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Gold(I)-Catalyzed Hydroxy Group Assisted C(sp^2)−H Alkylation of Enaminones with Diazo Compounds To Access 3-Alkyl Chromones

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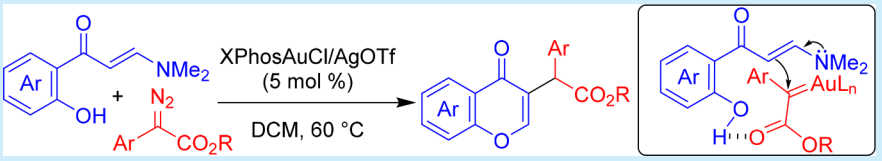
Supporting Information

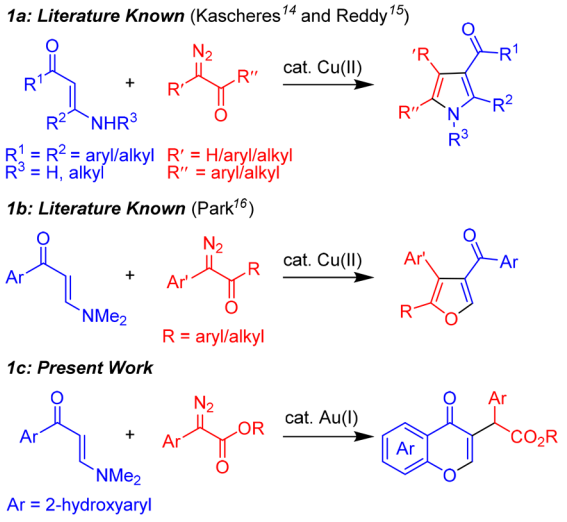


ABSTRACT: A strategy for expedient synthesis of 3-substituted chromones from easily available *o*-hydroxyarylenaminones and diazo compounds has been developed. Carefully conducted experimental and computational studies led us to propose an uncommon mechanistic pathway involving the hydroxyl group assisted alkylation of enaminones with *in situ* generated gold carbenes.

Transition metal catalyzed carbene transfer reactions that employ diazo reagents are powerful tools in organic synthesis. Catalysts based on rhodium[1] and copper[2] have been particularly effective, but gold has emerged as an interesting alternative, recently.[3] The reactivity observed with gold catalysts is unique, and selectivities were observed that were not possible with other metals. Moreover, these reactions are convenient because they can be conducted without syringe pumps, which are generally recommended in conventional carbene transfer chemistry. The very first example of a gold-catalyzed carbene transfer reaction of ethyl diazoacetate was reported by Nolan.[4] Since then, several remarkable efforts have been made including N−H/O−H insertions,[4,5] C−H functionalizations,[6] cyclopropanations,[7] cyclopropenations,[8] cycloadditions,[9] cross-couplings,[10] rearrangements,[11] and others.[12]

Enaminones have recently been recognized as versatile and valuable intermediates because of the ambident nucleophilic and electrophilic characters of the enamine and enone moieties, respectively, which was utilized by many researchers for accessing biologically important heterocycles.[13] As far as the reactions of enaminones with diazoketones are concerned, Kascheres and co-workers were the first to utilize the carbene transfer strategy for accessing *N*-substituted pyrroles by reacting the enaminones with diazoketones (Scheme 1a).[14] A similar strategy was disclosed by Reddy and co-workers to obtain pyrroles (Scheme 1a).[15] In 2012, Park demonstrated the carbene mediated cycloaddition of enaminones with diazo reagents to obtain multiply substituted furans (Scheme 1b).[16] Herein, we report the reaction of *o*-hydroxyarylenaminones with diazo compounds using a gold catalyst to obtain functionalized chromones[17]—the structural motif found in

Scheme 1. Reaction of Enaminones with Diazo Compounds: Known and Present Work



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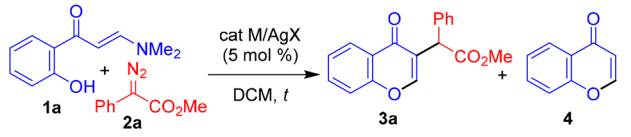
numerous natural products[18] and pharmaceutically important targets[19] (Scheme 1c). The mechanism of the reaction was established by carefully conducted experimental and computational studies. We propose that the reaction is triggered by a hydroxyl assisted C(sp^2)−H alkylation of enaminones. To date, there are only selected examples of a reaction where an acyclic enamine/enaminone engages a gold carbene, which was generated *in situ* from α-diazo compounds in the presence of a gold catalyst.[6h,12a]

At the outset, we utilized (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)-prop-2-en-1-one (**1a**) and methyl phenyldiazoacetate (**2a**) as model substrates to test our hypothesis. First, the utilization of $Ph_3PAuNTf_2$ (5 mol %) furnished methyl 2-(4-oxo-4*H*-chromen-3-yl)-2-phenylacetate (**3a**) in 14% yield with formation of undesired 4*H*-chromen-4-one (**4**) in 30% yield at 25 °C in dichloromethane (Table 1, entry 1). Next, a variety of gold catalysts were examined (entries 2−6). Gratifyingly, $XPhosAuNTf_2$ was found to be the best catalyst giving **3a** in 43% yield along with undesired **4** in 11% yield (entry 6). The yield of desired product **3a** was enhanced remarkably when the reaction was carried out at 60 °C, giving **3a** in 62% yield (entry 7). Next, various silver salts were screened in combination with XPhosAuCl. The use of $AgSbF_6$ and $AgBF_4$ did not improve the yield of the reaction (entries 8 and 9). However, the use of AgOTf furnished **3a** in 76% yield (entry 10) with the complete exclusion of undesired **4**. Switching the solvent to DCE, tetrahydrofuran, toluene, and acetonitrile did not produce any remarkable change to the reaction outcome.[20] The use of AgOTf alone gave the undesired **4** in 32% yield, and the dimerization of **2a** was the major product (entry 11). The catalytic efficiency of other catalysts, which are conventionally known for carbene transfer reactions, was thoroughly investigated.[21] For instance, when $Cu(CH_3CN)_4BF_4$ was used as a catalyst, **3a** was obtained only in 36% yield (entry 12). On the other hand, the use of $Rh_2(OAc)_4$ did not give **3a**; instead, the decomposition of **2a** was noticed (entry 13). Further, lowering of the catalyst loading to 3 mol % had a detrimental effect on the yield of the reaction (entry 14). In the absence of XPhosAuCl/AgOTf, no product was obtained indicating its importance (entry 15).

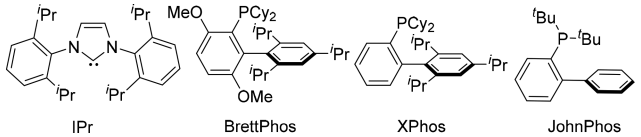
With an effective catalyst system identified, the substrate scope was explored (Scheme 2). For instance, substrates bearing alkyl and aryl substituents such as −Me and −Ph gave access to 3-alkyl chromones **3b** and **3c** in 76% and 73% yields, respectively. Various halo substituents on the phenyl ring did not affect the yield of the reaction (**3d**−**3f**), enabling the possibility for introduction of versatile functional groups *via* metal catalyzed cross-coupling reactions. The X-ray crystallography data for **3d** (**5i**, *vide infra*) have been obtained which unequivocally confirmed the structure.[20] It was found that substrates with electron-withdrawing substituents (acyl, −CN, $-NO_2$) at the *para*-position of the −OH group gave lower yields (**3h**−**3j**); whereas, substrates bearing an electron-donating substituent (−OMe) at the *para*-position of −OH group afforded a higher yield (**3g**, 80%). However, the *o*-hydroxyarylenaminones possessing alkyl (−Me), electron donating (−OMe) and halo (−F, −Br, −I) substituents at the *para*-position of the keto group gave **3k**−**3o** in 64−73%

Table 1. Optimization Studies[a]

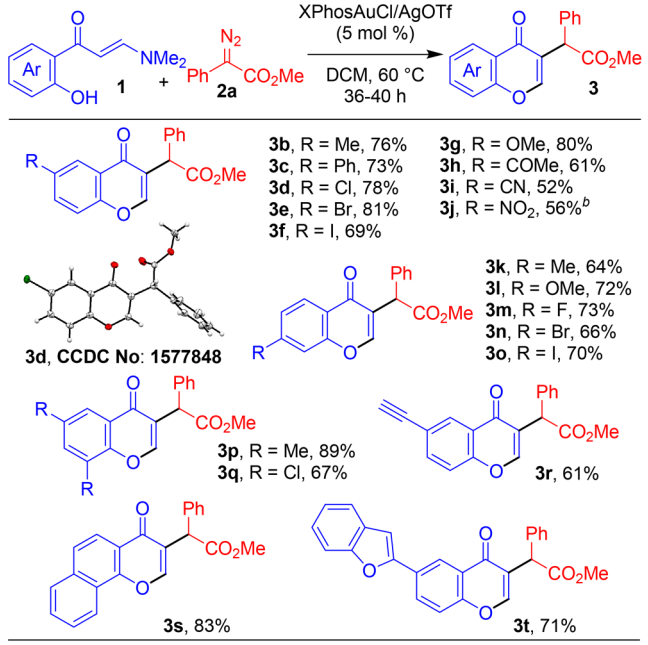


entry no.	cat M 5 mol %	AgX 5 mol %	t (°C)	yield (%)[b] 3a	4
1	Ph_3PAuCl	$AgNTf_2$	25	14	30
2	IPrAuCl	$AgNTf_2$	25	16	25
3	JohnPhosAuCl	$AgNTf_2$	25	–	22
4	CyJohnPhosAuCl	$AgNTf_2$	25	–	29
5	BrettPhosAuCl	$AgNTf_2$	25	26	28
6	XPhosAuCl	$AgNTf_2$	25	43	11
7	XPhosAuCl	$AgNTf_2$	60	62	15
8	XPhosAuCl	$AgSbF_6$	60	51	13
9	XPhosAuCl	$AgBF_4$	60	45	12
10	**XPhosAuCl**	**AgOTf**	**60**	**76**	–
11	–	AgOTf	60	–[c]	32
12[d]	$Cu(CH_3CN)_4BF_4$	–	30	36[e]	29
13[d]	$Rh_2(OAc)_4$	–	30	–[e]	–
14[f]	XPhosAuCl	AgOTf	60	59	–
15	–	–	60	–[g]	–

[a]Reaction conditions: 0.15 mmol of **1a**, 0.23 mmol of **2a**, catalyst (entries 1−10, 5 mol % Au(I) catalyst, 5 mol % Ag(I) catalyst; entries 11−13, 5 mol % respective metal catalyst), DCM (1 mL), 36 h (reaction was performed in a sealed tube). [b]Isolated yields (based on **1a**). [c]Dimerized product of **2a** was observed in 56% (based on **2a**). [d]Controlled addition of **2a** (0.23 mmol) in dry DCM (0.5 mL) was performed *via* syringe pump over 1 h. [e]Decomposition of **2a** was observed within 6−8 h. [f]3 mol % XPhosAuCl and 3 mol % AgOTf were used. [g]Starting materials **1a** and **2a** recovered quantitatively.



Scheme 2. Substrate Scope with *o*-Hydroxyarylenaminones[a]



[a]Reaction conditions: 0.15 mmol of **1**, 0.23 mmol of **2a**, 5 mol % XPhosAuCl, 5 mol % AgOTf, DCM (1 mL), 60 °C, 36−40 h. [b]Reaction was completed within 12 h.

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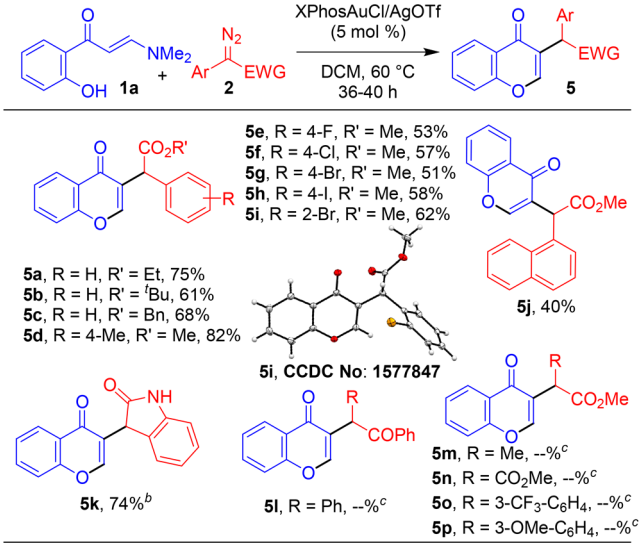
yields. Even the disubstituted *o*-hydroxyarylenaminones gave the corresponding 3-alkyl chromones in good yields (**3p**, 89%; **3q**, 67%). The reaction of the *o*-hydroxyarylenaminones equipped with an alkyne substituent gave 3-alkyl chromone **3r** without formation of any side product via cyclopropenation.[7] A fused analogue of chromone (**3s**) was also obtained in 83% yield, when respective *o*-hydroxyarylenaminones were subjected to the standard reaction conditions. The benzofuran appended substrate produced **3t** in 71% yield. Notably, a potential side product as a result of C3-functionalization of benzofuran was not observed.[11a]

Next, the scope and limitation of diazo compounds (**2**) were examined (Scheme 3). As expected, reactions of diazo ester

Scheme 3. Substrate Scope with Diazo Compounds[a]

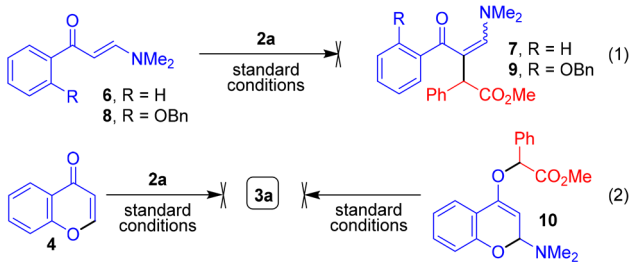


[a]Reaction conditions: 0.15 mmol of **1a**, 0.23 mmol of **2**, 5 mol % XPhosAuCl, 5 mol % AgOTf, DCM (1 mL), 60 °C, 36−40 h. [b]Reaction completed within 8 h. [c]The starting material **1a** was recovered quantitatively.

comprising ethyl, *tert*-butyl, and benzyl groups instead of the methyl group maintained the same reaction profile giving **5a**−**5c** in good yields (61%−75%). A diazo compound bearing an alkyl substituent such as −Me on the aromatic group reacted smoothly to give **5d** in 82% yield. Moreover, halide substituents had no significant effect on the outcome of the reaction giving **5e**−**5i** in yields ranging from 51% to 62%. The reaction of the diazo ester bearing a bulkier naphth-1-yl group probably succumbed to its steric effects giving a lower yield of the desired 3-alkyl chromone **5j** (40%). In addition to *α*-diazo esters, other diazo compounds including diazo-oxindole, dimethyl-2-diazomalonate, and *α*-diazo ketone were also examined. Among them, diazo-oxindole provided **5k** in 74% yield; whereas, *α*-diazo ketones (cf. **5l**), alkyl diazo ester (cf. **5m**), and dimethyl-2-diazomalonate (cf. **5n**) failed to react. Surprisingly, 3-substituted aryldiazoacetates were found to be inert under the present reaction conditions (cf. **5o** and **5p**).

To better understand the mechanism, a few control experiments were conducted (Scheme 4). When the reaction of phenylenaminone (**6**) with **2a** was performed under the standard reaction conditions, the expected product **7** was not obtained at all (eq 1). Similarly, the anticipated product **9** was not obtained when the benzyl protected substrate **8** was

Scheme 4. Mechanistic Studies



reacted with **2a** (eq 1). These experiments suggest that the C-alkylation of enaminones is assisted by the hydroxyl group on the aryl moiety. It is also possible that **4** is generated first and undergoes alkylation with **2a** in the presence of the gold catalyst. However, substrate **4** failed to provide **3a** under the established reaction conditions (eq 2, left side) which renders this possibility unlikely. Alternatively, the reaction might involve the *o*-alkylation in **1a** via gold-catalyzed carbene transfer to produce intermediate **10** which may spontaneously undergo a 1,3 alkyl shift[22] followed by loss of *N,N*-dimethylamine to form **3a**. To test for this mechanistic pathway, substrate **10** was prepared by NaH mediated reaction of **1a** with methyl 2-bromo-2-phenylacetate in THF.[20] However, failure of **10** to produce **3a** under the optimized reaction conditions clearly ruled out this possibility (eq 2, right side).

To conceptualize these observations into a complete catalytic cycle, quantum chemical calculations based on density functional theory (DFT) were carried out (Figure 1). The reaction leading to the formation of the key intermediate **11** is explained in the Supporting Information (see Figure S1). As shown in Figure 1, **11** can readily engage in a nucleophilic attack at the gold carbene[23] moiety to afford **12**, in a step that is very viable with an associated barrier of only 3.8 kcal/mol. To push the reaction forward, a proton transfer from the hydroxyl group to the carbene moiety is required. This is accomplished in a stepwise fashion, where the gold complex migrates first to bind to the carbonyl oxygen of the ester functionality, forming intermediate **13**. Now the carbon site is available for proton transfer, while the freshly formed phenoxide moiety will engage the metal fragment to give the stable intermediate **14**, traversing the **13-TS** with a barrier of 14.5 kcal/mol. Then, the proton migration from the C(sp^3)−H to the oxygen of the O−AuL_n fragment generates **15**, which is 5.1 kcal/mol higher in energy than **14**. The transition state **14-TS** connecting these two intermediates gives rise to a barrier of 9.9 kcal/mol. In order to initiate the final cyclization reaction, another proton transfer to the amine functionality takes place to form **16**, which is finally ready to undergo intramolecular cyclization to give the final product **3a** via spontaneous loss of *N,N*-dimethylamine with regeneration of the gold catalyst ($LnAu^+$). The overall free energy barrier for this ring formation step is computed to be 30.2 kcal/mol. This mechanism incorporated the experimental observations; most notably, it clarifies the importance of the hydroxyl group during the C(sp^2)−H alkylation of enaminones.

To demonstrate the synthetic potential of the reaction, the intramolecular Heck reaction[24] of **5i** under $Pd(OAc)_2$/JohnPhos catalysis was conducted (Scheme 5). Pleasingly, the biologically important rigid flavone **17** was obtained in 66% yield.[25]

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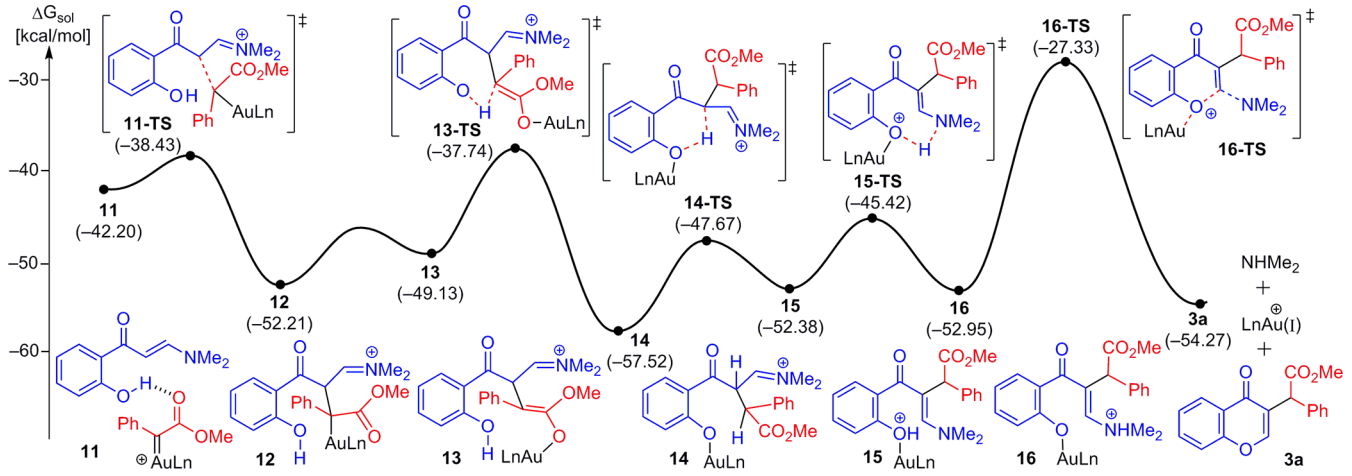
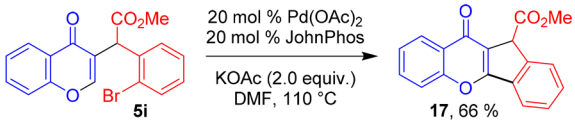


Figure 1. Free energy profile for the formation of **3a**.

Scheme 5. Product Modification



In summary, gold-catalyzed reactions of *o*-hydroxyarylenaminones with diazo compounds have been explored. The combined experimental and computational mechanistic studies led us to propose a mechanistic pathway involving the hydroxyl group assisted C(sp^2)−H alkylation of enaminones with diazo compounds. The idea of directing group assisted carbene transfer reactions in gold catalysis should be applicable to a vast number of substrates leading to a number of new reactivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03989.

All experimental procedure, analytical data, and copies of ^{1}H, ^{13}C NMR spectra of all newly synthesized products, and X-ray data for **3d**, **5i** and computational details (PDF)

Accession Codes

CCDC 1577847−1577848 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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