

Cross-Coupling of Meyer–Schuster Intermediates under Dual Gold– Photoredox Catalysis

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Supporting Information



Triple roles of ArN2⁺ : oxidants, coupling partners & activators of propargyl alcohols

ABSTRACT: Under dual gold/photoredox catalytic conditions, intermediates from the Meyer–Schuster rearrangement underwent an efficient cross-coupling with arene diazonium salts, leading to α -arylated enones. Diazonium salts assisted the dissociation of the propargyl hydroxyl group by forming alkoxydiazenes in the Meyer–Schuster rearrangement, and the coupling was proposed to proceed through an allenyl methyl ether.

T he Meyer–Schuster rearrangement converts readily available propargyl alcohols into α,β -unsaturated carbonyl compounds in an atom-economical fashion, and thus, considerable attention has been paid to the related catalytic methods.¹ A tandem reaction incorporating cross-coupling of the C(sp²)–M intermediate in this transformation would broaden its utility, providing an efficient route to diverse α -arylated enones that serve as precursors for many pharmaceutically interesting heterocycles as well as substrates for asymmetric organocatalysis.²

Although related *tandem* [3,3]-rearrangement/cross-coupling of propargyl esters has been documented in gold and indium catalysis employing propargyl esters,³ cross-coupling of the Meyer–Schuster intermediates obtained from propargyl alcohols has been achieved only through a Cu system (Scheme 1A).⁴ Recently, Glorius^{6a,b} and Toste^{6c,d} introduced a combination of visible-light photoredox with gold catalysis, leading to C(sp³)– C(sp²) coupling, employing aryl diazonium salts.^{5,6} These seminal reports spurred renewed interest in gold-catalyzed cross-coupling because the Au(I)–Au(III) redox cycle can be

Scheme 1. Cross-Coupling of C(sp²)-M Intermediates



accessed without using strong stoichiometric oxidants. Thus far, however, $C(sp^2)-C(sp^2)$ cross-coupling under these dual catalytic systems has been limited to stable vinyl gold intermediates that can be isolated and characterized (Scheme 1B).^{6c,e,7} For a successful cross-coupling of unstable $C(sp^2)$ -Au intermediates, both oxidative addition and reductive elimination must be faster than the competing proto-demetalation. Such in situ cross-coupling of $C(sp^2)$ -metal species has intrinsic advantages over the current cross-coupling technology via C-H functionalization in that no directing group (and its installation/detachment steps) is required to obtain regioselective coupling, and more diverse cyclic or acyclic $C(sp^2)-M$ intermediates could be utilized in the cross-coupling by virtue of the complexity-generating power of gold catalysis. This aspect underscores the importance of cross-coupling of transient $C(sp^2)$ -M intermediates in electrophilic metal catalysis.

Toward cross-coupling of unstable $C(sp^2)$ -Au species, the Meyer-Schuster rearrangement was selected because gold complexes are one of the most selective catalysts for this transformation over competing side pathways, such as dehydration or Rupe rearrangements. Through our previous study on a Au-catalyzed tandem Meyer-Schuster rearrangement/ring expansion,⁸ we determined that a π -bound allenol, **I**, plays a key role in the stereodetermining step by racemization of the allene axis and inducing ring expansion. We posited that the corresponding σ -bound enone-Au complex **II** would couple with a photo-redox-generated aryl radical, leading to α -arylated enones. Under these photocatalytic conditions, this methodology would raise an interesting issue of Z/E selectivity.⁹

With a tertiary propargyl alcohol 1a and diazonium 2a as test substrates, we examined various conditions for the tandem Meyer–Schuster/cross-coupling (Table 1). Initially, finding

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 Table 1. Optimized Conditions for the Tandem Meyer–

 Schuster Rearrangement/Arylative Cross-Coupling^a

MeO	OH N-BF4 Ph_9PAUCI (2.5 mol %) Me + NO ₂ Ru(bpy)s(PF02 (2.5 mol %) MeOH MeOH MeOH	Me + MeC	O Me Me
	1a 2a	3aa NO ₂	4a
entry	deviation from standard conditions	3aa (%) ^b	4aa (%) ^b
1	none	92	6
2	[(Ph ₃ P)Au]OTf (2.5%) ^{<i>c</i>,<i>d</i>}	32	38
3	Ph ₃ PAuI ^c	42	45
4	Ph ₃ PAuBr ^c	71	19
5	Ph ₃ PAuF ^c	63	31
6	additive (NaHCO ₃ , 1 equiv)	69	10
7	$(NH_4)_2 Fe(SO_4)_2 \cdot 6H_2O (10\%)^e$	47	10
8	$Fe(OTf)_2 (10\%)^e$	45	8
9	$\operatorname{Fe}(\operatorname{acac})_3 (10\%)^e$	41	5
10	riboflavin (20%) ^f	70	14
11	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6(2.5\%)^f$	41	34
12	Ir(dFppy) ₂ (phen)PF ₆ (2.5%) ^f	43	32
13	$Ir(ppy)_2(dtbbpy)PF_6(2.5\%)^f$	40	36
14	fac-Ir(ppy) ₃ (2.5%) ^f	56	16
15	ArN_2BF_4 (3 equiv)	87	8
16	ArN_2BF_4 (2 equiv)	60	13
17	ArN_2BF_4 (1 equiv)	34	11
18	Ph ₂ IOTf ^g	0	0
19	no Au catalyst	0	0
20	no photocatalyst	trace	0
21	no light	trace	0
22	no photocatalyst, 50 °C	32	61

^{*a*}**1a** (0.1 mmol), **2a** (0.4 mmol) in the presence of Ph₃PAuCl (2.5 mol %), and Ru(bpy)₃(PF₆)₂ (2.5 mol %) in degassed MeOH. ^{*b*}Isolated yields. ^{*c*}Instead of Ph₃PAuCl. ^{*d*}Generated in situ from Ph₃PAuCl and AgOTf (2.5 mol % each) in CH₂Cl₂, followed by filtration and evaporation of solvents. ^{*c*}Instead of Ru(bpy)₃(PF₆)₂ with no light. ^{*f*}Instead of Ru(bpy)₃(PF₆)₂. ^{*g*}Instead of **2a**.

optimal conditions was deemed challenging because protonated enone II, due to its strong acidity, may rapidly undergo protodemetalation. After substantial trials, we found that 1a undergoes an efficient cross-coupling with *p*-nitrophenyldiazonium 2a, affording 3aa in 92% isolated yield (entry 1). Suppression of proto-demetalation to 4aa was not effective using a cationic Au(I) catalyst (entry 2). Other Au(I)-halides, unfortunately, proved to be less efficient than $Au(PPh_3)Cl$ (entries 3–5). Use of base additive adversely affected the desired Meyer-Schuster rearrangement/cross-coupling (entry 6). Other Au(I)-SET catalysts (entries 7-9) and photocatalysts (entries 10-14) in place of $Ru(bpy)_3^{2+}$ proved to be less efficient, giving a significant amount of 4aa. Notably, riboflavin (20 mol %) in place of $\operatorname{Ru}(\operatorname{bpy})_{3}^{2+}$ gave 70% of 3aa. Use of smaller amount of 2a led to lower yield, and diphenyliodonium salt^{6b} was completely inactive (entries 15-18). The reaction did not proceed at all in the absence of gold catalyst, photocatalyst, or in the dark (entries 19–21), and the thermally generated aryl radical^{6e} gave only a modest yield of 3aa (entry 22). It is important to note that, while 10 mol % of gold catalyst was required in previous dual Au/ photoredox systems,⁶ Au loading could be reduced significantly (2.5 mol % of Ph₃PAuCl).

With these optimized conditions, the scope of the α -arylative Meyer–Schuster rearrangement was examined (Scheme 2). In terms of the arene diazonium salts, electron-deficient arenes generally gave yields of the coupled products (**3aa–3ae**) higher than that of electron-rich ones (**2f**). Various tertiary propargyl

Scheme 2. Substrate Scope for Au/Photoredox α -Arylative Meyer–Schuster Rearrangement^{*a*}



^{*a*}**1a** (0.1 mmol), **2a** (4 equiv) in the presence of Ph₃PAuCl (2.5 mol %), and Ru(bpy)₃(PF₆)₂ (2.5 mol %) in degassed MeOH (0.1 M). Isolated yields after chromatography. ^{*b*}E/Z ratio.

alcohols were widely accommodated in this reaction, as demonstrated in the formation of 3ba-3la. In the case of substrates with different R^2 and R^3 groups, a mixture of double bond isomers of modest E/Z ratio was obtained (3ia-3la, vide infra in eqs 1–3). Substrates bearing secondary propargyl alcohols were also viable substrates (3ma-3og), although the yields were somewhat lower than that of tertiary propargyl alcohols.

$$\begin{array}{c} \begin{array}{c} \begin{array}{c} \mathsf{OH} \\ \mathsf{Ph} \end{array} + \underbrace{\mathbf{2a}}_{(4 \text{ equiv})} & \underbrace{\mathsf{PPh}_{3}\mathsf{AuCl}(5\%)}_{\text{riboflavin}(20\%)} & \mathsf{O} & \mathsf{Me} \\ & \underbrace{\mathsf{Ne}\mathsf{OH}(0.1 \text{ M})}_{\text{blue} \text{ LED}} \\ \mathbf{1i} \end{array} & \underbrace{\mathsf{Ne}\mathsf{OH}(0.1 \text{ M})}_{\text{blue} \text{ LED}} \\ \mathbf{3ia}, 59\% (Z/E = 32:68) \end{array} & \begin{array}{c} (1) \\ \underbrace{\mathsf{A}-\mathsf{NO}_2\mathsf{C}_6\mathsf{H}_4}_{4.8} \\ \mathbf{3ia}, 59\% (Z/E = 32:68) \end{array} \\ \begin{array}{c} \mathsf{Sia}(Z/E = 36:64) \end{array} & \underbrace{\mathsf{Ru}(\mathsf{bpy})_3(\mathsf{PF}_6)_2 (2.5 \text{ mol }\%)}_{\mathsf{Me}\mathsf{OH}-d_4, \text{ blue LED}} \\ \mathbf{7t}, 24 \text{ h} \end{array} & \begin{array}{c} \mathsf{O} & \mathsf{Ph} \\ \underbrace{\mathsf{Ph}}_{4-\mathsf{NO}_2\mathsf{C}_6\mathsf{H}_4} \\ \mathbf{3ia}, 98\%, (Z/E = 72:28) \end{array} \\ \begin{array}{c} \mathsf{Sia}(Z/E = 72:28) \end{array} \\ \begin{array}{c} \mathsf{Sia}(\mathsf{only} \mathsf{E}) \end{array} & \underbrace{\mathsf{Ru}(\mathsf{bpy})_3(\mathsf{PF}_6)_2 (2.5 \text{ mol }\%)}_{\mathsf{Me}\mathsf{OH}-d_4, \text{ blue LED}} \\ \underbrace{\mathsf{Ru}(\mathsf{bpy})_3(\mathsf{PF}_6)_2 (2.5 \text{ mol }\%)}_{\mathsf{Me}\mathsf{OH}-d_4, \text{ blue LED}} \end{array} & \begin{array}{c} \mathsf{Sia}(\mathsf{S}) \\ \mathsf{Sia}(\mathsf{S}) \\$$

Considering the possible photocatalyzed E/Z isomerization under the current conditions,⁹ the E/Z ratio in the formation of **3ia–3la** likely results from the differential excitation of *E*- and *Z*isomers to the photostationary equilibrium (energy ratchet)^{9b} and not from the Meyer–Schuster mechanism. Thus, it was of interest whether the *E* to *Z* isomerization occurs during the formation of α -arylated enones. As in eq 1, changing the photocatalyst from Ru(bpy)₃²⁺ (2.5 mol %) to riboflavin (20 mol %) in the formation of **3ia** indeed led to an increased *E* preference (*Z*/*E* = 32:68, cf. **3ia** (*Z*/*E* = 48:52) in Scheme 2). In addition, when the isolated **3ia** (with *Z*/*E* = 36:64) was subject to blue LED irradiation (~460 nm), *E* to *Z* isomerization occurred to give a *Z*-enriched mixture (*Z*/*E* = 72:28). Among the other products tested, only enyne **3ja** displayed photoresponsive behavior, giving *Z*/*E* isomerization (eq 3).

To further probe the mechanism of this *tandem* Meyer– Schuster/cross-coupling, the following control experiments were conducted (Scheme 3). Mixing propargyl alcohol 1a with

Scheme 3. Reaction of Propargyl Alcohols with Diazonium Salts



diazonium salt 2e in methanol led to a Nicholas reaction, affording propargyl methyl ether 5a in 18 h at rt (eq 4). Surprisingly, this substitution could be effected even with a catalytic amount of diazonium salt 2e (20 mol %) over an extended time period. We interpreted that the substitution is mediated by (propargyloxy)diazene I for the activation and dissociation of the hydroxyl group. Thus, formed propargyl methyl ether 5a turned out to be a viable Meyer–Schuster substrate, as well, to form 3ae (eq 5).

Based on the above results and our previous work,^{6e,8} we propose the mechanism of the tandem Meyer-Schuster arylation as follows (Scheme 4): Photoredox oxidative addition of aryl diazonium into neutral (L)AuCl would form cationic Au(III) complex II,^{6c-e} which, in turn, activates propargyl alcohol 1 (or I) to form III. Here, the R group can also be a diazenyl group (N=NAr, eq 4) or Me group (eq 5). The hydrogen-bond-guided addition of methanol and elimination of ROH from IV^8 would give a π -complex of the allenyl ether $V.^{10}$ Finally, reductive elimination from the subsequent σ complex VI would afford the coupled product 3. The higher yields of tertiary propargyl alcohol substrates, compared to those of the secondary alcohols, suggest a rate-limiting dissociation of the OR group, which is facilitated by forming labile alkoxydiazene III. Also notable in this mechanism is the formation of the allenyl methyl ether complex V rather than an allenol,⁸ which suppresses undesired proto-deauration. Finally, the α -aryl enones could be readily transformed into pharmaceutically interesting pyrazoles and pyrazolines according to Scheme 5.

In summary, we have reported herein a dual gold/photocatalyzed tandem Meyer–Schuster/cross-coupling of propargyl alcohols into α -arylated enones under low catalyst loading of

Scheme 4. Proposed Mechanism



Scheme 5. Synthesis of Pyrazoles and Pyrazolines



both Ru(II) and Au(I) catalysts at rt. We propose that the keys for the successful cross-coupling with the labile $C(sp^2)$ -Au include the formation of the allenyl ethers, and in this protocol, arene diazonium salts play triple roles as oxidants, coupling partners, and catalytic activators for the dissociation of propargyl alcohols. The latter aspect will have interesting implications in the transformations of propargyl alcohols, which is currently sought after in this laboratory.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03531.

Full characterization data of all new products and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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