangement: A New Entry to 5-Alkylidene-2-cyclopentenones

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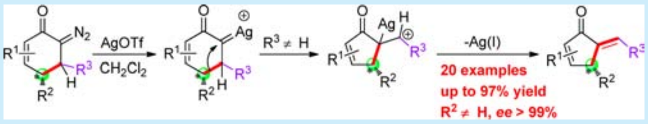
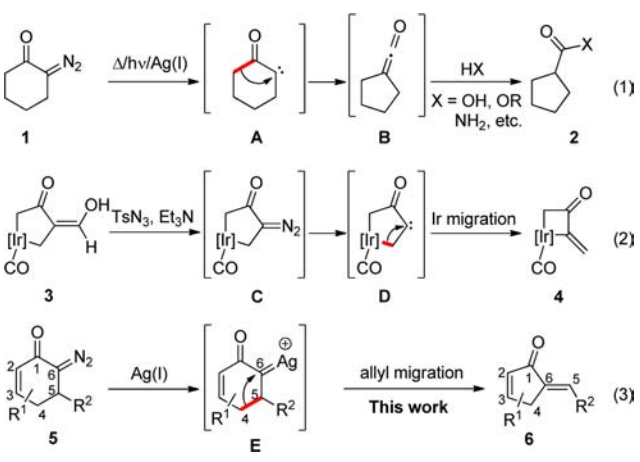
Ⓢ *Supporting Information*

ABSTRACT: A novel silver(I)-catalyzed ring-contractive rearrangement of 5-substituted 6-diazo-2-cyclohexenones has been developed, providing a new and efficient access to 5-alkylidene-2-cyclopentenones. The AgOTf-catalyzed reaction proceeds through metal−carbenoid formation followed by endocyclic allyl [1,2] migration with excellent stereoselectivity and broad substrate scope.



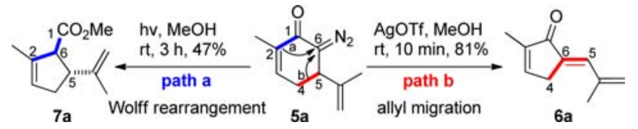
Ring contraction reactions have been extensively used to build cyclopentyl-containing molecules,[1] such as pinacol rearrangement,[1b−d] Favorskii rearrangement,[1e] oxidative rearrangement,[1f,g] photochemical rearrangement,[1h] and Wolff rearrangement.[2] Diazo-cycloketones **1** give the corresponding ring contraction products through intermediary ketene **B** (eq 1, Scheme 1)[3] under thermal, photolytical, or transition metal-catalyzed conditions. The migratory aptitude of a certain bond depends on its environment,[4] as demonstrated in an iridium-containing compound (**3**, eq 2).[5] However, transition metal-catalyzed/promoted ring contraction reactions of unsaturated diazocycloenones have not been reported.[6] For instance, migration of the C4−C5 bond in silver-carbenoid **E** [generated from **5** in the presence of Ag(I)] would afford 5-alkylidene-2-cyclopentenone **6** (eq 3). Furthermore, molecules with a cyclopentenone (especially alkylidene-2-cyclopentenone) motif, such as Δ^7-PGA$_1$, punaglandin 4,[7] and leucodin,[8] are important in natural products and pharmaceuticals. Although there are known synthetic strategies for alkylidene-2-cyclopentenone units including Nazarov cyclization,[9] sulfoxide elimination followed by retro-Diels−Alder reaction,[10] condensation/dehydration elimination,[11] and so on,[2c,12] all these methods involve multistep operations and have limitations in terms of atom economy. Thus, there is an urgent demand in developing efficient, versatile, and practical protocols for the synthesis of 5-alkylidene-2-cyclopentenones. Herein, we wish to report an unprecedented Ag(I)-catalyzed[13] ring-contractive rearrangement, constituting a concise approach to such useful structures starting from readily available 5-substituted 6-diazo-2-cyclohexenones.

Scheme 1. Rearrangement of α-Diazoketones and the New Approach to 5-Alkylidene-2-cyclopentenones



The investigations were commenced with irradiation of **5a**[14] in MeOH under an argon atmosphere with a high-pressure mercury lamp (500 W; $\lambda \geq 300$ nm) at room temperature (Scheme 2).

Scheme 2. Wolff Rearrangement and Silver(I)-Catalyzed Ring-Contractive Rearrangement of 5a



The classic Wolff rearrangement turned out to be the predominant reaction pathway, and the methyl ester **7a** was obtained as the major product (47%) along with the minor products such as **6a** (2%) and (*Z*)-**6a** (5%). In contrast, treatment of **5a** with AgOTf in MeOH induced a reaction pathway different from Wolff rearrangement,[15] through which alkylidene-2-cyclopentenone **6a** was exclusively produced (81%).

The reaction conditions were optimized for the rearrangement with **5a** as the substrate. Solvents for the reaction were first examined (entries 1−4, Table 1). The reaction in MeCN,

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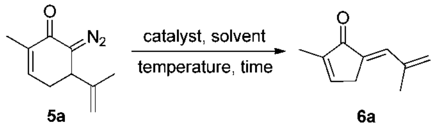
Table 1. Optimization for the Reaction Conditions[a]

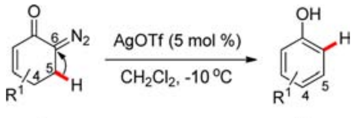


5a **6a**

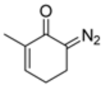
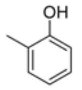
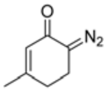
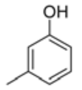
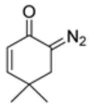
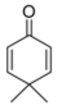
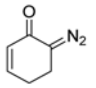
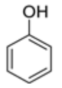
entry	catalyst	solvent	temp (°C)	time	yield^{b} (%)
1	AgOTf	MeCN	rt	12 h	85
2	AgOTf	Et$_2$O	0	40 min	73
3	AgOTf	PhH	0	1 h	69
4	AgOTf	CH$_2$Cl$_2$	0	10 min	86
5	Ag$_2$O	CH$_2$Cl$_2$	rt	12 h	85
6	Ag$_2$CO$_3$	CH$_2$Cl$_2$	rt	24 h	82
7	PhCO$_2$Ag	CH$_2$Cl$_2$	rt	10 h	78
8	AgBF$_4$	CH$_2$Cl$_2$	0	10 min	84
9^{c}	AgOTf	CH$_2$Cl$_2$	0	10 min	89
10^{c,d}	AgOTf	CH$_2$Cl$_2$	−10	30 min	92
11^{c}	In(OTf)$_3$	CH$_2$Cl$_2$	−10	30 min	14
12^{c}	TMSOTf	CH$_2$Cl$_2$	−10	30 min	trace
13^{c}	TsOH	CH$_2$Cl$_2$	−10	12 h	NR^{e}

[a] Reaction conditions: **5a** (0.5 mmol), catalyst (10 mol %), solvent (10 mL). [b] Isolated yield. [c] Catalyst (5 mol %). [d] Less than 2% of (*Z*)-**6a** was isolated. [e] NR = no reaction.

Table 2. 6-Diazo-2-cyclohexenones of Different Substitution Patterns and Their Reaction Behavior[a]



5 **8**

entry	substrate		product		yield^{b}
1	**5b**		**8b**		45%
2	**5c**		**8c**		47%
3	**5d**		**8d**		53%
4	**5e**		**8e**		43%

[a] Reaction conditions: **5** (0.5 mmol), AgOTf (5 mol %), solvent (10 mL), −10 °C, 3 h. [b] Isolated yield.

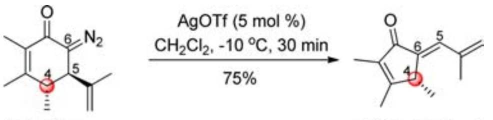
an aprotic solvent, gave the rearrangement product in a yield comparable to that observed in CH$_2$Cl$_2$. A moderate yield was obtained when the reaction was performed in diethyl ether or benzene. With AgOTf as the catalyst and CH$_2$Cl$_2$ as the solvent, the rearrangement of **5a** went to completion in 10 min at 0 °C to furnish **6a** as the single product in 86% yield (entry 4). After switching the catalyst from AgOTf to Ag$_2$O, Ag$_2$CO$_3$ or PhCO$_2$Ag (entries 5−7), the reaction proceeded smoothly at room temperature and afforded **6a** in 78−85% yield, although longer reaction time was required (10−24 h). AgBF$_4$ (entry 8) performed with similar catalytic efficiency to AgOTf. On the basis of the above findings, AgOTf seemed to be the optimal catalyst for this ring-contractive rearrangement. Moreover, decreasing the catalyst loading to 5 mol % (entries 9, 10) or lowering the reaction temperature to −10 °C (entry 10) resulted in a slightly improved yield of **6a**. With Lewis acids and Brønsted acid as the catalysts (entries 11−13), however, less or even none of **6a** was isolated.

Subsequently, we examined the rearrangement with some other substrates. It was found that the presence of a substituent at C5 was critical for the above rearrangement, as evidenced by the fact that treatment of 6-diazo-2-cyclohexenones **5b−e** of different substitution patterns with AgOTf in CH$_2$Cl$_2$ afforded phenols **6b−e** as the major products (Table 2). The generation of phenol products in the latter case was assumed to result from the migration of a hydrogen atom at C5 rather than the endocyclic allylic moiety to the adjacent C6 atom.

To explore the scope of the current ring-contractive rearrangement, a series of substrates were scrutinized with the optimized reaction conditions (Table 3). Ketodiazo compounds **5f−n**, each bearing only one alkyl (methyl, cyclohexyl, allyl, or benzyl), vinyl, or aryl (phenyl or naphthyl) group (at C5), underwent the rearrangement to give the corresponding 5-alkylidene-2-cyclopentenones **6f−n** in 67−82% yields. For the phenyl-containing substrates **5k−m**, the order of the yields [**6m** (*p*-MeO-C$_6$H$_4$−) > **6k** (C$_6$H$_5$−) > **6l** (*p*-Cl-C$_6$H$_4$−)] was consistent with the proposed carbocation mechanism. As for the 2,5-disubstituted and 2,3,5- and 3,5,5-trisubstituted ketodiazo compounds **5o−u** (featuring various types of substituents), the rearrangement proceeded as anticipated to form **6o−u** in 76−97% yields. The fully substituted substrates **5v** and **5w** exhibited excellent reactivity to produce cyclopentenoes with multiple substituents. Note that the (*E*)-configuration was observed for the exocyclic carbon−carbon double bond in the major product in every case.[16]

Since the stereochemistry of C5 was removed during the ring-contractive rearrangement, the enantiomerically pure (4*S*,5*R*)-**5x** containing two adjacent stereochemical centers was synthesized and then treated with AgOTf under the standard reaction conditions (Scheme 3). The product **6x** was isolated in 75% yield with 99% ee, demonstrating that the rearrangement presumably occurred with retention of the stereochemistry at the migratory center, i.e., no racemization took place at C4.[17] Therefore, the current protocol provides an efficient access to chiral 5-alkylidene-2-cyclopentenoes.

Scheme 3. Ag(I)-Catalyzed Rearrangement of (4*S*,5*R*)-5x

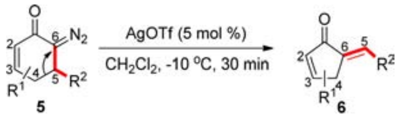


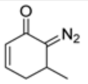
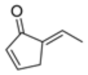
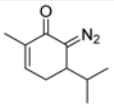
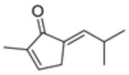
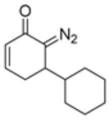
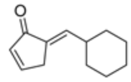
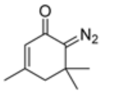
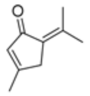
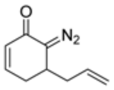
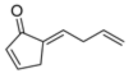
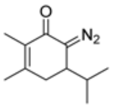
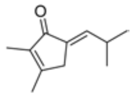
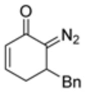
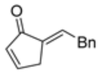
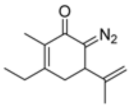
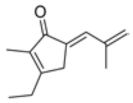
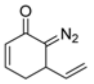
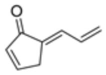
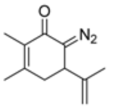
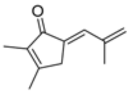
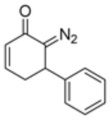
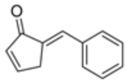
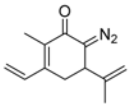
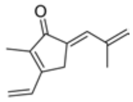
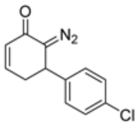
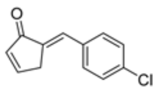
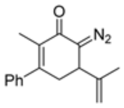
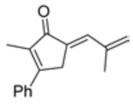
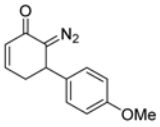
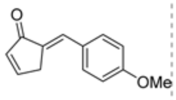
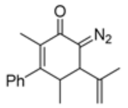
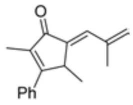
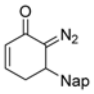
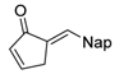
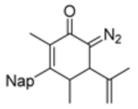
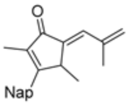
(4*S*,5*R*)-**5x** (*R*)-**6x** (99% ee)

A plausible mechanism for the ring-contractive rearrangement is proposed in Scheme 4. The reaction is presumably initiated by loss of nitrogen gas from **5** in the presence of Ag(I) forming silver−carbenoid **E**.[18] When R^2 ≠ H (path a), intermediate **E** undergoes endocyclic allyl migration to produce carbocation **F**, which delivers 5-alkylidene-2-cyclopentenone **6** with concomitant regeneration of the active Ag(I) catalyst. On the other hand, when R^2 = H (path b), one of the hydrogen atoms at C5 migrates to afford carbocation **G**, and extrusion of Ag(I) provides phenol **8** via the dienone **H** intermediate.

In conclusion, we have developed a novel method for the one-step synthesis of 5-alkylidene-2-cyclopentenones, an important

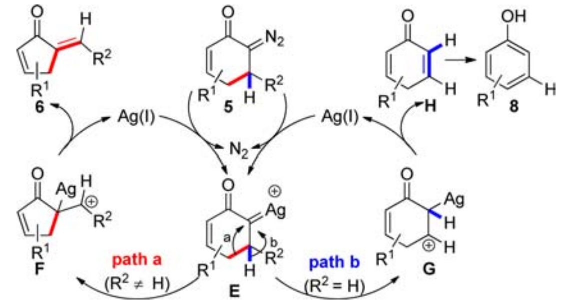
Table 3. Ag(I)-Catalyzed Rearrangement of Substrates 5[a]



substrate	product[b]	substrate	product[b]
 **5f**	 **6f**, 72%	 **5o**	 **6o**, 83%
 **5g**	 **6g**, 68%	 **5p**	 **6p**, 97%
 **5h**	 **6h**, 67%	 **5q**	 **6q**, 82%
 **5i**	 **6i**, 76%	 **5r**	 **6r**, 94%
 **5j**	 **6j**, 72%	 **5s**	 **6s**, 85%
 **5k**	 **6k**, 76%	 **5t**	 **6t**, 90%
 **5l**	 **6l**, 70%	 **5u**	 **6u**, 76%[c]
 **5m**	 **6m**, 82%	 **5v**	 **6v**, 81%
 **5n**	 **6n**, 78%	 **5w**[d]	 **6w**, 78%

[a] Reaction conditions: **5** (0.3 mmol), AgOTf (5 mol %), CH_2Cl_2 (6 mL), −10 °C, 30 min. [b] All yields refer to those of the isolated products. [c] The reaction was run at rt. [d] Nap = 2-naphthalenyl.

Scheme 4. Proposed Mechanism



type of structural motif present in natural products, through Ag(I)-catalyzed ring-contractive rearrangement of 5-substituted 6-diazo-2-cyclohexenones. The process presumably involves an endocyclic allyl [1,2] migration. A series of substrates have been tested, and the corresponding products have been obtained in moderate to excellent yields. On the basis of its efficiency, generality, and practicality, this protocol might find broad applications in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedural, spectral, and crystallographic data and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ DEDICATION

Dedicated to the memory of Professor Puzhu Cong, who passed away on Nov. 19, 2014.

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Author Contributions

§L.Z. and J.W. contributed equally.

Notes

The authors declare no competing financial interest.

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(15) Upon treatment of **5a** with Ag_2O (50 mol %) as catalyst, Et_3N (5 equiv) as additive, and MeOH as solvent, **6a** was obtained as the major product (61%) along with the O−H inserted product (12%) (see the Supporting Information for details).

(16) On the basis of the ^{1}H and ^{13}C NMR experiments, the (*E*)-configuration was assigned for the exocyclic carbon−carbon double bond in **6f−o**, **6q−w**, as well as **6a**. The structures of **6a** and **6k** were confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information for details).

(17) The configuration of **6x** could be deduced as the (*R*)-stereoisomer by comparing the calculated electronic circular dichroism (ECD) spectra of **6x** with the experimental data (see the Supporting Information for details).

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