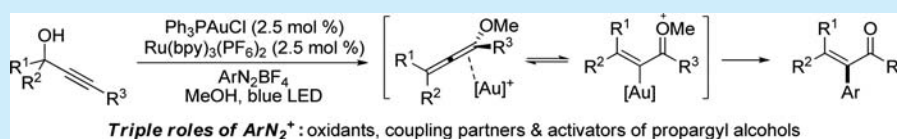


Cross-Coupling of Meyer–Schuster Intermediates under Dual Gold–Photoredox Catalysis

Jiwon Um, Hokeun Yun, and Seunghoon Shin*

Department of Chemistry and Center for New Directions in Organic Synthesis (CNOS), Research Institute for Natural Sciences, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 133-791, Korea

Supporting Information



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.

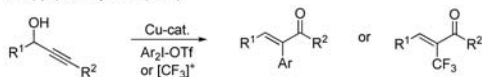
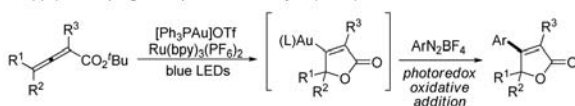
The Meyer–Schuster rearrangement converts readily available propargyl alcohols into α,β -unsaturated carbonyl compounds in an atom-economical fashion, and thus, considerable attention has been paid to the related catalytic methods.¹ A tandem reaction incorporating cross-coupling of the $C(sp^2)$ –M intermediate 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 organo-catalysis.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^{5a,b} and Toste^{6c,d} introduced a combination of visible-light photoredox with gold catalysis, leading to $C(sp^3)$ – $C(sp^2)$ 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

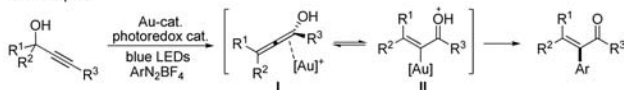
accessed without using strong stoichiometric oxidants. Thus far, however, $C(sp^2)$ – $C(sp^2)$ cross-coupling under these dual catalytic systems has been limited to stable vinyl gold intermediates that can be isolated and characterized (Scheme 1B).^{6c,e,7} For a successful cross-coupling of unstable $C(sp^2)$ –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

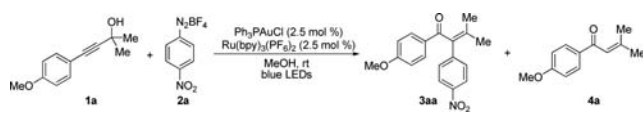
Scheme 1. Cross-Coupling of $C(sp^2)$ –M IntermediatesA. $C(sp^2)$ –Cu arylation (ref 3)B. $C(sp^2)$ –Au coupling under photoredox catalysis (ref 6e)

C. This report



Received: December 12, 2015

Published: January 13, 2016

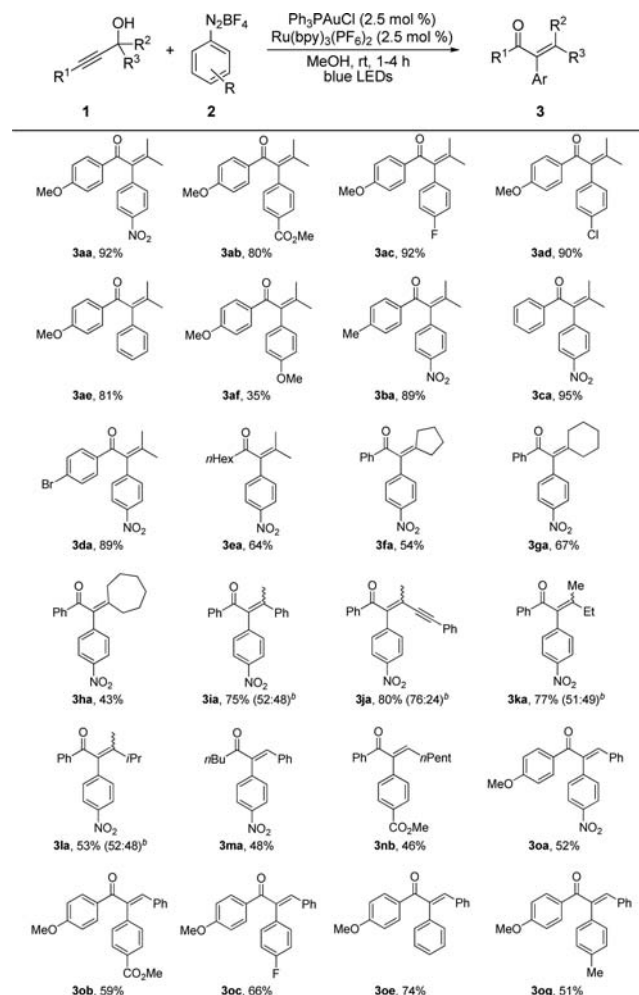
Table 1. Optimized Conditions for the Tandem Meyer–Schuster Rearrangement/Arylative Cross-Coupling^a


entry	deviation from standard conditions	3aa (%) ^b	4aa (%) ^b
1	none	92	6
2	[(Ph ₃ P)Au]OTf (2.5%) ^{c,d}	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 ·6H ₂ O (10%) ^e	47	10
8	Fe(OTf) ₂ (10%) ^e	45	8
9	Fe(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 (dtbpy)PF ₆ (2.5%) ^f	40	36
14	fac-Ir(ppy) ₃ (2.5%) ^f	56	16
15	ArN ₂ BF ₄ (3 equiv)	87	8
16	ArN ₂ BF ₄ (2 equiv)	60	13
17	ArN ₂ BF 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

^a1a (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. ^bIsolated yields. ^cInstead of Ph₃PAuCl. ^dGenerated in situ from Ph₃PAuCl and AgOTf (2.5 mol % each) in CH₂Cl₂, followed by filtration and evaporation of solvents. ^eInstead of Ru(bpy)₃(PF₆)₂ with no light. ^fInstead of Ru(bpy)₃(PF₆)₂. ^gInstead of 2a.

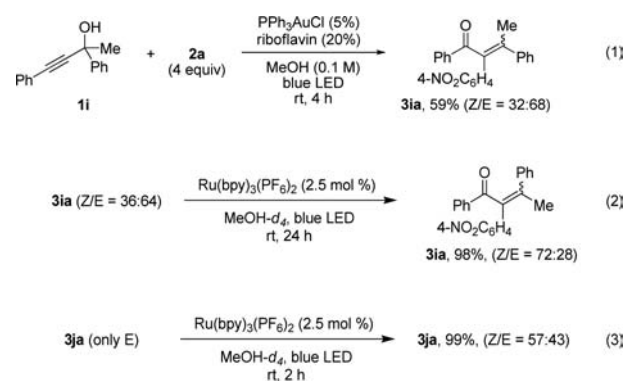
optimal conditions was deemed challenging because protonated enone **II**, due to its strong acidity, may rapidly undergo protodemetalation. After substantial trials, we found that **1a** undergoes an efficient cross-coupling with *p*-nitrophenyldiazonium **2a**, affording **3aa** in 92% isolated yield (entry 1). Suppression of protodemetalation 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(PPh₃)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)₃²⁺ proved to be less efficient, giving a significant amount of **4aa**. Notably, riboflavin (20 mol %) in place of Ru(bpy)₃²⁺ 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^{6c} 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 -arylate 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 -Arylate Meyer–Schuster Rearrangement^a

^a1a (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. ^bE/Z ratio.

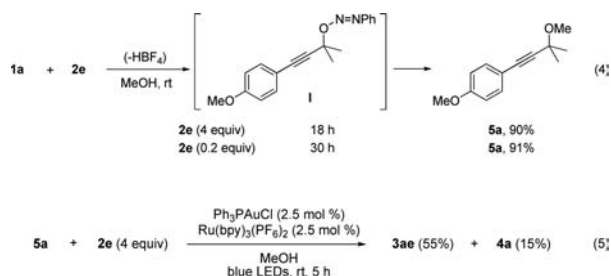
alcohols were widely accommodated in this reaction, as demonstrated in the formation of **3ba**–**3la**. In the case of substrates with different R² and R³ groups, a mixture of double bond isomers of modest E/Z ratio was obtained (**3ia**–**3la**, vide infra in eqs 1–3). Substrates bearing secondary propargyl alcohols were also viable substrates (**3ma**–**3og**), although the yields were somewhat lower than that of tertiary propargyl alcohols.



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

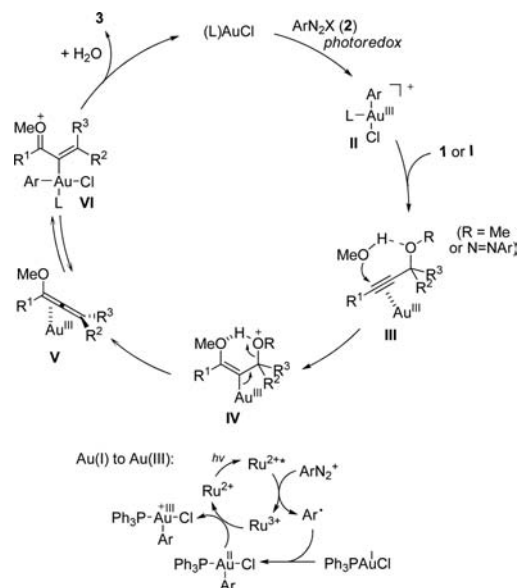


diazonium salt **2e** in methanol led to a Nicholas reaction, affording propargyl methyl ether **5a** in 18 h at rt (eq 4). Surprisingly, this substitution could be effected even with a catalytic amount of diazonium salt **2e** (20 mol %) over an extended time period. We interpreted that the substitution 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).

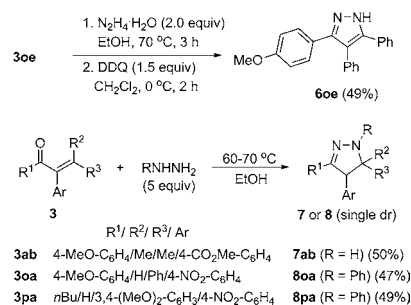
Based on the above results and our previous work,^{6e,8} we propose the mechanism of the tandem Meyer–Schuster arylation as follows (Scheme 4): Photoredox oxidative addition of aryl diazonium into neutral (L)AuCl would form cationic Au(III) complex **II**,^{6c–e} which, in turn, activates propargyl alcohol **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/photo-catalyzed 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(sp²)–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

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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sshin@hanyang.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Research Foundation of Korea (NRF- 2012M3A7B4049653 and NRF-2014-011165) for generous financial support. We thank KBSI for HR-MS analysis.

■ REFERENCES

- (1) (a) Cadierno, V.; Crochet, P.; Garcia-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, 39, 4015. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, 7, 4149. (c) Mauleon, P.; Toste, F. D. In *Modern Gold Catalyzed Synthesis*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley-VCH: Weinheim, Germany, 2012; pp 75–134. (d) Ye, L.; Zhang, L. *Org. Lett.* **2009**, 11, 3646. (e) Trost, B. M.; Luan, X. *J. Am. Chem. Soc.* **2011**, 133, 1706.
- (2) (a) Cuberes, R.; Berrocal, M.; Contijoch, M.; Frigola, J. Patent Appl. WO 99/62884, 1999. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, 51, 9748.
- (3) (a) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009**, 48, 3112. (b) Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2014**, 16, 1176.
- (4) (a) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, 52, 5799. (b) Xiong, Y.-P.; Wu, M.-Y.; Zhang, X.-Y.; Ma, C.-L.; Huang, L.; Zhao, L.-T.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, 16, 1000. (c) Xu, Z.-F.; Cai, C.-X.; Liu, J.-T. *Org. Lett.* **2013**, 15, 2096.
- (5) For a merger of visible-light photoredox with transition metal catalysis (selected examples), see: (a) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, 133, 18566. (b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, 134, 9034.
- (6) (a) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, 135, 5505. (b) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, 356, 2794. (c) Shu, X.-Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, 136, 5844. (d) He, Y.; Wu, H.; Toste, F. D. *Chem. Sci.* **2015**, 6, 1194. (e) Patil, D. P.; Yun, H.; Shin, S. *Adv. Synth. Catal.* **2015**, 357, 2622. For C(sp)–C(sp²) coupling that does not involve photoredox conditions, see: (f) Cai, R.; Lu, M.; Aguilera, E. Y.; Xi, Y.; Akhmedov, N. G.; Petersen, J. L.; Chen, H.; Shi, X. *Angew. Chem., Int. Ed.* **2015**, 54, 8772.
- (7) (a) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, 130, 17642. Compared to C(sp²)–Au, the protodemetalation of C(sp³)–Au is much slower: (b) LaLonde, R. L.; Brenzovich, W. E., Jr.; Benitez, D.; Tkatchouk, E.; Kelley, K.; Goddard, W. A., III; Toste, F. D. *Chem. Sci.* **2010**, 1, 226. For a successful coupling of vinyl gold intermediates using SelectFluor as oxidant, see: (c) Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B. *Angew. Chem., Int. Ed.* **2010**, 49, 7247.
- (8) An, J.-H.; Yun, H.; Shin, S.; Shin, S. *Adv. Synth. Catal.* **2014**, 356, 3749. Through H₂¹⁸O experiment, it was demonstrated that addition of external water occurs in the rearrangement (III to V), which, in this case, supports addition of MeOH in III (Scheme 4).
- (9) (a) Hammond, G. S.; Saltiel, J. *J. Am. Chem. Soc.* **1962**, 84, 4983. For E to Z isomerization of enones, see: (b) Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, 137, 11254.
- (10) Gandon, V.; Lemièrre, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, 47, 7534.