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COMMUNICATION

A gold(I)-catalysed chemoselective three-component reaction of phenols, α-diazocarbonyl compounds and allenamides

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Sifan Yu, Jinzhou Chen, Gengxin Liu, Jinping Lei, Wenhao Hu* and Huang Qiu*

Gold(I) catalysts are considered to be efficient in promoting sp^2 C-H bond insertion at para position of unprotected phenols because of the exceptionally chemical reactivity of gold-stabilized carbophilic carbocations. Herein, we present a gold(I)-catalysed three-component reaction of phenols, diazo carbonyl compounds and allenamides, affording the corresponding three-component reaction products with excellent geometric selectivity (E:Z > 20:1) in moderate to high yields (up to 90%) under mild condition. Additionally, a gram-scale transformation and diverse transformations of the resulting product show the high synthetic utility of present three-component protocol.

Due to the importance of phenol motifs in natural products and drug scaffolds,[1] transformations of commercially available and easily obtained simple phenols into their structurally complex derivatives have attracted considerable attention of organic synthetic chemists as well as medicinal chemists.[2-3] Particularly, phenol derivatives that contain a quaternary carbon at oxygen position have shown unique biological activities and receptor binding characteristics to diverse human cancers as well as neurologic diseases (Scheme 1a).[4-6] Thus, developing highly efficient synthetic methods toward these compounds is highly in demand. Transition metal-catalyzed carbene migratory insertion reaction of α-diazocarbonyl compounds into phenolic O-H bonds is among the most versatile, efficient and rapid transformations for synthesis of α-aryloxy carbonyl compounds.[7] An array of typical transition metals (e.g., Rh, Pd, Cu, Fe, Ru) have been proved to be highly selective to the O-H bond insertion,[8] and pioneer works on the asymmetric vision of O-H bond insertion have been achieved by Zhou[8e] and Fu's groups.[9] Very recently, highly selective C(sp^2)−H bond functionalization of unprotected phenols with α-aryl-α-diazoesters at specific position have been extensively explored,[10] and gold catalysts are efficient in promoting C(sp^2)−H bond insertion at para position of unprotected phenols because of the exceptional chemical reactivity of gold-stabilized carbophilic carbocations.[11] Herein, we present a gold(I)-catalyzed O-H selectivity of unprotected phenols and α-diazocarbonyl compounds in the presence of an electrophile (Scheme 1b).

Our research group and others have previously reported a series of novel multicomponent reactions (MCRs) via trapping of reactive intermediates with diverse electrophiles. These novel MCRs have not only provided efficient synthetic methods for the construction of highly polyfunctional organic molecules, but also shed light on the mechanism of their corresponding parent X−H (X = C(sp^2), N, O, S) insertion reactions.[12-14] The rapid development and wide application of these reactive intermediates, especially protic oxonium ylides and zwitterionic intermediates in novel MCRs, have prompted us to consider the chemoselectivity of unprotected phenols with α-aryl-α-diazoesters when electrophiles are added. And following explorations on this topic have resulted in the discovery of a gold(I)-catalysed chemoselective three-component reaction of phenols, α-aryl-α-diazoesters and an allenamide.[15-17]

We initiated our studies with the investigation of the Rh-, Pd-, Cu-, B-, Au-catalyzed three-component reactions of 4-bromo-phenol **1a** and methyl α-phenyl α-diazoacetate **2a** with various electrophiles including imines, aldehydes, isatins, chalcones, α, β-unsaturated γ-keto esters and allenamides. Fortunately, reaction of 4-bromophenol **1a** and methyl α-phenyl α-diazoacetate **2a** with allenamide **3a** in the presence of 5.0 mol% commercially available JohnPhosAu(MeCN)SbF_6 at 25 ℃ in 1,2-dichloroethane (DCE) afforded three-component coupling product **4a** in 36% yield during the course of our explorations of those MCRs (Table 1, entry 1). Other $(C_6F_5)_3B$, Cu(I), Cu(II), Pd(II) and Rh(II) catalysts failed to give **4a** (Table 1, entries 2-8). We further explored the ancillary ligands and

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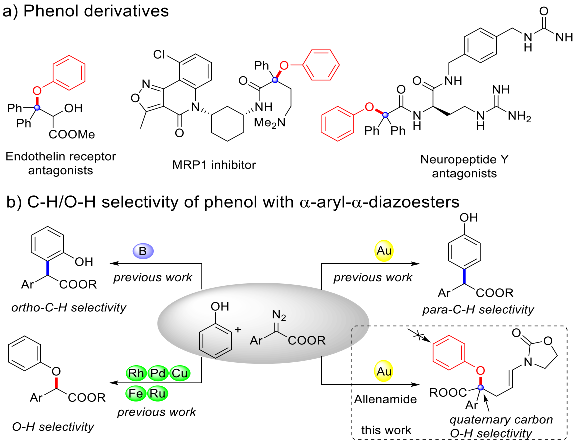
Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China. E-mail: huwh9@mail.sysu.edu.cn; qiuhuang@mail.sysu.edu.cn

† Electronic Supplementary Information (ESI) available: Copies of NMR spectra for all products related to this article; and X-ray single crystal structure analysis data for **4i**. CCDC 1887654. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x



Scheme 1 Phenol derivatives and transformations with various catalysts.

counter anions of the gold catalysts for the three-component reaction (Table 1, entries 10-16). Disappointingly, no enhanced yield of **4a** was obtained. Interestingly, we observed that gold catalysts with different ancillary ligands and counter anions heavily influenced the selectivity of selected reaction, which is in agreement with current reports.[10c] We then explored different solvents for the three-component reaction (Table 1, entries 17-20). Dichloromethane (DCM) was proved to be the best solvent so far, giving **4a** in 69% yield; chloroform ($CHCl_3$) and toluene were capable for this transformation, albeit in lower yield of the product **4a**; whereas tetrahydrofuran (THF) was incompatible with this reaction. Disappointingly, a decrease or increase in temperature failed to improve the yield of this transformation (Table 1, entries 21&22).

With the optimized reaction conditions in hand, we then sought to examine the substrate scope of the present transformation, which was summarized in Table 2. To our delight, simple phenol **1b** was well tolerated in current reaction system and gave **4b** in 66% yield (the para C-H insertion product **14** was also obtained in 12% isolated yield). A range of structurally diverse phenols that contain alkyl-, alkoxy-, aryl-, hydroxyl, ester groups as well as halides at para and / or meta position were proven to be compatible with this reaction, affording the corresponding three-component products in moderate to good yields. Particularly, we were also pleased to find that hydroquinone can be tolerated, furnishing the mono-substituted product **4f**, albeit in 35% yield; Additionally, the structure of **4i** was confirmed by X-ray crystal diffraction analysis (CDCC 1887654). Gratifyingly, estrone was also worked well and successfully afforded **4r** in 62% yield. When sterically hindered ortho-bromophenol was employed, corresponding three-component product **4s** was obtained in synthetically interesting yield (39%). Various α-aryl-α-diazoesters were then screened, furnishing their respective products **4t** – **4y** with excellent geometric selectivity (*E*: *Z* > 20:1) in satisfying yields (64 – 75% yield). α- Aryl-α-diazo ketones reacted with **1a** and **3a** smoothly to afford the corresponding **4z**, **4A** in satisfying yields. Notably, N-tosyl- derived allenes **3b** and **3c** were also suitable substrates, furnishing **4B** and **4C** in 36% and 43% yields, respectively.

Table 1 Optimization of the reaction[a]

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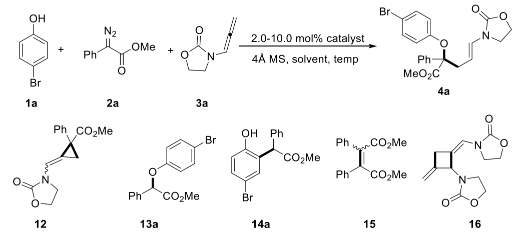

Entry[a]	Catalyst/mol%	Solv.	T./°C	Yield[b]/% of **4a/12/13a/14a/15/16**
1	$L_1Au(MeCN)SbF_6$(5.0)	DCE	25	36/ <5/ 17/ 7/ 14/ 15
2	$(C_6F_5)_3B$(10.0)[c]	DCE	25	<5/ <5/ <5/ 70/ 12/ <5
3	CuI(5.0)[d]	DCE	25	<5/ <5/ <5/ <5/ <5/ <5
4	$Cu(MeCN)_4PF_6$(5.0)[c]	DCE	25	<5/ <5/ 15/ <5/ 40/ <5
5	$Cu(MeCN)_4BF_4$(5.0)[c]	DCE	25	<5/ <5/ 73/ <5/ 9/ <5
6	CuOTf(5.0)[c]	DCE	25	<5/ <5/ 34/ <5/ 25/ <5
7	$[PdCl(allyl)]_2$(5.0)[e]	DCE	25	<5/ <5/ 48/ <5/ 20/ <5
8	$Rh_2(OAc)_4$(2.0)[e]	DCE	25	<5/ <5/ 35/ <5/ 25/ <5
9	PPh_3AuNTf_2(5.0)[f]	DCE	25	<5/ 23/ 21/ 16/ 15/ <5
10	PPh_3AuSbF_6(5.0)[f]	DCE	25	<5/ 35/ 30/ 18/ 9/ 18
11	L_1AuNTf_2(5.0)[f]	DCE	25	33/ <5/ 16/ <5/ 15/ 13
12	L_1AuSbF_6(5.0)[f]	DCE	25	30/ <5/ 15/ <5/ 16/ 11
13	L_2AuNTf_2(5.0)[f]	DCE	25	<5/ 61/ <5/ <5/ 10/ 15
14	L_2AuSbF_6(5.0)[f]	DCE	25	<5/ 54/ <5/ <5/ 15/ 10
15	^{i}PrAuNTf$_2$(5.0)[f]	DCE	25	<5/ 54/ <5/ <5/ 15/ 10
16	^{i}PrAuSbF$_6$(5.0)[f]	DCE	25	<5/ 30/ <5/ 10/ 29/ 22
17	$L_1Au(MeCN)SbF_6$ (5.0)	DCM	25	69(67)[g]/ <5/ 13/ <5/ 10/ 15
18	$L_1Au(MeCN)SbF_6$ (5.0)	PhMe	25	18/ <5/ 14/ <5/ 9/ 16
19	$L_1Au(MeCN)SbF_6$(5.0)	$CHCl_3$	25	50/ <5/ 19/ 8/ 5/ <5
20	L_1Au $(MeCN)SbF_6$(5.0)	THF[h]	25	<5/ <5/ <5/ <5/ 40/ <5
21	$L_1Au(MeCN)SbF_6$(5.0)	DCM	0[h]	50/ <5/ 23/ <5/ 5/ 15
22	$L_1Au(MeCN)SbF_6$(5.0)	DCM	40	42/ <5/ 27/ 7/ 6/ 13

[a]Standard conditions: **1a/2a/3a** = 0.40/0.48/0.48 mmol, **2a** and **3a** in 2.0 mL solvent were introduced by syringe pump to a solution of **1a**, catalyst in 4.0 mL solvent at 25°C under N_2 atmosphere for 1.0 h, and the resulting mixture was stirred for another 2.0 h. L_1 = JohnPhos, L_2 = $(2,4\text{-ditBu}_2C_6H_3O)_3P$. [b]Determined by ^1H NMR spectroscopy analyses using 1, 3, 5-trimethoxybenzene as an internal standard. [c]The resulting mixture was stirred for another 5.0 h. Most of **3a** are unconverted. [d]The resulting mixture was stirred for another 5.0 h. All components are unconverted. [e]The resulting mixture was stirred for another 1.0 h. Most of **1a** and **3a** are unconverted. [f]0.02 mmol L_nAuCl was added in dry DCE (1.0 mL), and then AgX (X = SbF_6, NTf_2) (1.0 equiv) was added. After the mixture was stirred under N_2 atmosphere at 25 °C for 20 min, the precipitation of AgCl was removed by filtration through needle filter. The filtrate was directly used without further purification. [g]Isolated yield. [h]Reaction time is 6.0 h.

To demonstrate the synthetic utility of present protocol (Scheme 2), we have performed a gram-scale three-component reaction of 4-phenylphenol **1g**, methyl α-phenyl-α-diazoester **2a**, and allenamide **3a** in the presence of reduced catalyst loading (4.0 mol % JohnPhosAu(MeCN)SbF_6) at 25 ℃ in DCM for2.0 h, affording **4g** in satisfactory yield (1.11 g, 84% yield). When treated with H_2 in the presence of Pd/C, **4g** could easily be reduced to the corresponding product **5** in 78% yield; $LiBH_4$ enabled an efficient access to alcohol product **6** in 85% yield, respectively. Furthermore, treatment of **4g** with LiOH solution and subsequent 6.0 N HCl solution afforded **7** that contains a formyl and carboxyl group in 80% yield. Treatment of **4g** with 6N HCl afforded enamine hydrolysis product **8** in 88% yield, while in the presence of methanol, **4g** underwent a subsequent enamine hydrolysis / acetalisation process and afforded acetal

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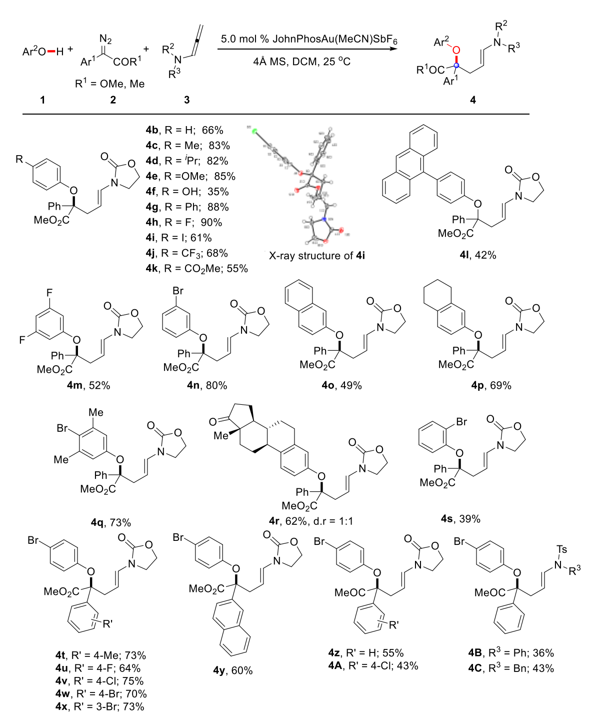
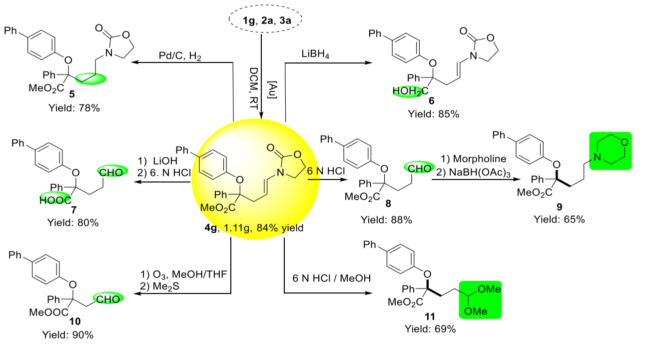
Table 2 Substrate scope[a]



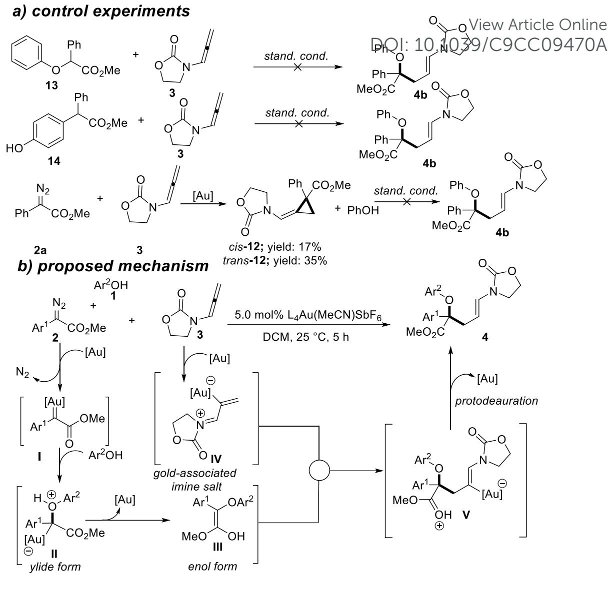
[a] Reaction condition same as Table 1, entry 17.

11 in 69% yield. Moreover, product **8** could be readily converted into corresponding amine **9** in 65% yield though reductive amination. Remarkably, ozonolysis of **4g** and subsequent reductive work-up successfully furnished **10** in 90% yield.

To gain more mechanistic insights of present three-component reactions, further control experiments were performed (Scheme 3a). Firstly, treatment of either O-H insertion product or C-H insertion product of with allenamide **3** under optimized reaction conditions failed to afford detectable three component reaction product **4b**. The cyclopropane **12** was also a possible intermediate, which might undergo a ring-opening process with phenol to furnish the observed product. To clarify this issue, we successfully prepared both trans- and cis-cyclopropane **12** by treating allenamide **3** with methyl phenyldiazoacetate **2a** in the presence of 5.0 mol % JohnPhosAu(MeCN)SbF$_6$. However, upon addition of phenol **1b**, three-component product **4b** was not observed under standard reaction conditions by LC-MS or ^{1}HNMR. These control reactions excluded the possibility that the multicomponent reaction products were formed from the addition of the O-H insertion product **13** or C-H insertion product **14** to **3** or the cyclopropane **12** ring-opening transformations with phenol **1b** by a stepwise process. With these control experiments in hand, we proposed a plausible mechanism for this three-component reaction, which was shown in Scheme 3b. The reaction proceeded through Au(I)-associated protic oxonium ylide intermediate **II**, which was generated from gold carbene **I** and phenols **1**. Dissociation of the gold catalyst from **II** afforded enol intermediate **III**. Subsequently, **III** reacted with electrophilic gold-associated iminium salt **IV**,[17] affording key intermediate **V**, which further underwent protodeauration to give observed three-component product **4**.



Scheme 2 Gram-scale reaction and synthetic applications of **4g**



Scheme 3 Control experiments and proposed mechanism.

In order to further understand the chemoselectivity and validate the proposed mechanism of this three-component reaction, we performed DFT calculations for the O-H and C-H reactions, which was shown in Fig. 1. These results indicated that the three-component reaction dominantly proceeded with the O-H insertion pathway, because the free energy barrier for the O-H insertion (6.06 kcal/mol) was significantly much lower than the C-H insertion (22.14 kcal/mol). And the C-H insertion in three-component reaction was unfavored because of the high energy barrier. While for the two-component reactions, both the O-H and C-H insertions were possible, and the O-H insertion is only slightly more favored than the C-H insertion. These calculation results agreed well with the controlled experimental observations, in which the yields of the **Pro-O**:**Pro-C** (O-H:C-H product) increased from 51%:34% in two-component to about 66%:0% in three-component reactions.

In summary, we have disclosed a gold-catalyzed chemoselective three-component reaction of phenols, α-diazocarbonyl compounds and allenamides under mild reaction conditions. The present transformation can be very easily scaled up and shows high functional group tolerance. Furthermore, in the presence of easily obtained simple reagents, corresponding three-component product can be readily transformed into diverse products that contain versatile functional groups (e.g. hydroxyl, formyl, carboxyl, acetal) in satisfying yields. Work

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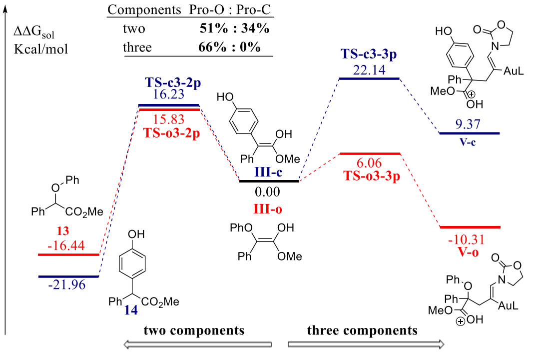

Fig 1 The chemoselectivity of the three and two component reactions of phenol. All values of free energies are related to the enol intermediates of the O-H (III-o) and C-H (III-c) insertion reactions. TS: transition state, pro-O: product of the O-H process, pro-C: product of C-H process. The transition state structures are shown in Fig. S4. Phenol derivatives and transformations with various catalysts.

toward expanding the scope of the multicomponent reactions with allenamides as the electrophile (3rd component) under the catalysis of π-acid complexes and investigations toward the biological activities of these phenol derivatives are currently ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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