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Authors: Yuan-Yuan Ren, Mo Chen, Ke Li, and Shou-Fei Zhu

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Gold-Catalyzed Formal C–C Bond Insertion Reaction of 2-Aryl-2diazoesters with 1,3-Diketones

Yuan-Yuan Ren, Mo Chen, Ke Li, and Shou-Fei Zhu*

Abstract: The transition-metal-catalyzed formal C-C bond insertion reaction of diazo compounds with monocarbonyl compounds is well established, but the related reaction of 1,3-diketones instead gives C-H bond insertion products. Herein, we report a protocol for a goldcatalyzed formal C-C bond insertion reaction of 2-aryl-2-diazoesters with 1,3-diketones, which provides efficient access to polycarbonyl compounds with an all-carbon quaternary center. The aryl ester moiety plays a crucial role in the unusual chemoselectivity, and the addition of a Brønsted acid to the reaction mixture improves the yield of the C-C bond insertion product. A reaction mechanism involving cyclopropanation of a gold carbenoid with an enolate and ringopening of the resulting donor-acceptor-type cyclopropane intermediate is proposed. This mechanism differs from that of the traditional Lewis-acid-catalyzed C-C bond insertion reaction of diazo compounds with monocarbonyl compounds, which involves a rearrangement of a zwitterion intermediate as a key step.

Diazo compounds have found a wide variety of applications in synthetic organic chemistry.¹ For example, they have been used as carbene precursors in transition-metal-catalyzed carbene transfer reactions.² In addition, because diazo compounds have a partial negative charge on the carbon connected to the diazo group, they can undergo formal C-C bond insertion reactions with carbonyl compounds in the presence of Lewis acid catalysts (Scheme 1a).³ Several widely used name reactions,⁴ including the Arndt-Eistert reaction, the Buchner-Curtius-Schlotterbeck reaction, the Tiffeneau-Demjanov rearrangement, and the Roskamp reaction, are formal C-C bond insertion reactions of diazo compounds with various aldehydes or ketones (also known as homologation reaction) and are believed to proceed via nucleophilic addition of the diazo compounds to the carbonyl compounds followed by rearrangement of the resulting zwitterionic intermediate via TS-1 (Scheme 1a). Despite this considerable progress, most of the above-mentioned reactions involve monocarbonyls as electrophiles.

[*] Y.-Y. Ren, M. Chen, K. Li, Prof. S.-F. Zhu State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University Tianjin 300071 (China) E-mail: sfzhu@nankai.edu.cn

Prof. S.-F. Zhu Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071 (China)

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Scheme 1. Metal-catalyzed reaction of diazo compounds with carbonyl compounds

Although 1,3-diketones are commonly used in organic synthesis, catalytic C-C bond insertion reactions of 1,3-diketones with diazo compounds remain unknown. In 2014, Shi and coworkers⁵ reported that gold-catalyzed reactions of 1,3-diketones and a-aryl diazoesters produce C-H bond insertion products in good yields (Scheme 1b). Herein we report a protocol for a goldcatalyzed formal C-C insertion reaction of aryl diazoesters 1 with 1,3-diketones 2 to form polycarbonyl compounds 3 with an allcarbon quaternary center (Scheme 1c). The aryl ester moiety of the diazoesters plays a key role in the unusual chemoselectivity, and the addition of a Brønsted acid to the reaction mixture improves the yield of the C-C bond insertion product. While we were preparing this manuscript, Bi and coworkers⁶ reported an elegant AgOTf-catalyzed C-C bond insertion reaction of 2-aryl-2diazoacetates with aryl 1,3-ketones 2 (where R¹ or R² is an aryl group). Compared with this silver-catalyzed system, our goldcatalyzed system exhibits higher activity (reaction time: 1 h for gold versus 6 h for silver; catalyst loading: as low as 0.5 mol% for gold versus 10 mol% for silver) and can be extended to alkyl 1,3ketones (where R¹, R², or both are alkyl).

Initially, we studied the reaction of methyl 2-diazo-2phenylacetate and 1,3-diketone **2a** with $(ArO)_3PAuNTf_2$ (Ar = 2,4-^tBu₂C₆H₃) as a catalyst (Table 1, entry 1). As described by Shi and coworkers,⁵ this reaction afforded the C–H insertion product in high yield (83%); however, we also isolated unexpected C–C bond insertion product **3** in 11% yield. To our delight, further experiments revealed that the distribution of the C–H and C–C bond insertion products was strongly affected by the ester moiety

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of the diazo compound (entries 1-7). In particular, the use of an aryl ester substantially increased the ratio of C-C bond insertion to C-H insertion (to >95:5, entries 6 and 7). In addition, the presence of an acidic additive affected both the yield and the product distribution, and the addition of 2 mol% H₃PO₄ increased the C-C insertion product yield to 89% (entries 8-11). The solvent also strongly influenced the outcome of the reaction. The use of CHCl₃ or toluene lowered the yields as well as the selectivity for C-C insertion (entries 12 and 13). The use of Et₂O slightly affected the yield and selectivity but remarkably slowed down the reaction (entry 14). Finally, we explored other metal catalysts that have been successfully used in transformations of diazo compounds. Rh₂(OAc)₄ and Pd(OAc)₂ failed to give the desired product (entries 15 and 16). Cu(PF₆)(MeCN)₄ and AgOTf afforded the desired C-C bond insertion product but in a much lower yield than that obtained with a gold catalyst (entries 17 and 18). It is worth mentioning that the reaction could be performed on a gram scale at a gold catalyst loading as low as 0.5 mol% without compromising the yield or selectivity (entries 19 and 20).



	^O `R	+ O O Ph	2 mol % Ph CH ₂ Cl ₂ , 2	[M] 25 °C ► Ph		⊨0 , Ph	
1		2a			ة ن ا	1	4
Entry	R	[M]	Acid	Solv.	t (h)	3 (%) ^[b]	4 (%) ^[b]
1	Me	[Au] ^[c]	none	CH_2CI_2	1	11	83
2	Et	[Au]	none	CH_2CI_2	0.5	28	50
3	′Pr	[Au]	none	CH ₂ Cl ₂	1	11	38
4	^t Bu	[Au]	none	CH_2CI_2	1	2	37
5	Bn	[Au]	none	CH_2CI_2	0.5	9	50
6	Ph	[Au]	none	CH ₂ Cl ₂	0.5	61	2
7	Ar ^[d]	[Au]	none	CH ₂ Cl ₂	1	71	3
8	Ar	[Au]	PhCO ₂ H	CH_2CI_2	0.5	65	19
9	Ar	[Au]	TsOH	CH_2CI_2	1	73	9
10	Ar	[Au]	(D)-CSA ^[e]	CH_2CI_2	1	74	3
11	Ar	[Au]	H ₃ PO ₄	CH_2CI_2	1	89	4
12	Ar	[Au]	H ₃ PO ₄	CHCl₃	1	65	24
13	Ar	[Au]	H_3PO_4	toluene	12	36	24
14	Ar	[Au]	H_3PO_4	Et ₂ O	12	74	4
15	Ar	Rh ₂ (OAc) ₄	H ₃ PO ₄	CH_2CI_2	0.5	ND ^[f]	ND
16	Ar	Pd(OAc) ₂	H ₃ PO ₄	CH_2CI_2	12	ND	ND
17	Ar	[Cu] ^[g]	H ₃ PO ₄	CH_2CI_2	1	49	2
18	Ar	AgOTf	H ₃ PO ₄	CH_2CI_2	1	30	1
19 ^[h]	Ar	[Au]	H ₃ PO ₄	CH_2CI_2	3	84	3
20 ^[i]	Ar	[Au]	H ₃ PO ₄	CH_2CI_2	12	83	8

[a] Reaction conditions: diazoester 1 (0.2 mmol), **2a** (1.0 mmol), solvent (1.0 mL), [M] (0.004 mmol), acid additive (0.004 mmol), 25 °C. [b] ¹H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c] [Au] is $(ArO)_3PAuNTf_2$, Ar = 2,4-⁴Bu₂C₆H₃. [d] Ar = 2,6-Cl₂C₆H₄. [e] (*D*)-camphorsulfonic acid. [f] Not detected. [g] [Cu] = Cu(PF₆)(MeCN)₄. [h] Performed with 1 mol% catalyst at gram scale (3.3 mmol 1 was used and 1.4 g **3aa** was isolated). [i] Performed with 0.5 mol% catalyst.

We next evaluated the reactivities of various 1,3-diketones with **1a** under the optimal conditions (Scheme 2). First, the effects of substituents on the phenyl groups of the aromatic 1,3-diketones were explored (3aa-3al). We found that the reaction outcome depended strongly on the electronic and steric properties of the phenyl-group substituents. Ketones with electron-donating groups (3aa-3ag, 3ai-3al) gave higher yields than a ketone with an electron-withdrawing group (3ah). Unlike ketones having paraor meta-substituted phenyl groups, more sterically hindered ketones with ortho-substituted phenyl groups failed to give the desired C-C bond insertion products (data not shown). In addition to phenyl-substituted ketones, 1,3-ketones with naphthyl (3am), piperonyl (3an), and thienyl (3ao and 3ap) groups smoothly underwent the C-C bond insertion reactions and gave satisfactory yields. More importantly, we found that even aliphatic 1,3-diketones underwent C-C bond insertion reactions with good yields (3aq-3as, 70-79% yield). It is worth noting that the AgOTfcatalyzed reaction of methyl 2-diazo-2-phenylacetate with a typical aliphatic 1,3-ketone (2q) under the optimal conditions described by Bi and coworkers⁶ gave a poor yield (18%) of the C-C insertion product. The structure of **3ab** was confirmed by means of single-crystal X-ray analysis.7



Scheme 2. Gold(I)-catalyzed formal C–C bond insertion reactions of 2-diazo-2-phenylacetate 1a with various 1,3-diketones 2. The isolated yields were given.

Next, we investigated the effects of the substituents on the Ar group of diazoesters **1b–1h** (Scheme 3). All the tested reactions ran smoothly and generally gave the desired products in good yields. In reactions of aromatic 1,3-diketone **2a**, 2-aryl-2-diazoacetates having *para-* and *meta-*methoxy substituents (**1c** and **1f**) afforded relatively low yields. The reactions of aliphatic

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1,3-diketone **2q** with various 2-aryl-2-diazoesters also ran smoothly but gave lower yields of the C–C bond insertion products (**3bq–3hq**) compared with the corresponding reactions of aromatic 1,3-diketone **2a**.



Scheme 3. Gold(I)-catalyzed formal C–C bond insertion reactions of 2-aryl-2-diazoacetates 1 with 1,3-diketones **2a** or **2q**. The isolated yields were given.



Interestingly, unsymmetrical phenyl alkyl 1,3-diketones 2t–2v were also suitable substrates, giving desired C–C bond insertion

products **3at–3av** in good yields (Scheme 4). The insertion occurred regiospecifically at the alkyl ketone side. Moreover, even an unsymmetrical aryl 1,3-diketone with a strongly electron-withdrawing group (–CF₃) on one of the phenyl rings and a strongly electron-donating group (–OMe) on the other underwent the C–C bond insertion exclusively at the electron-deficient ketone side and produced a single product (**3aw**) in 74% yield. However, the reactions with the 1,3-diketones having two different substituents with similar electron properties (**2x**) exhibited poor regioselectivity. The structures of **3at–3aw** were confirmed by single-crystal X-ray analysis.⁷

1,4-Diketones like the ones generated in this study have diverse potential applications in organic synthesis.⁸ For example, simple treatment of **3aa** with NH₂NH₂·H₂O in EtOH at reflux gave 4,5-dihydro-3(2H)-pyridazinone **5** (81% yield), which is the core structure of various pharmaceuticals⁹ (Scheme 5, eq. a).¹⁰ Furthermore, **3aa** could be readily converted into 5-hydroxy-1,5-dihydro-2H-pyrrol-2-one **6** (in 86% yield), which is also a core structure of several bioactive compounds¹¹ (Scheme 5, eq. b).¹²







Scheme 6. Proposed mechanism

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On the basis of the above-described experimental results and the known reactivity of metal carbenoids,1 we propose the reaction mechanism shown in Scheme 6. The reaction starts with the generation of electrophilic carboncation gold species I via decomposition of 1a promoted by the cationic gold complex.13 Gold carbenoid I then undergoes a cyclopropanation reaction with the enol isomer of the 1,3-diketone to afford cyclopropane intermediate II.¹⁴ The phosphoric acid additive may promote the transformation of the 1,3-diketone to its enol isomer.15 Intermediate II, which is a typical donor-acceptor type cyclopropane, easily undergoes a ring-opening reaction involving a proton transfer.¹⁶ Both bond a and bond b of **II** are polar bonds and can undergo cleavage: cleavage of bond a gives the formal C-C insertion product 3aa, whereas cleavage of bond b gives the formal C-H insertion product 4aa. To gain additional insight into the chemoselectivity, we performed density functional theory calculations on cyclopropane intermediate II at the B3LYP/6-31G* level. (Note that the most stable isomer of this intermediate is shown in Scheme 6; the energies of the other isomers are included in the supplementary information.) Compared with methyl ester III, aryl ester II has a shorter bond b and a slightly longer bond a. The H₃PO₄ additive may further increase the length of bond a of II. It is reasonable to assume that the longer bond, that is, bond a, is more easily broken, to give formal C-C bond insertion product 3aa.

In summary, we have developed a protocol for a goldcatalyzed formal C-C insertion reaction of diazo compounds with 1,3-diketones. Both aryl and alkyl 1,3-diketones smoothly underwent the reaction, and even unsymmetrical diketones bearing substituents with different electronic characteristics gave good yields and excellent selectivities toward the C-C bond insertion. This protocol provides a new method for constructing polycarbonyl compounds with an all-carbon guaternary center, which have a variety of potential applications. A reaction mechanism involving cyclopropanation of a gold carbene with an enolate and ring-opening of the resulting donor-acceptor-type cyclopropane was proposed. The aryl ester moiety and the acidic additive control the ring-opening direction so that the C-C bond insertion product is formed. This mechanism differs from that of the traditional Lewis-acid-catalyzed C-C bond insertion reaction of diazo compounds with monocarbonyl compounds, which involves a rearrangement of a zwitterion intermediate as a key step.

Experimental Section

The (2,4-'Bu₂C₆H₃O)₃PAuNTf₂ (4.5 mg, 0.004 mmol, 2 mol%) and **2a** (224.3 mg, 1.0 mmol) were introduced into an oven-dried Schlenk tube in an argon-filled glovebox. After H₃PO₄ (0.4 mg, 0.004 mmol, 2 mol%) in 0.2 mL CH₂Cl₂ was injected into the Schlenk tube, the mixture was stirred at 25 °C. A solution of **1a** (61.4 mg, 0.2 mmol) in 0.8 mL CH₂Cl₂ was introduced into the mixture in one portion. The reaction accomplished in 1 hour. Then the reaction mixture was concentrated and purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1, *v/v*) to give **3aa** as a white solid.

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Gold-Catalyzed Formal C-C Bond Insertion of α-Aryl Diazoesters with 1,3-Diketones 2 mol% (ArO)₃PAuNTf₂ 2 mol% H₃PO₄ Ar¹ CH₂Cl₂, 25 °C Ar ö_{ci} $Ar = 2,4-{}^{t}Bu_{2}C_{6}H_{3}$ up to 93% yield 0 CI CI A١ CI $Ar^2 = 4 - CF_3C_6H_4$ $Ar^3 = 4-OMeC_6H_4$