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Communications

Palladium-Catalyzed Carboauration of Alkynes and Palladium/Gold Cross-Coupling

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Summary: A new palladium-catalyzed syn carboauration of alkynes proceeds in 2 h at ambient temperature with complete regioselectivity. The resulting α -ester vinyl—gold intermediates are resistant to rapid protodemetalation, permitting their participation in new one-pot palladium-and-gold cross-coupling reactions and electrophilic trapping reactions.

Recently, transient vinyl–gold intermediates have been reported to participate in a variety of intramolecular trapping and rearrangement reactions.^{1–3} Carboauration of alkynes offers an attractive possibility for accessing vinyl–gold intermediates from readily available starting materials; however, the uncatalyzed intermolecular carborauration of alkynes requires multipleweek reaction times and Puddephatt reports it for only one substrate, bis(trifluoromethyl)acetylene.^{4,5} A general intermolecular carboauration in coupling and functionalization reactions for the synthesis of regiochemically and diasteromerically pure di- and trisubstituted olefins. As part of our ongoing work employing the unique reactivity of two metals to develop dual-catalyzed reactions,^{6–8} we now report a new Pd-catalyzed carborauration of alkynes that proceeds in 2 h at ambient

Table 1. Effect of Catalyst Composition on Product ¹H NMR Yield^a

MeO₂C—≡	≡—CO₂Me	$\begin{array}{c} PPh_{3}Au \\ \hline \\ cat. 5 mol \% \\ CD_{2}Cl_{2}, 2 h \end{array}$	MeO ₂ C	AuPPh ₃ ={ CO ₂ Me	
entry	cat.		¹ H NMR yield (%)		
1	$Pd_2(dba)_3$		trace		
2	Pd(PPh ₃) ₄		5		
3	PdCl ₂ (1	PdCl ₂ (PPh ₃) ₂		73	
4	none	none		0	
5^b	$BF_3 \cdot OMe_2$		0		
6^b	Sc(OT)	Sc(OTf) ₃		0	
7^b	PPh ₃ AuPF ₆		0		

^a Relative to mesitylene internal standard. ^b Conditions: 20% catalyst.

temperature with complete regioselectivity and diastereoselectivity for the product of syn addition.

Treatment of dimethyl acetylenedicarboxylate (DMAD) with vinyl(triphenylphosphine)gold⁹ in the presence of 5 mol % of PdCl₂(PPh₃)₂ gave the carboaurated product **1** in 73% ¹H NMR yield (Table 1, entry 3). Palladium was required for conversion; in its absence, **1** was not produced. We considered the

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Table 2. Scope of the Pd-Catalyzed Carboauration Reaction

MeO ₂ C− 1.0 ¢	─ <u>─</u> ─R ¹ + equiv	PPh ₃ AuR ² – 1.0 equiv	Pd cat. 5 mol % 25 °C, 2 h	MeO ₂ C Ph ₃ PAu	R ¹ =∕ R²
Entry	R ¹	\mathbb{R}^2	Pd cat.	(¹ H NMR Yie Isolated Yiel	ld) ^a ld
1	CO ₂ Me	vinyl	(PPh ₃) ₂ PdCl ₂	(73) 51	1
2	Н	vinyl	(PPh ₃) ₂ PdCl ₂	(100) 84	2
3	CO ₂ Me	Ph	Pd ₂ (dba) ₃	(86) 61	3
4	Н	Ph	(PPh ₃) ₂ PdCl ₂	(89) 62	4
5	Me	Ph	Pd ₂ (dba) ₃	(66) 49	5^{b}
6	CO ₂ Me	p-OMePh	Pd ₂ (dba) ₃	(81) 65	6
7	CO ₂ Me	p-CF ₃ Ph	Pd ₂ (dba) ₃	(70) 58	7
8	CO ₂ Me	ξ − <i>t</i> Bu	Pd ₂ (dba) ₃	(75) 52	8
9	CO ₂ Me	Me	Pd ₂ (dba) ₃	(49) 35	9°

 a Relative to mesitylene internal standard. b Conditions: 15 mol % Pd, 48 h. c Conditions: 2.0 equiv of DMAD, 30 min. 10



Figure 1. ORTEP structures of 8 (left) and 9 (right). Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

hypothesis that the Pd catalyst served as a Lewis acid to activate DMAD toward Michael addition of vinyl(triphenylphosphine)gold. Replacement of Pd by either hard or soft Lewis acids (i.e., BF_3 , Sc(OTf)₃, PPh₃AuPF₆), however, did not result in formation of 1 (entries 5–7), suggesting an alternative catalytic role for Pd that is more closely tied to its specific reactivity.

The utility of the Pd-catalyzed carboauration reaction is illustrated by a range of gold starting materials (i.e., sp, sp^2 , sp³, electron-poor and electron-rich aryl; Table 2).¹⁰ Each gold starting material was synthesized in one step from commercially available reagents.9 We identified two classes of reactivity: one that proceeds in the highest conversion with PdCl₂(PPh₃)₂ as the precatalyst and the other with $Pd_2(dba)_3$.¹¹ The carborauration of methyl propiolate and methyl butynoate further expanded the substrate scope (entries 2, 4, and 5). The reaction's insensitivity to water and oxygen permitted employment of commercial solvents and open glassware. The carboaurated products 1-9 were resistant to protodemetalation by mild acids, permitting isolation by silica gel and alumina chromatography. In all cases, a reaction selectivity for syn addition yielded diastereomerically pure products, as confirmed by ¹H NMR spectroscopy and by X-ray crystallographic studies of 8 and 9 (Figure 1). Syn addition is opposite to the selectivity reported by Toste for the uncatalyzed intramolecular carboauration of alkynes.12-14

Two proposed mechanisms for the Pd-catalyzed carboauration reaction are detailed in Scheme 1. In cycle A, the gold reagent participates in two sequential transmetalation reactions and the Pd(II) oxidation state remains constant throughout the reaction. A possible equilibrium between the gold/palladium transmetalation partners would be driven toward product formation by the carbon–carbon bond-forming step (formation of migratoryinsertion product **12**),¹⁵ in analogy to the driving forces for the Nozaki–Hiyama–Kishi reaction.^{16,17} Migratory insertion of DMAD into sp²-carbon–palladium bonds has been previously reported.^{18,19} The transmetalation step to form product **10** could be initiated by PPh₃AuCl or PPh₃AuR (i.e., X = Cl, R).²⁰ In cycle B, the mechanism proceeds through an oxidative addition, transmetalation, reductive elimination cycle that involves both Pd(II) and Pd(0) in analogy to the mechanisms of palladiumcatalyzed cross-coupling reactions.^{15,17} In this case, the backbonding from the Pd(0) center is invoked to establish a formal "oxidative addition" to the electron-deficient alkyne.^{7,21,22}

Although intermediates could not be observed by ¹H NMR spectroscopy in the above reaction, we identified an analogous reaction, with carboauration across two alkynes rather than one, in which an intermediate could be isolated (eq 1). Addition of DMAD to stoichiometric Pd₂(dba)₃ resulted in formation of the known metallacycle **15**,²³ by oxidative cyclization. Subsequent addition of methyl–gold produced the carboauration product **17** (>98% NMR yield, 73% isolated). This reaction is consistent with the intermediacy of **16**, which demonstrates the viability of a vinyl transmetalation reaction between Pd and Au which is similar to that proposed in Scheme 1, cycles A and B (in cycle A, when X = R).²⁴ This reaction is also consistent with the accessibility of an oxidative addition, transmetalation, and reductive elimination cycle for the mixed Pd/Au system, as proposed in cycle B.

Since Pd(0) and Pd(II) precatalysts are known to access both Pd(0) and Pd(II) catalyst states for cross-coupling reactions, either oxidation state of palladium is possible, regardless of the oxidation state of our precatalyst.¹⁵ To further probe the oxidation state requirements of the palladium during the reaction, we examined the reaction's sensitivity to oxygen by performing the carboauration reaction under an atmosphere of oxygen gas in the presence of the PdCl₂(PPh₃)₂ catalyst. No change in conversion was observed under these oxidizing conditions when compared to performing the reaction under rigorously air-

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Scheme 1. Proposed Catalytic Cycles for the Pd-Catalyzed Carboauration of Alkynes



free conditions, suggesting that a low-oxidation-state palladium(0) complex may not be critical for reactivity; however, currently cycle B cannot be ruled out.

We next explored the reactivity of the vinyl-gold products. The resistance of this class of α -ester vinyl-gold complexes to rapid protodemetalation permits their participation in intermolecular functionalization reactions, rather than being limited by intramolecular trapping,²⁵ which greatly expands their synthetic utility. A range of Pd and Au cross-coupling reactions proceeded in high yield with retention of configuration, opening synthetic access to trisubstituted olefins with complete regioand diastereocontrol (Scheme 2; 18, 20, and 22).²⁶ In each functionalization reaction, the crude vinyl-gold species 2 was employed without isolation, and the residual Pd catalyst from the carboauration reaction remained viable for the subsequent cross-coupling step, establishing a one-pot tandem carboauration/functionalization protocol. For example, after 2 h, addition of allyl bromide to crude 2 in the same solution used for the carboauration reaction produced allylated product 18 (87%, two steps), presumably through a π -allyl-palladium intermediate.²⁷ Palladium was required for cross-coupling reactivity. When intermediate 2 was isolated, no product formation was observed in the absence of Pd with allyl bromide, methyl iodide, or 4-iodotoluene. Addition of 2.5 mol % of Pd₂(dba)₃ to isolated 2 restored the cross-coupling reactivity. These new crosscoupling reactions proceed through a fully characterized homogeneous gold intermediate, removing ambiguity pertaining to the nature of the reactive gold species.²⁸

The strongly electrophilic reagents HCl and Bu₃SnOTf trapped the vinyl–gold species **2** in the absence of a Pd catalyst (both 97%, two steps).²⁹ In these cases, purified **2** displayed

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Scheme 2. One-Pot Carboauration/Functionalization^a



^a Two-step ¹H NMR yields relative to mesitylene internal standard.

reactivity similar to that of crude **2**. Mechanistic work in this paper suggests a reinterpretation of the catalytic carbostannylation reaction we previously reported, to include the intermediacy of a vinyl–gold compound.⁷

In conclusion, we have developed a diastereo- and regioselective Pd-catalyzed carboauration reaction of alkynes. This reaction provides synthetic access to fully characterized vinyl-gold intermediates. These intermediates participate in a series of intermolecular palladium-catalyzed cross-coupling reactions and electrophilic trapping reactions to produce di- and trisubstituted olefins with high diastereoselectivity and absolute regioselectivity. In a broader sense, the reactions reported herein provide a demonstration of reactivity available to Au/Pd systems and expand the synthetic utility of vinyl-gold intermediates. Application of these principles to the development of new Auand Pd-cocatalyzed reactions (i.e., catalytic in both metals rather than just palladium) are ongoing in our laboratory. Given the prolific role of both Pd and Au separately in organic synthesis, more "combined concepts" are likely forthcoming as this fundamental understanding grows.

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Supporting Information Available: Text, figures, and tables giving experimental procedures and compound characterization data and CIF files giving crystal data for **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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