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Entry to β-Alkoxyacrylates via Gold-Catalyzed Intermolecular Coupling of Alkynoates and Allylic Ethers

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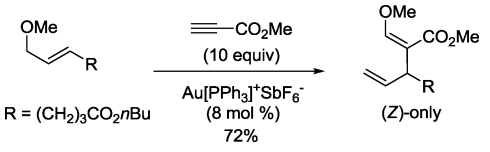
ABSTRACT



The first gold-catalyzed intermolecular coupling of alkynoates and allylic ethers invoking alkoxy addition and [3,3]-sigmatropic rearrangement as the key mechanism has been developed. Remarkably, the reaction showed complete chemoselectivity toward the pathway initiated by the alkoxy addition to alkynes. This unprecedented reactivity led to a new access to diversely substituted β-alkoxyacrylates in a highly efficient manner.

Over the past decades, the use of metal catalysts for alkyne activation attracted much attention in organic chemistry.[1] In particular, intramolecular alkoxy addition with the concomitant alkyl shift (formal intramolecular carboalkoxylation) led to the development of novel catalytic syntheses of various furan heterocycles and carbocycles with excellent chemical efficiency.[2] Despite the notable advances in this area, the more challenging intermolecular version of this reaction remains underdeveloped. Recently, a number of Au-catalyzed tandem processes have been reported which combine the intramolecular alkoxy addition with the concomitant allyl shift.[3] A key feature of this transformation is the efficient charge-induced [3,3]-sigmatropic rearrangement of the oxonium-ion intermediate. We envisioned that the *inter*molecular variant of

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(1) For selected reviews of transition-metal-catalyzed reactions of alkyne, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (b) Corma, A.; Leyva-Perez, A.; Sabataer, M. J. *Chem. Rev.* **2011**, *111*, 1657. (c) Sohel, S.; Md, A.; Liu, R. *Chem. Soc. Rev.* **2009**, *38*, 2269. (d) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (e) Michelet, V.; Toullec, P. Y.; Genêt, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (g) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (h) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (i) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (j) Gorin, D. J.; Toste, F. D. *Nature* **2007**, 446. (k) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (l) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(2) For selected recent examples on the Pt- or Au-catalyzed carboalkoxylation, see: (a) Kim, H.; Rhee, Y. H. *J. Am. Chem. Soc.* **2012**, *134*, 4011. (b) Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464. (c) Kim, C.; Bae, H. J.; Lee, J. H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14460. (d) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2009**, *351*, 1089. (e) An, S. E.; Jeong, J.; Baskar, B.; Lee, J.; Seo, J.; Rhee, Y. H. *Chem.—Eur. J.* **2009**, *15*, 11837. (f) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (g) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (h) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (i) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *45*, 4473. (j) Nakamura, I.; Bjracharya, G. B.; Wu, h.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423. (k) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785.

(3) For selected examples on the intramolecular alkoxy addition–[3.3]-sigmatropic rearrangement, see: (a) Istrate, F. M.; Gagosz, F. *Beilstein J. Org. Chem* **2011**, *7*, 878. (b) Cheong, J. Y.; Im, D.; Lee, M.; Lim, W.; Rhee, Y. H. *J. Org. Chem.* **2011**, *76*, 324. (c) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263. (d) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 2605. (e) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; Becker, J. D. B.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133. (f) For a related study on the pyrrole formation, see: Istrrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

(4) Compared to allyl ethers, the more nucleophilic allyl alcohols are known to undergo alkoxylation–Claisen rearrangement under Ag(I) or Au(I) catalysis: (a) Kataoka, Y.; Matsumoto, O.; Tani, K. *Chem. Lett.* **1996**, 727. (b) Ketcham, J. M.; Biannic, B.; Aponick, A. *Chem. Commun.* 2013, DOI: 10.1039/c2cc37166a. However, these products need derivatizing steps under highly basic conditions to obtain the corresponding β-alkoxyacrylates.

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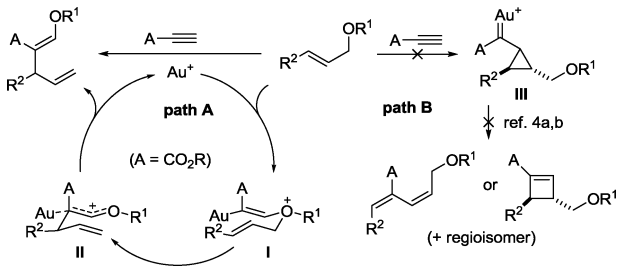
Scheme 1. Basic Scheme of the Coupling Reaction of Alkynoates and Allylic Ethers



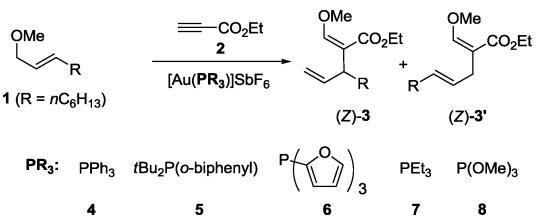
this reaction,[4] i.e., coupling of the allylic ethers and alkynes, would provide a new access to synthetically useful α-allyl-β-alkoxyacrylates (path A, Scheme 1) with (*Z*)-geometry that could not be synthesized via conventional methods.

This unprecedented reaction raises a number of challenging issues. In addition to the inherently higher entropic barrier for the intermolecular alkoxy addition step compared with the intramolecular version, the olefin moiety can compete with the ether for the attack onto the alkyne (path B, Scheme 1). In fact, some related intermolecular coupling reactions of alkyne with various olefins invoking this mechanism have recently been reported.[5] Thus, a key issue in designing the proposed catalytic cycle shown in Scheme 1 is the chemoselectivity of the coupling event that can drive the reaction toward the pathway mediated by alkoxy-addition step.

We commenced our study with the coupling reaction of easily available allylic ether **1** and various terminal alkynes. The reaction of **1** with the unactivated 1-heptyne or phenylacetylene in the presence of various cationic Au complexes led to formation of intractable mixture of compounds.[6] We reasoned that the initial alkoxy addition might be too slow when unactivated alkynes were employed. Based upon the related studies on the intermolecular hydroarylation of alkynoate esters,[7] we surmised that a cooperative polarization of the alkyne by an acceptor-substituent and a gold(I)-catalyst might enhance the charge interaction to facilitate the initial alkoxy addition step.

Indeed, commercially available ethyl propiolate **2** (1 equiv) in the presence of pregenerated cationic Au complex of ligand **4** (10 mol %) showed significant conversion for the desired tandem process, giving the β-alkoxyacrylate product **3** in 56% yield with the recovery of the starting material **1** in ~20% yield (Table 1, entry 1). In this case, formation of some side products such as the homodimer

Table 1. Optimization of the Reaction Conditions[a]



entry	**2** (equiv)	cat. (mol %)	solvent	time (h)	conv (%)	**3**[b] (%)
1	1	**4** (10)	CH_2Cl_2	3	81	56 (70)
2	5	**4** (10)	CH_2Cl_2	3	88	63 (72)
3	10	**4** (10)	CH_2Cl_2	3	95	74 (78)
4	10	**4** (5)	CH_2Cl_2	10	29	18 (62)
5	10	**4** (5)	CH_3NO_2	10	86	70 (82)
6	10	**4** (8)	CH_3NO_2	10	99	86 (87)
7	10	**5** (8)	CH_3NO_2	10	66	36 (55)
8	10	**6** (8)	CH_3NO_2	10	65	34 (52)
9	10	**7** (8)	CH_3NO_2	10	59	26 (44)
10	10	**8** (8)	CH_3NO_2	10	57	35 (61)
11[c]	10	**4** (8)	CH_3NO_2	10	94	92 (98)

[a] Typical procedure: A mixture of substrate (0.4 M), pregenerated gold complexes, and ethyl propiolate was stirred at −15 °C. [b] Isolated yield (yields based on the recovered starting material in parentheses). [c] Methyl propiolate was used instead of **2**.

of **2** was observed.[8] Thus, we used an excess amount of alkynoate ester **2**. Employing 5 eq of **2** gave the desired product in 63% yield with 88% conversion (Table 1, entry 2). Further increasing the amount of **2** (to 10 equiv) improved the yield to 74% with 95% conversion (Table 1, entry 3). Lowering the catalyst loading to 5 mol % slowed the reaction significantly, generating the product in only small yield even after prolonged reaction time (Table 1, entry 4). Interestingly, using nitromethane as the solvent dramatically improved the conversion. For example, using 5 mol % catalyst **4** gave the product in satisfactory 70% isolated yield with 86% conversion (Table 1, entry 5). Simply increasing the catalyst loading to 8 mol % completed the reaction, producing the desired product in 86% yield (Table 1, entry 6). Varying the steric and electronic effects on the phosphine ligands only slowed the formation of the product (Table 1, entries 7−10). Finally, using the smaller methyl propiolate in place of **2** slightly improved the yield (Table 1, entry 11). Remarkably, no products derived from the alkyne−olefin coupling (path B, Scheme 1) was observed, which showed a complete chemoselectivity toward the alkoxy addition-induced pathway (path A, Scheme 1).[9] In addition, only the less stable (*Z*)-isomer of the β-alkoxyacrylate was obtained with no indication of (*E*)-isomer formation.[10,11] It should also be noted that the linear product **3′** was not observed, supporting a concerted [3,3]-sigmatropic rearrangement in

(5) (a) Yeom, H.-S.; Koo, J.; Park, H.-S.; Wang, Y.; Liang, Y.; Yu, Z.-X.; Shin, S. *J. Am. Chem. Soc.* **2012**, *134*, 208. (b) López-Carrilo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292. (c) Dateer, R. B.; Shaibu, B. S.; Liu, R. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 113. (d) Hashmi, A. S. K.; Blanco, M. C.; Kurpejovic, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709. For *inter*molecular three-component coupling: (e) Melhado, A. D.; Brenzovich, W. E., Jr.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8885.

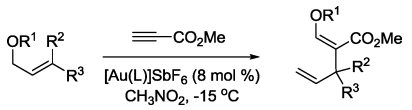
(6) In our case, internal alkynes with or without a CO_2R (or SO_2Ar) group did not work.

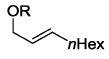
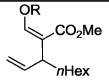
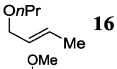
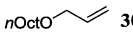
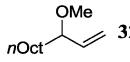
(7) (a) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (b) Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

(8) (a) Chen, C.-K.; Tong, H.-C.; Hsu, C.-Y. C.; Lee, C.-Y.; Fong, Y. H.; Chuang, Y.-S.; Lo, Y.-H.; Lin, Y.-C.; Wang, Y. *Organometallics* **2009**, *28*, 3358. (b) Werner, H.; Schwab, P.; Heinemann, A.; Steinert, P. *J. Organomet. Chem.* **1995**, *496*, 207.

(9) Presumably, the electron-withdrawing alkoxy group slows formation of the intermediate **III** in path B (Scheme 1).

Table 2. Scope of the Reaction[a]



entry	substrate, R	condition	product	yield (%)[b]
				
1	**9**, R = *n*Pr	A, 10 h	**10**	71 (75)
2	**11**, R = *i*Pr	A, 20 h	**12**	59 (60)[c]
				
3	**13**, R_1 = *n*Pr, R_2 = H	A, 20 h	**14**	85 (86)
4	**15**, R_1 = H, R_2 = *n*Pr	A, 30 h	**14**	70 (74)
5	 **16**	A, 20 h	**17**	76 (77)
				
6	**18**, R = $(CH_2)_5$Ph	A, 20 h	**19**	83 (84)
7	**20**, R = $(CH_2)_6$OMe	A, 10 h	**21**	70 (78)
8	**22**, R = $(CH_2)_4$OTBS	A, 30 h	**23**	55 (65)
9	**24**, R = $(CH_2)_7CHCH_2$	A, 20 h	**25**	69 (70)
10	**26**, R = $(CH_2)_3CO_2$*n*Bu	A, 40 h	**27**	72 (80)
11	**28**, R = $(CH_2)_4$CN	A, 40 h	**29**	53 (72)
12	 **30**	A, 30 h	**31**	21 (36)
13		B, 20 h	**31**	52 (69)
14	 **32**	A, 40 h	**33**	30 (43)
15		C, 40 h	**33**	55 (73)

[a] Typical procedure: A mixture of substrate (0.4 M in CH_3NO_2), pregenerated [Au(**L**)]SbF_6 (8 mol %) and methyl propiolate (10 equiv) was stirred at −15 °C. Method A: **L** = **4**. Method B: **L** = **6**. Method C: **L** = **8**. [b] Isolated yield (based on recovered starting material in parentheses). [c] Mixture of *E* and *Z* isomers was obtained.

the allyl shift and no intervention of allyl cation. As control experiments, we have also screened other catalysts ($AgSbF_6$ (10 mol %), $AgNTf_2$ (10 mol %), or $HNTf_2$ (10 mol %) in CH_3NO_2); under these conditions, no reaction was observed.

With the optimized conditions in hand, we then explored an array of the allylic ethers for the formation of β-alkoxyacrylate products (Table 2). First, we explored the steric effect of the alkoxy moiety of allyl ethers. Using *n*-propryl ether **9** generated the desired product **10** in 71% yield (Table 2, entry 1). Employing the larger isopropyl ether **11** gave the product **12** in somewhat lower 59% yield (Table 2, entry 2). Interestingly, an equimolar mixture of (*Z*)- and (*E*)-isomers of the product was obtained in the latter case. Then, we investigated the effect of the olefin structure. As described in entries 3 and 4, the (*E*)-isomer of the olefin **13** gave the product **14** in 85% yield, while the (*Z*)-isomer **15** generated **14** in somewhat lower 70% yield.

Using the crotonyl alkyl ether **16** uneventfully gave the product **17** in 76% yield (Table 2, entry 5). Notably, the reaction showed an excellent compatibility with the functional groups that potentially interfere with the desired transformation. For example, the phenyl, alkoxy, and terminal olefin groups were well tolerated, and TBMDS silyl ether survived the reaction condition (Table 2, entries 6−9). In addition, the reaction well tolerated base-sensitive functional groups such as an alkyl ester and a nitrile group (Table 2, entries 10−11). These two examples underscore a unique feature of the current synthesis because these β-alkoxyacrylate products cannot be easily accessed by the conventional strongly basic conditions. As is the case for the previous intramolecular alkoxy addition−sigmatropic processes,[2,3] the unsubstituted allyl ether **30** reacted much slower than the γ-substituted allyl ethers (Table 2, entries 12−13 vs entries 1−11). Interestingly, in this case, a change of ligand to **6** in place of **4** proved more efficient, improving the yield to 52% yield (Table 2, entry 13). Also, the reaction of an α-branched allyl ether **32** was sluggish under the standard protocol (Table 2, entry 14). In this case, a smaller ligand **8** proved more effective producing **33** in 55% yield (Table 2, entries 14 and 15). In all the above examples in Table 2, the regioselectivity of the products was consistent with a sigmatropic mechanism in the alkyl shift.

From a synthetic viewpoint, the current method represents a highly efficient and stereoselective method for the synthesis of β-alkoxyacrylates. These types of compounds are easily found in various bioactive natural products such as elenolic acid,[12a] alkaloid mitragynine,[12b] oudemansin,[12c] and secologanin and other derivatives.[12d] In addition, β-alkoxyacrylates serve as useful radical acceptors for the synthesis of oxacyclic natural products.[13] Moreover, highly functionalized 1,4-diene fragments with (*Z*)-geometry should find additional use in synthetic organic chemistry. The conventional multistep syntheses of the β-alkoxyacrylates requires reactive reagents and are usually performed under highly basic conditions.[14] As demonstrated by the examples in Table 2, the current synthesis can be operated under very mild conditions. Finally, generation of a stereogenic center in the product proposes an interesting asymmetric synthesis of these highly useful compounds.

To further investigate the effect of acceptor substituents on the alkynes in the intermolecular coupling, the more polarizing *p*-Ts substituted alkyne **34** was examined

(10) The stereochemistry of the product was confirmed by the NOE study. Moreover, the (*Z*)-**3** (methyl ester) was completely converted into the thermodynamically more stable (*E*)-**3** by treatment with TsOH (10%) in CH_2Cl_2. For details, see the Supporting Information. No product isomerization into the conjugate 1,3-diene was observed.

(11) This (*Z*)-stereochemistry is opposite to those observed for related Pt-catalyzed intramolecular reactions (ref 2d and 2k). Once *trans*-addition of ether oxygen to form **I** occurs, the following allyl migration and deauration must be faster than C−C rotation of **II** (Scheme 1).

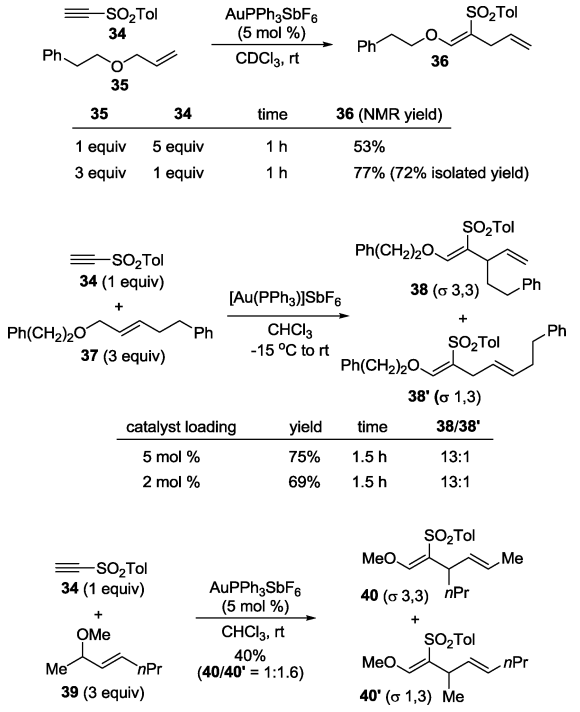
(12) (a) Hatakeyama, S.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 865. (b) Ma, J.; Yin, W.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491. (c) Wood, K. A.; Kau, D. A.; Wrigley, S. K.; Beneyto, R.; Renno, D. V.; Ainsworth, A. M.; Penn, J.; Hill, D.; Killaky, J.; Depledge, P. *J. Nat. Prod.* **1996**, *59*, 646. (d) Isoe, S.; Katsumura, S.; Okada, T.; Yamamoto, K.; Takemoto, T.; Inaba, H.; Han, Q.; Nakatani, K. *Tetrahedron Lett.* **1987**, *47*, 5865.

(13) For a review, see: Lee, E. *Pure Appl. Chem.* **1996**, *68*, 631. The current synthesis of conventionally unavailable (*Z*)-alkoxyacrylates might lead to new routes to oxacycles having a complementary stereochemistry.

(14) For examples on the conventional synthesis of highly substituted β-alkoxyacrylates, see: (a) Kondo, M.; Tsuzuki, K.; Hamada, H.; Yamaguchi, Y.; Uchigashima, M.; Saka, M.; Watanabe, E.; Iwasa, S.; Narita, H.; Miyake, S. *J. Agri. Food. Chem.* **2012**, *60*, 904. (b) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.* **2012**, *14*, 1070. (c) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5397.

(Scheme 2). The reaction of **34** with allylic ether **35** under the optimized condition for propiolate esters gave the desired 1,4-diene **36** in somewhat lower yield (53%). However, using the allylic ether **35** in excess (3 equiv) improved the yield to 77% with essentially complete conversion within 0.5 h at 5 mol % of catalyst loading. The comparable reactivity of **34** with lower amount of catalyst and the lower substrates ratio indicated that the stronger charge-interaction induced by *p*-Ts substituent is beneficial for the formation of initial adduct **I** (Scheme 1) and/or the [3,3]-sigmatropic rearrangement.

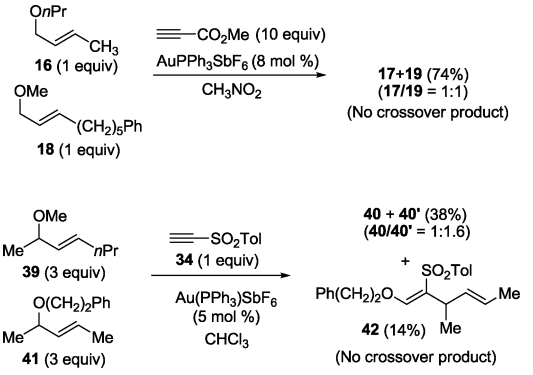
Scheme 2. Reactions of Alkynyl Sulfone **34**



When γ-substituted allyl ether **37** was used, the catalyst loading could be further reduced to 2 mol % without significant loss in the yield of the product 1,4-diene. Interestingly, formation of the branched product **38** was accompanied by a small amount of linear product **38′** (**38**/**38′** = 13:1).[15] This stands in sharp contrast to the reaction of propiolate ester **2** that only showed the formation of the branched product. Most strikingly, **39** having α-substituted allyl unit delivered a mixture of the [3,3]- and [1,3]-shift product (**40**/**40′** = 1:1.6).[16]

Even though the reaction of propiolate ester gave no [1,3]-migration product, the above reaction of alkynyl sulfone **34** raises a question on the mechanism of the reaction, particularly with regard to the concerted nature of the allyl shift process. Thus, we performed a crossover experiment. As shown in Scheme 3, subjection of a 1:1 mixture of the compounds **16** and **18** under the optimized condition gave no crossover products. Even in the reaction of α-branched allyl ether **39** and **41** with alkynyl sulfones **34**, where [1,3]-migration is favored, no crossover product was observed by GC–MS or crude NMR spectra. These experiments unambiguously confirmed the concerted [3,3]- or [1,3]-migration of the allyl group, respectively.

Scheme 3. Crossover experiments



In summary, we developed a new and highly efficient access to substituted (*Z*)-*β*-alkoxyacrylates using Au-catalyzed intermolecular coupling of alkynoates and allylic ethers. Of particular note is the chemoselectivity of the reaction. Mechanistic investigation as well as synthetic application of this catalytic reaction is in progress and will be reported in due course.

Acknowledgment. This work was supported by the National Research Foundation funded by the Korean government (NRF-2010-0009458, NRF-2012-015662).

Supporting Information Available. Experimental details and spectral data; ^{1}H and ^{13}C scan of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The ratio was determined by the integration of ^{1}H NMR. See ref 2d for a possible *Z*/*E* isomerization mechanism.

(16) The α-substituted allyl ethers, such as **39**, were generally inefficient presumably because of premature ionization from the intermediate **I** (Scheme 1). In fact, a significant amount of (*Z*)-2-methoxyvinyl sulfone was observed from the reaction of **39** with **34**.

The authors declare no competing financial interest.