

Stereoselective Synthesis of Tetrasubstituted Furylalkenes via Gold-Catalyzed Cross-Coupling of Enynones with Diazo Compounds

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Supporting Information

ABSTRACT: A stereoselective, gold-catalyzed, cross-coupling reaction of enynones with diazo compounds has been developed, affording 2-alkenylfurans in moderate to good yields with excellent *E*-stereoselectivity. Upon using diazo compounds as nucleophiles to trap the in situ formed gold furyl carbene, this protocol provides a novel path toward the formation of unsymmetrical tetrasubstituted alkenes.

T ransition-metal-catalyzed cross-coupling reaction of two diazo moieties represents an important protocol in constructing carbon-carbon double bonds.^{1,2} Typically, this reaction involves the initial generation of electrophilic metal-carbene species followed by nucleophilic attack by another diazo reagent to give the bond formation (Scheme 1a). In the past

Scheme 1. Olefin Formation Involving Metal–Carbene Species: Previous Reports and Our Strategy



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decades, the cross-coupling reactions between acceptor-H/ acceptor-H, acceptor-H/donor-H, acceptor-H/acceptordonor, and acceptor-donor/acceptor-donor diazo compounds have been well investigated, providing an interesting way to access di-, tri-, and tetrasubstituted alkenes.^{1,2} However, some unavoidable limitations still exist with respect to reaction stereoselectivity as well as scope of diazo compounds (Scheme 1a). Nevertheless, the competition between cross-coupling versus homocoupling processes often leads to low efficiency. A breakthrough was made by Davies and co-workers,³ who reported an elegant rhodium-catalyzed cross-coupling reaction of diazo compounds to prepare trisubstituted alkenes. Later, our group successfully developed a gold-catalyzed protocol to synthesize unsymmetrical tetrasubstituted alkenes.^{4a} Alternatively, using diazo compounds as the key partners, chemists developed useful methodologies to prepare functionalized alkenes by coupling with other readily available substrates.⁵ Despite these advances, the chemoselective and stereoselective synthesis of tetrasubstituted alkenes still remains underdeveloped.

Recently, López and Vicente reported ZnCl₂-catalyzed crosscoupling reactions of enynones with diazoacetates/vinyl diazoacetates to generate 2-alkenylfurans containing trisubstituted olefin moieties in moderate to good stereoselectivities (Scheme 1b).⁶ However, they mentioned that this approach was not applicable for phenyl diazoacetates.^{6a} Namely, the synthesis of tetrasubstituted alkenes cannot be accomplished via their protocol. In connection with our research interest in olefin formation through metal-catalyzed diazo cross-coupling reactions,⁴ we conceived that gold-catalyzed cross-coupling of enynones with donor/acceptor diazo compounds would probably result in the formation of tetrasubstituted alkenes (Scheme 1c). If possible, this reaction would significantly expand the scope of such carbene involved olefin formation.

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Table 1. Optimization of the Reaction Conditions^a



entry	cat.	additive (mol %)	solvent	yield (%) ^b 3aa/1a'/2a'
1	Ph ₃ PAuCl	$AgSbF_6(5)$	CH_2Cl_2	10/-/-
2	JohnPhosAuCl	$AgSbF_6(5)$	CH_2Cl_2	34/8/0
3	XPhosAuCl	$AgSbF_6(5)$	CH_2Cl_2	38/15/<5
4	^t BuXPhosAuCl	$AgSbF_6(5)$	CH_2Cl_2	30/11/<5
5	XantPhos(AuCl) ₂	$AgSbF_6(10)$	CH_2Cl_2	68/6/<5
6	$(2,4-^{t}Bu_{2}C_{6}H_{3}O)_{3}PAuCl$	$AgSbF_6(5)$	CH_2Cl_2	7/—/—
7	IPrAuCl	$AgSbF_6(5)$	CH_2Cl_2	51/21/6
8	XantPhos(AuCl) ₂	AgOTf(10)	CH_2Cl_2	56/12/<5
9	Xantphos(AuCl) ₂	$AgNTf_2(10)$	CH_2Cl_2	68/13/<5
10	XantPhos(AuCl) ₂	$AgBF_4(10)$	CH_2Cl_2	75/6/<5
11	XantPhos(AuCl) ₂	$NaBAr_{F}(10)$	CH_2Cl_2	66/7/<5
12	XantPhos(AuCl) ₂		CH_2Cl_2	5/-/-
13		$AgBF_4(10)$	CH_2Cl_2	
14	XantPhos(AuCl) ₂	$AgBF_4(10)$	DCE	70/14/10
15	XantPhos(AuCl) ₂	$AgBF_4(10)$	THF	61/12/6
16	XantPhos(AuCl) ₂	$AgBF_4(10)$	toluene	68/13/11
17	XantPhos(AuCl) ₂	$AgBF_4(10)$	dioxane	55/12/13
18	CuBr		CH_2Cl_2	33/16/<5
19	CuCl		CH_2Cl_2	25/18/0
20	$Rh_2(OAc)_4$		CH_2Cl_2	
21	$Rh_2(Oct)_4$		CH_2Cl_2	
22	$Rh_2(esp)_2$		CH_2Cl_2	

^{*a*}The reactions were carried out with **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (5 mol %), and additive (5 or 10 mol %) in solvent (5 mL) at rt for 1 h. ^{*b*}Isolated yields.



Recently, metal-carbenes generated in situ from enynones have been widely employed in various transformations. Inspired by the former reports, at the outset, we utilized envnone 1a and phenyl diazoacetate 2a as model substrates to investigate the optimal reaction conditions (Table 1). The reactions were initially performed in dichloromethane at room temperature. First, utilization of Ph₃PAuCl/AgSbF₆ (5 mol %) furnished cross-coupling product 3aa in 10% yield (entry 1). Replacing gold catalyst with JohnPhosAuCl, XPhosAuCl, and ^tBuXPhosAuCl slightly improved the reaction (entries 2-4). The homocoupling product 1a' was isolated in nearly 10% yield. Gratifyingly, when XantPhos(AuCl)₂ was used, 68% yield of 3aa was isolated associated with 6% yield of 1a' (entry 5). However, more electron-deficient phosphinate gold catalyst was inert to this reaction (entry 6). Next, the use of IPrAuCl/AgSbF₆ delivered 3aa in 51% yield together with 21% yield of 1a' (entry 7). By using XantPhos(AuCl)₂ as the gold catalyst, the silver salts were then screened. The use of AgOTf and AgNTf₂

did not improve the reaction (entries 8 and 9). To our delight, the addition of $AgBF_4$ furnished **3aa** in 75% yield with *E*configuration associated with trace amount of homocoupling products **1a'** and **2a'** (entry 10). The combination of XantPhos(AuCl)₂ with NaBAr_F gave **3aa** in 66% yield (entry 11). Both gold complex and silver salt played crucial role in the reaction (entries 12 and 13). Moreover, other solvents such as 1,2-dichloroethane (DCE), tetrahydrofuran (THF), toluene and dioxane are not suitable to the reaction (entries 14–17). Furthermore, the use of copper catalysts led to very low yield (entries 18 and 19), whereas rhodium catalysts were totally inert in this reaction (entries 20–22).

With the optimal conditions in hand, we next explored the scope of diazo compounds (Scheme 2). First, the reaction of enynone **1a** with an array of aryl diazoacetates was examined. Both electron-rich and electron-deficient aryl diazo compounds were tolerated, providing the corresponding products in moderate to good yields, although *o*-methyl phenyl diazoacetate

Scheme 2. Substrate Scope for Diazo Compounds^{a-c}



"All reactions were performed with 1a (0.2 mmol), 2 (0.22 mmol), XantPhos(AuCl)₂ (5 mol %), and AgBF₄ (10 mol %) in CH₂Cl₂ (5 mL) at rt for 1 h. ^bIsolated yields. ^cThe products were isolated in single isomer.

gave 3ac only in 31% yield. The use of thiophene diazoacetate produced 3ah in 63% yield. Gratifyingly, alkyl diazoacetates were also suitable substrates, and the desired 2-alkenylfurans were obtained in 64% yield (3ai) and 51% yield (3aj), respectively. In contrast, alkyl diazoacetates are not appropriate in metalcatalyzed diazo cross-coupling reactions.¹⁻⁴ Furthermore, benzoyl diazo compound was also applicable in this reaction, and the desired product 3ak was isolated in 48% yield. Notably, the reaction of 1a with phenyl vinyl diazoacetate delivered diene **3al** in 64% yield. The double bonds formed in the α -position rather than γ -position to the carboxylic ester, which was quite different with the zinc-catalyzed reaction of vinyl diazoacetate with enynones.^{6a} It also should be noted that the reaction is stereoselective. All of the alkene moieties were obtained in excellent E-configuration. The structures of 3ae, 3ak, and 3al were confirmed by X-ray analysis.⁸

Next, the reaction of various enynones with phenyl diazoacetate 2a was carried out (Scheme 3). The use of enynones substituted with alkyl groups (1b and 1c) furnished 2-alkenylfurans 3ba and 3ca in 69% and 70% yield, respectively. Enynone 1d bearing terminal alkyne was tolerated and the corresponding product 3da was isolated in 52% yield. The

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^{*a*}All reactions were performed with 1a (0.2 mmol), 2 (0.22 mmol), XantPhos(AuCl)₂ (5 mol %), and AgBF₄ (10 mol %) in CH₂Cl₂ (5 mL) at rt for 1 h. ^{*b*}Isolated yields. ^{*c*}The products were isolated in single isomer.

reaction of enynones **1e** and **1f** with **2a** also proceeded smoothly to produce the final products in moderate yields.

Our previous work disclosed that the metal-catalyzed coupling of donor/donor diazo compounds did not yield alkenes but symmetrical azines.⁹ When donor/donor diazo compounds **4a** and **4b** were subjected to this gold-catalyzed protocol, the expected 2-alkenylfurans were not obtained. Instead, unsymmetrical azines **5aa** and **5ab** were isolated in moderate yields (Scheme 4), which provided an interesting approach toward unsymmetrical azines.

Scheme 4. Reaction of Enynone with Donor/Donor Diazo Compounds



Different reaction mechanisms for the formation of 2alkenylfurans and azines have been proposed (Scheme 5). The reaction of enynone 1a with gold catalyst generates gold– carbene species I,^{7c,h} which undergoes carbon nucleophilic attack by 2a to give gold intermediate II with a newly formed C–C bond. Subsequent extrusion of N₂ and deauration provides the final product 3aa with tetrasubstituted olefins. In contrast, the nitrogen nucleophilic attack of 4a to gold–carbene delivers gold intermediate III with C–N bond formation, which followed by deauration to give rise to azine 5aa. Moreover, for the high stereoselectivity of olefins, a possible explanation is transition state-I (TS-I) might be the most stable one than TS-II and TS-III, which led to the preferential formation of *E*-configuration.

Scheme 5. Proposed Reaction Mechanisms



In summary, we have developed a novel gold-catalyzed crosscoupling reaction of enynones and diazo compounds. The corresponding 2-alkenylfurans bearing tetrasubstituted alkenes were obtained in moderate to good yields with excellent stereoselectivity. Typically, these unsymmetrical tetrasubstituted alkenes cannot be easily accomplished by other approaches.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01467.

Experimental procedures, characterization data, and NMR spectra (PDF)

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The authors declare no competing financial interest.

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