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Practical Synthesis of Linear α-Iodo/Bromo-α,β-unsaturated Aldehydes/Ketones from Propargylic Alcohols via Au/Mo Bimetallic Catalysis

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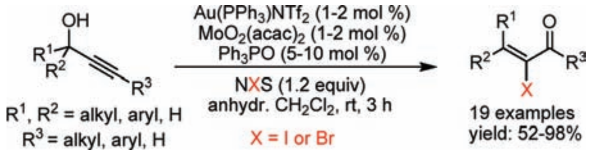
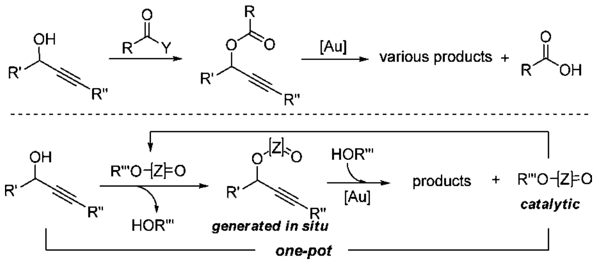
ABSTRACT



An efficient synthesis of α-iodo/bromo-α,β-unsaturated aldehydes/ketones directly from propargylic alcohols is described. This reaction is catalyzed collaboratively by two metal complexes, $Ph_3PAuNTf_2$ and $MoO_2(acac)_2$, and Ph_3PO as an additive helps suppress undesired enone/enal formation. Notable features of this method include low catalyst loadings, mild reaction conditions, and mostly good to excellent diastereoselectivity. In comparison with our previously developed method based on propargylic acetate substrates, this chemistry omits the need to prepare acetate derivatives and, moreover, has a much broader substrate scope.

Propargylic carboxylates, prepared from propargylic alcohols and activated carboxylic acids, are arguably the most versatile substrates[1] for gold and platinum catalysis,[2] and some of their gold-catalyzed reactions resulted in the formation of products without retaining the acyl group.[1c,d,g,3] For those reactions, it is in theory possible to replace the acyl group with an in situ installed and subsequently cleavable surrogate or equivalent in a catalytic fashion. In this manner, significant economic and environmental benefits can be garnered with shortened synthetic routes and less chemical waste generated (Scheme 1).

Scheme 1. Carboxyl Group Surrogate for Gold-Catalyzed Reactions of Propargylic Carboxylates



Last year, Akai and co-workers reported a bimetallic catalysis[4] using a combination of $Ph_3PAuCl/AgOTf$[5] and $MoO_2(acac)_2$ (Scheme 2). In this efficient Meyer−Schuster

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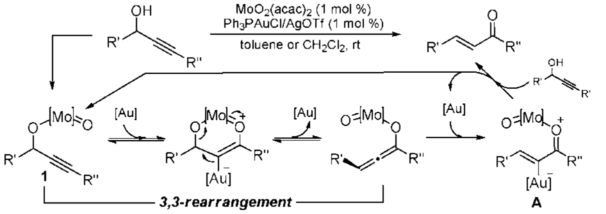
(1) For selected examples, see: (a) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505–8513. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805. (c) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443. (d) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003. (e) Marion, N.; Diez-Gonzalez, S.; de Fremont, P.; Noble, A. R.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647–3650. (f) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615. (g) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 1465–1468. (h) Luo, T.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8250–8253. (i) Zou, Y.; Garayalde, D.; Wang, Q. R.; Nevado, C.; Goeke, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10110–10113. (j) Cho, E. J.; Lee, D. S. *Adv. Synth. Catal.* **2008**, *350*, 2719–2723. (k) Lu, L.; Liu, X. Y.; Shu, X. Z.; Yang, K.; Ji, K. G.; Liang, Y. M. *J. Org. Chem.* **2009**, *74*, 474–477.

10.1021/ol901346k CCC: $40.75

Scheme 2. Akai's Chemistry and Our Conceived Mechanism



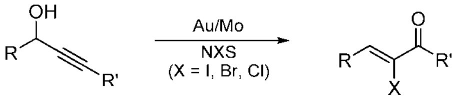
reaction, several features are noteworthy: mild reaction conditions (mostly at room temperature), low catalyst loadings (1 mol % for both Au and Mo complexes), and a broad substrate scope.

Although Meyer–Schuster reactions catalyzed only by gold complexes[6] have been reported, the propargylic alcohol substrates invariably contained features capable of substantially stabilizing carbon cations. The broad scope and the ease of Akai's chemistry calls for, in our opinion, a mechanism similar to that of propargylic carboxylates, where a gold-catalyzed 3,3-rearrangement[1b,c] occurs en route to enone formation.[3a] The difference is, as in our conceived mechanism (Scheme 2), that the oxomolybdenum moiety acts as an equivalent of the carbonyl group. Due to the labile nature of the RO–Mo bond, intermediate **1** was generated in situ and the Mo complex was rendered catalytic.

We were attracted to the synthetic advantage of this revelation as propargylic carboxylates in a range of gold catalysis could be replaced with their precursors (i.e., propargylic alcohols) and thus decided to look into applying this approach to some of the chemistry previously developed in our laboratory.

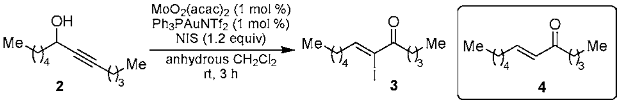
We recently reported a preparative method of linear α-iodo/bromo-α,β-unsaturated ketones based on gold catalysis using propargylic acetate substrates.[3b,d] These functionalized enones are versatile synthetic intermediates and can be readily converted to a range of α-substituted enones via transition metal-catalyzed cross-coupling reactions.[7] Though efficient, the reaction required propargylic acetates as substrates and, moreover, did not work well with substrates without substitution at either end of the propargyl moiety. We reasoned that a Mo complex such as $MoO_2(acac)_2$ could replace the acetyl moiety in this chemistry, similar to Akai's case, allowing the formation of α-halo-α,β-unsaturated carbonyl products directly from propargylic alcohols and likely with an improved scope (Scheme 3).

Scheme 3. Preparation of α-Halo-α,β-unsaturated Carbonyl Compounds from Propargylic Alcohol: Design



We first studied the formation of α-iodo enones/enals using $MoO_2(acac)_2$ and Ph_3AuNTf_2[8] as the catalyst combination and anhydrous CH_2Cl_2 as solvent. To our delight, α-iodo enone **3** was indeed formed from propargylic alcohol **2** at room temperature in 3 h (Table 1, entry 1). The drawback was the competitive formation of enone **4**. While other metal complexes such as $VO(acac)_2$ and $MeReO_3$ failed to improve this reaction, we turned to modify $MoO_2(acac)_2$. It was recently reported that dinuclear molybdenum complexes $Mo_2O_5(acac)_2L_2$ (L = DMF, Ph_3PO, DMSO, H_2O, HMPA, etc.) could be readily prepared from $MoO_2(acac)_2$ and polar compounds (i.e., L) in 96% ethanol.[9] While our attempts to

Table 1. Bimetallic Au/Mo Catalysis: Conditions Optimization



		3		
entry[a]	additive	yield (%)[b]	*Z/E*[c]	**4** (%)
1		54	6/1	36
2	DMSO (5 mol %)	72	24/1	12
3	DMF (5 mol %)	69	11/1	28
4	HMPA (5 mol %)	80	26/1	<2
5	**Ph_3PO (5 mol %)**	**>98**[d]	**16/1**	**<2**
6	Ph_3PO (1 mol %)	71	12:1	9
7	Ph_3PO (5 mol %), no gold	13[e]	18/1	<1
8	no gold	3[e]		
9	Ph_3PO (5 mol %), no Mo	7[e]		<1
10	no Mo	7[e]		<1

[a] Reaction concentration was 0.05 M. [b] Estimated by ^1H NMR using diethyl phthalate as internal reference. [c] The geometries of **3** were determined by NOESY1D experiments. [d] 98% isolated yield. [e] The rest of the starting material remained unreacted.

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(2) For selected reviews on gold catalysis, see: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (e) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938. (f) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (h) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (i) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (j) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200–203.

(3) (a) Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871–875. (b) Yu, M.; Zhang, G.; Zhang, L. *Org. Lett.* **2007**, *9*, 2147–2150. (c) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436–7437. (d) Yu, M.; Zhang, G.; Zhang, L. *Tetrahedron* **2009**, *65*, 1846–1855.

(4) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867–1870.

(5) AgOTf was used to generate Ph_3PAu^+ OTf^- and presumably does not participate in the catalysis.

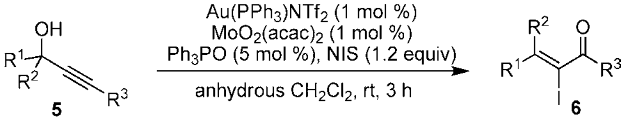
(6) (a) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029. (b) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767–1773.

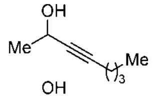
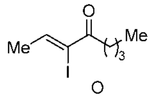
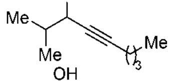
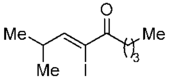
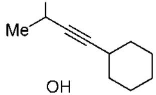
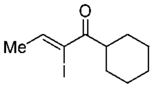
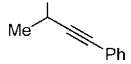
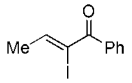
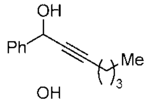
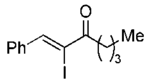
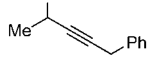
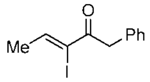
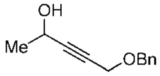
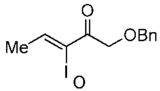
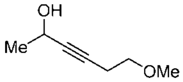
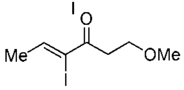
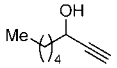
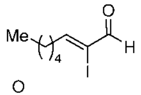
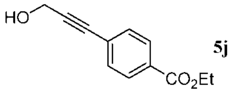
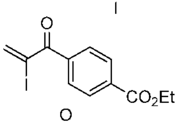
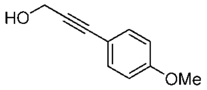
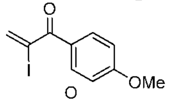
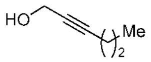
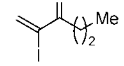
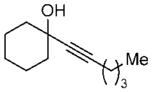
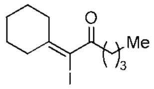
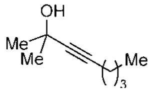
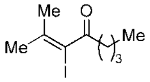
(7) For a review, see: Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179–194.

(8) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(9) Pedrosa, M. R.; Escribano, J.; Aguado, R.; Díez, V.; Sanz, R.; Arnáiz, F. J. *Polyhedron* **2007**, *26*, 3695–3702.

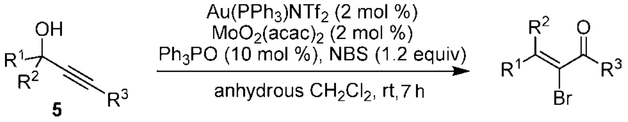
Table 2. Reaction Scope for the Formation of α-Iodo Enones/Enals

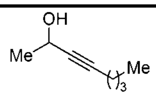
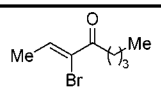
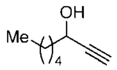
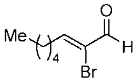
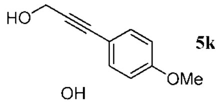
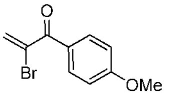
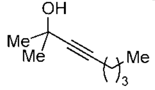
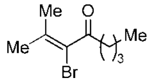


entry[a]	propargylic alcohol **5**	α-iodoenone **6**	Z/E	yield [%][b,c]
1	 **5a**	 **6a**	36:1	90 (<2)
2	 **5b**	 **6b**	17:1	93 (3)
3	 **5c**	 **6c**	10:1	81 (<2)
4	 **5d**	 **6d**	6:1	82[d] (<2)
5	 **5e**	 **6e**	6:1	83 (5)
6	 **5f**	 **6f**	30:1	52 (<2)
7	 **5g**	 **6g**	34:1	87[e] (4)
8	 **5h**	 **6h**	11:1	88[e] (6)
9	 **5i**	 **6i**	>50:1	73[d,e] (<2)
10	 **5j**	 **6j**	-	72[e] (<2)
11	 **5k**	 **6k**	-	78[e] (<2)
12	 **5l**	 **6l**	-	85 (<2)
13	 **5m**	 **6m**	-	87 (<2)
14	 **5n**	 **6n**	-	96 (3)

[a] The substrate concentration was 0.05 M. [b] Isolated yield. [c] The yield of the corresponding enone was shown in parentheses. [d] Reaction time: 15 h. [e] 2 mol % of Au(PPh$_3$)NTf$_2$, 2 mol % of MoO$_2$(acac)$_2$, and 10 mol % of Ph$_3$PO were used.

Table 3. Reaction Scope for the Formation of α-Bromo Enones/Enals



entry[a]	propargylic alcohol **5**	α-bromoenone	Z/E	yield [%][b,c]
1	 **5a**	 **7**	20:1	80 (5)
2	 **5i**	 **8**	>50/1	78[d,e] (<1)
3	 **5k**	 **9**	-	82[e] (<1)
4	 **5n**	 **10**	-	94 (3)

[a] The substrate concentration was 0.05 M. [b] Isolated yield. [c] The yield of the corresponding enone is shown in parentheses. [d] Reaction time: 11 h. [e] 5 mol % of Au(PPh$_3$)NTf$_2$, 5 mol % of MoO$_2$(acac)$_2$, and 15 mol % of Ph$_3$PO were used.

prepare these complexes in pure form always met with difficulty, we screened these polar compounds as additives to the reaction. To our delight, the formation of enone **4** was significantly suppressed with DMSO (entry 2) and almost completely prevented with HMPA (entry 4) or Ph$_3$PO (entry 5). In the case of Ph$_3$PO, the reaction proceeded with an excellent yield with 5 mol % of the additive, while significant enone formation was observed with 1 mol % (entry 6). The role of Ph$_3$PO in the reaction, though not clear at this point, is likely to modify MoO$_2$(acac)$_2$ instead of Ph$_3$PAuNTf$_2$ (comparing entries 7, 8 and 9, 10). Notably, the reaction did not proceed well using only one of the catalysts (entries 7−10).

With the optimized mild reaction conditions in hand, the scope of this reaction was promptly studied. As shown in Table 2, the reaction scope was broad and substantially improved over that of our previous method[3b,d] based on propargylic acetates (vida supra). Besides propargylic alcohols with substititions at both ends of the propargyl moiety (i.e., R^1 or $R^2 \neq$ H and $R^3 \neq$ H, entries 1−8, 13, and 14), substrates with $R^1 = R^2 =$ H (entries 10−12) worked smoothly, affording 1-iodovinyl ketones efficiently. Moreover, when R^3 = H, α-iodo enal **6i** was isolated in 73% yield (entry 9). Notable is that α-iodo enals are versatile synthetic substrates and their syntheses frequently require multiple steps[10] or strong reaction conditions[11] or were limited by substrate scope.[12] For functional group tolerance, aryl groups (entries 4−7, 10, and 11), benzyl/methyl ethers (entries 7, 8, and 11), and ester (entry 10) were allowed although a TBS ether appeared to be labile under the reaction conditions. The reaction yields were generally good to excellent, and enone formation was mostly minimal. In some cases, more catalysts were required to drive the reactions to completion in acceptable time periods (entries 7−11). For the double-bond geometry, good to excellent *Z*-selectivities were observed except for substrates with phenyl substitution (*Z*/*E* = 6:1, entries 4 and 5). In comparison, α-iodo enone **6d** was formed without much stereoselectivity ($Z/E = 1.2/1$) using the acetate of **5d**.[3b,d]

This reaction protocol could be readily applied to the synthesis of α-bromo enones/enals by replacing NIS with NBS (Table 3).[3d,13] However, the reactions proceeded slowly with 1 mol % of catalysts (e.g., 38 h for **5a**). By increasing the catalyst/additive loadings, all of the reactions were complete in less than 12 h and afforded products with good yields. Moreover, excellent diastereoselectivities were observed in the cases of **5a** and **5i**.

Attempts to extend this chemistry to the synthesis of α-chloro/fluoro analogues were not successful, and further studies in this direction are currently ongoing.

In summary, we have developed a highly efficient synthesis of linear α-iodo/bromo-α,β-unsaturated ketones/aldehydes from propargylic alcohols. In this chemistry, two metal complexes, $Ph_3PAuNTf_2$ and $MoO_2(acac)_2$, catalyze this reaction collaboratively, and Ph_3PO is used as an additive to suppress undesired enone/enal formation. Notable features of this method include low catalyst loadings, mild reaction conditions, and mostly good to excellent diastereoselectivity. In comparison to our previously developed method based on propargylic acetate substrates, this chemistry omits the need to prepare acetate derivatives and, moreover, has a much broader substrate scope.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139–2142.

(11) Chen, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 4993–4996.

(12) Antonioletti, R.; D'Auria, M.; Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* **1981**, *22*, 1041–1042.

(13) Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F. *J. Organomet. Chem.* **2009**, *694*, 592–597.