Conference paper

Seunghoon Shin*

The effect of acceptor-substituted alkynes in gold-catalyzed intermolecular reactions[1]

Abstract: Alkynes substituted with electron-withdrawing groups participated in various intermolecular reactions with olefin substrates, including [4 + 2] annulation of propiolic acids, intermolecular metathesis-type reaction and carboalkoxylation involving allylethers.

Keywords: alkenes; alkynes; annulations; [4 + 2] annulations; atom economy; carboalkoxylation; catalysis; enyne cross-metathesis; gold catalysis; intermolecular reactions; OMCOS-17.

[1]A collection of invited papers based on presentations at the 17th International IUPAC Conference on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-17), Fort Collins, Colorado, USA, 28 July–1 August 2013.
***Corresponding author: Seunghoon Shin,** Department of Chemistry, Hanyang University, Seoul 133-791, Korea, e-mail: sshin@hanyang.ac.kr

Introduction

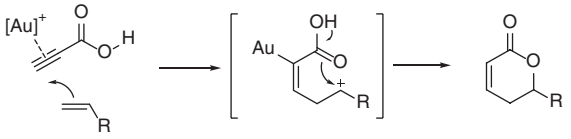
In the past decade, homogeneous gold catalysis has been one of the most active areas of research in transition metal catalysis [1]. Due to the exceptional alkynophilic ability of gold complexes to activate π-bonds toward nucleophilic attack, a variety of tandem transformations have been made possible that occurs with rapid increase in the molecular complexity. In the interaction of Au-activated alkyne with nucleophile, substituents on the alkyne may have a pronounced effect on the regioselectivity and more importantly in promoting intermolecular reactions. Intermolecular reactions often do not require elaborate, pre-assembled substrates and thus should have more diverse applications. However, gold catalyzed intermolecular reactions have been less frequently reported than the intramolecular counterpart [2], presumably due to the inherent entropic penalty as well as the dominant role of orbital interactions in the transition states in gold catalysis.

Here the donor- or acceptor substituents may induce an enhanced charge interaction and thus cooperative activation of alkynes along with π-acids could promote efficient intermolecular reactions. Compared to the widespread use of ynamides [3], the effect of acceptor-substituents such as an ester or a sulfone has been less explored. In this paper, we report our recent study on the effect of these substituents in intermolecular gold-catalyzed reaction.

[4 + 2] Annnulation of propiolic acids

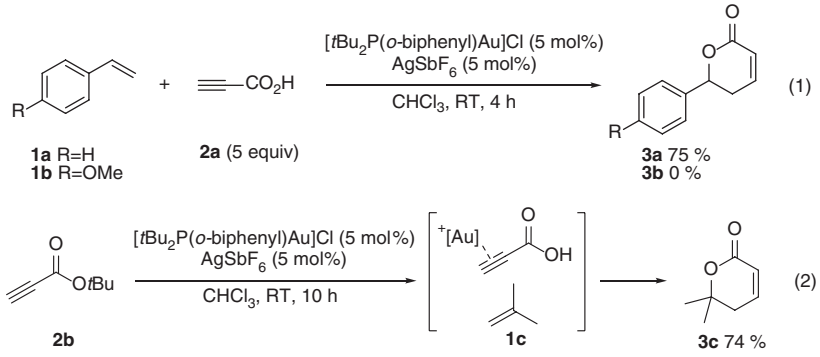
The slow intermolecular reaction involving alkenes could lead to competitive side reactions, such as olefin polymerization and isomerization [4]. We projected acceptor-substituted alkynes such as propiolic acid might promote faster reaction of alkenes with gold-activated alkynes relative to these side pathways. A synergistic activation of the triple bond of propiolic acids by the Au-catalyst and by the acceptor substituents (-COOH) may result in an intermolecular nucleophilic addition of olefins onto alkynes, followed by the intramolecular trapping of the carbenium ion by the carboxylic acid, leading to a formal [4 + 2] cycloaddition (Scheme 1) [5]. The resulting products, α,β-unsaturated-δ-lactones form the core of diverse biologically active compounds, such as fostriecin and leustroducins.

Our initial tests started with styrene derivatives employing catalysts formed in-situ from [tBu$_2$P(o-biphenyl)Au]Cl (5 mol%) and $AgSbF_6$ (5 mol%) in $CHCl_3$. The reaction of styrene **1a** efficiently afforded the



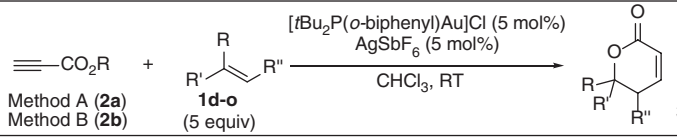
Scheme 1 Formal [4 + 2] cycloaddition of propiolic acid.

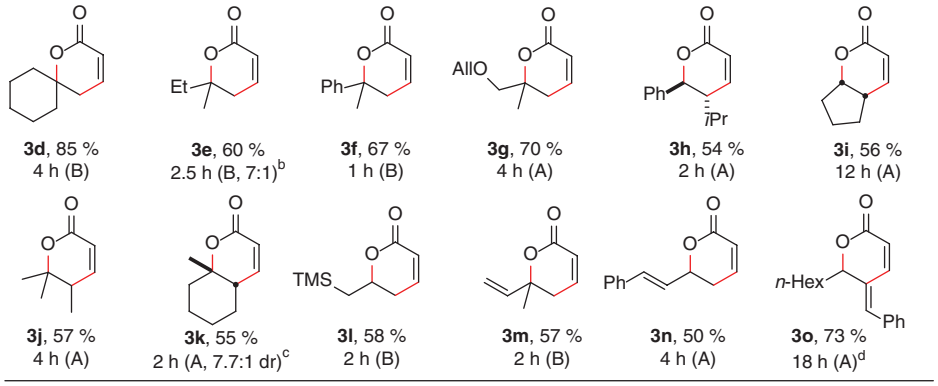
corresponding lactone **3a** in 75 % after 4 h at room temperature (eq. 1). However, electron-rich 4-MeO derivative **1b** failed to give the desired product and instead resulted in an extensive oligo- and polymerization of **1b** that presumably catalyzed by the gold complex itself [4a] or by the acid [4c]. Based on our previous study on the cationic trapping by *tert*-butyl ester [6], *t*-butyl propiolate **2b** was employed as a surrogate of propiolic acid (eq. 2). To our delight, the reaction of **2b** in the absence of added alkenes resulted in an efficient formation of **3c** (74 %), where Au-catalyst likely induced liberation of isobutene **1c**, followed by the [4 + 2] annulation. This experiment indicated that relatively polarized 1,1-disubstituted alkenes, such as **1c**, participated as efficient olefin donors.



As shown in Table 1, the scope of [4 + 2] annulation covers not only 1,1-disubstituted alkenes (**1d-g**), but also 1,2-disubstituted (**1h-i**) and tri-substituted (**1j-k**) alkenes, although symmetrical 1,2-disubstituted alkenes

Table 1 [4 + 2] Annulations with alkenes[a].

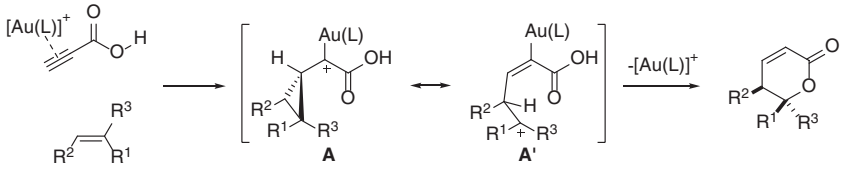




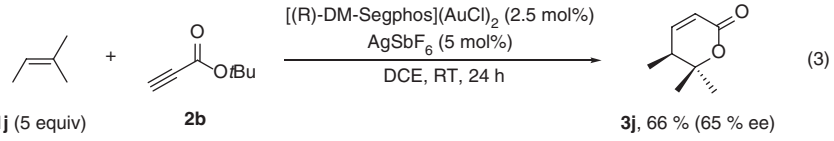
[a]Method A: propiolic acid (**2a**); Method B: *tert*-butyl propiolate (**2b**).
[b]The ratio of **3e**:**3j**.
[c]Diastereomeric ratio.
[d]Allene (1 equiv) and **2a** (5 equiv).

such as cyclopentene (**1i**) underwent markedly slower reaction. For substrates such as 2-methylbut-1-ene, **1e** that are sensitive to acid-catalyzed isomerization (i.e. into **1j**), use of *tert*-butyl propiolate (**2b**) gave the better yield of **3e** than **2a** because the concentration of propiolic acid can be kept to a minimum during the reaction. With a silyl substituent that can stabilize β-cation, even mono-substituted alkene (**1l**) produced the **3l** albeit with a mediocre efficiency. The scope of the current reaction could be extended to 1,3-dienes (**1m-n**) and an allene (**1o**). Direct conversion of commercially available 1-phenyl-1,3-butadiene into goniothalamin (**3n**) showcased the utility of the current protocol.

Working model for the [4 + 2] annulation was based on the analogy to the gold-catalyzed intramolecular cyclization of 1,n-enynes [1] and the key intermediate involves the resonance between the cyclopropyl gold carbene (**A**) and the homoallyl cation (**A'**) (Scheme 2) [7]. The overall *cis*-addition in the [4 + 2] annulation observed in **3h**, **3i** and **3k** can be attributed to a faster intramolecular trapping than the rotation of C-C bond in **A'**. Preliminary asymmetric [4 + 2] reaction was also attempted based on the above mechanism employing commercially available ligands. Given that the initial adduct from the alkynes and alkenes takes the form of **A** and **A'**, the key interaction necessary for the enantiofacial discrimination of the alkene was assumed to be steric repulsion between R^3 and carboxylic acid. In accord with this analysis, a tri-substituted alkene (**1j**) gave a better enantioselectivity than styrene (**1a**) and *tert*-butyl propiolate (**2b**) gave better enantioselectivity than propiolic acid (**2a**). Using (R)-DM-Segphos, upto 65 %*ee* of **3j** was obtained as a preliminary result.



Scheme 2 Working model for the interaction of propiolic acid with alkenes.

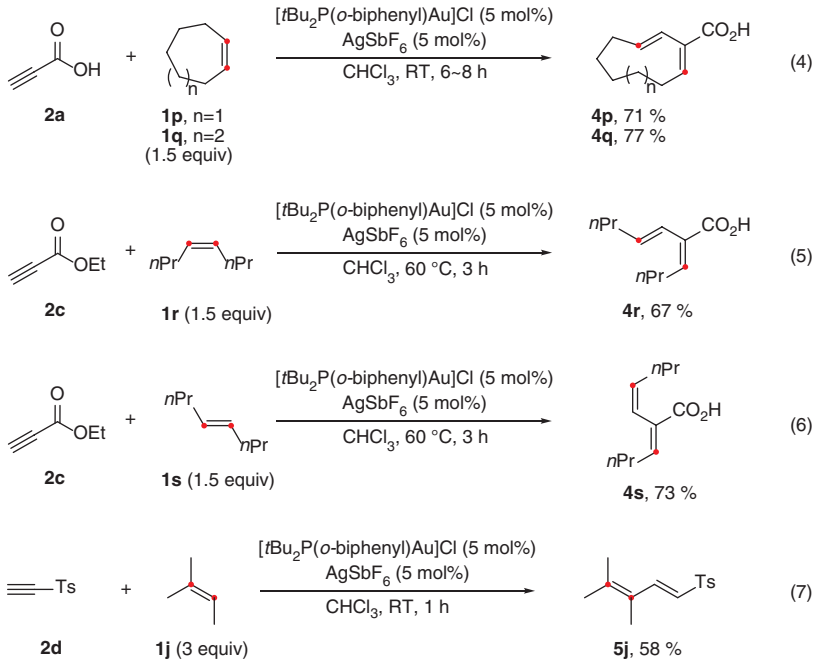


Skeletal reorganization leading to metathesis-type reaction

Within the vast body of literature on the 1,n-eyne cycloisomerization, skeletal reorganization leading to metathesis-type reactivity has attracted a considerable attention [8], due to the intriguing mechanism as well as synthetically utility of the 1,3-dienes formed in an atom-economical manner. In the intermolecular metathesis-type structural reorganization between alkenes and alkynes, stereocontrol of the two double bonds in the acyclic 1,3-diene products is a prime issue, similar to the case of Ru-catalyzed enyne cross metathesis [9].

In the course of our study on the intermolecular [4 + 2] reaction, we found that medium-sized cycloalkenes (**1p** and **1q**) gave unexpected enyne cross metathesis-type product (eq. 4, Scheme 3) [5]. Notably, this intermolecular transformation required as little as 1.5 equiv of excess alkenes for effective coupling of alkynes and alkenes. In the reaction of symmetrical acyclic alkenes, such as *cis*- and *trans*-oct-4-ene (**1r** and **1s**), an interesting stereospecificity was observed; the stereochemistry of starting olefin determined the E/Z stereochemistry of the unconjugated double bond in the diene product (eqs. 5 and 6). Notably, stereoisomerically pure **4r** and **4s** (by GC) were obtained from the respective Z or E isomers of starting olefins. In addition to propiolic acid (**2a**), ethyl propiolate (**2c**) as well as *p*-toluenesulfonyl acetylene (**2d**) also effectively coupled into the corresponding 1,3-dienes in a stereospecific manner. However, terminal alkyne such as 1-octyne or phenylacetylene did not participate in this reaction.

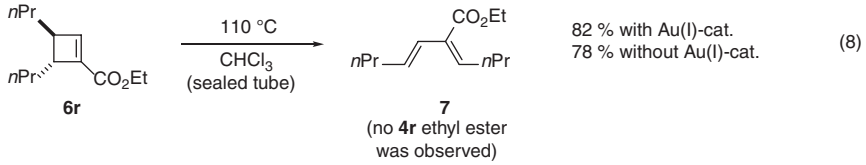
Interestingly, the same catalytic system used for the [4 + 2] annulation ([tBu$_2$P(o-biphenyl)Au]Cl and $AgSbF_6$ in $CHCl_3$) also proved best for the enyne cross metathesis-type structural reorganization and the



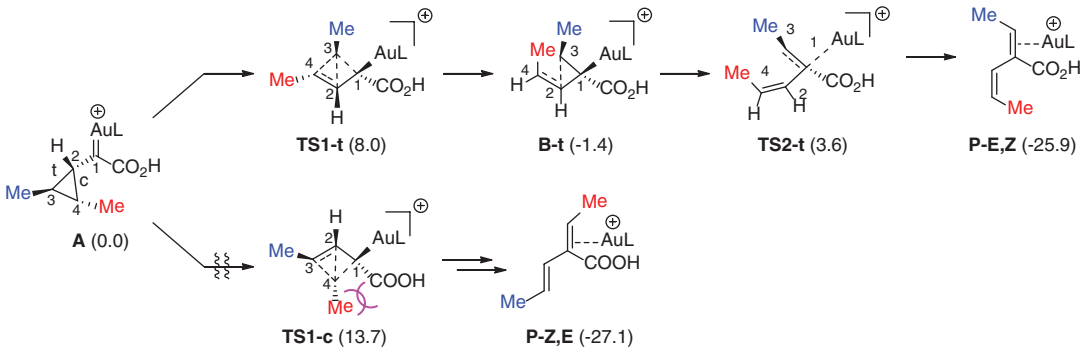
Scheme 3 Enyne cross metathesis-type structural reorganization.

nature of olefins **1** dictated the reaction pathways. Relatively polarized olefins such as those in Table 1 that can effectively stabilize the carbenium ion in the reaction with the Au-activated alkyne (Scheme 2) underwent smooth [4 + 2] annulation with propiolic acid (**2a**). However, these olefins were generally poor substrates toward metathesis. For example, the reaction of 2-methylbut-2-ene (**1j**) with **2c** was sluggish, but the reaction with more polarized **2d** gave instead a conjugate addition product **5j** (eq. 7).

The fact that the same catalyst promote both [4 + 2] annulation and metathesis-type rearrangement highly indicates a common intermediate **A/A'** in this reaction dichotomy (Schemes 2 and 4). The first mechanistic scenario that was examined was a possibility that the cyclopropyl Au-carbenoid (such as **A**) from **1r** and **2c** may evolve into a cyclobutene derivative **6r**, followed by electrocyclic con-rotatory ring opening. However, when an independently prepared **6r** was ring-opened at 110 °C in $CHCl_3$ (sealed tube), 1,3-diene **7** was obtained with the known torque-selectivity (eq. 8, '*outward*' con-rotatory) [10] and no trace of **4r** ethyl ester was observed in the reaction mixture. The reaction in the presence of the Au(I) catalyst also required heating at 110 °C and provided the same 1,3-diene isomer. This clearly ruled out a possible involvement of a cyclobutene intermediate **6r** in this metathesis product formation.



Further mechanistic insight for the stereospecific σ-bond reorganization was obtained from DFT computational study (Scheme 4) [5]. Once the cyclopropyl Au-carbenoid **A** forms, preferential migration of distal bond (C3–C4) over the vicinal bonds (C2–C4 or C2–C3) occurs via **TS1-t** to form C1–C3 bond (**B-t**) with concomitant weakening of C2–C3 bond. The following cleavage of C2–C3 is accompanied by the formation of two double bonds between C2–C4 and C1–C3. The alternative migration of C3–C4 bond through **TS1-c** to form C4–C1 bond has higher activation barrier than **TS1-t** by 5.7 kcal/mol, because the formation of C4–C1 bond is accompanied by an increasing steric repulsion between C4–Me and COOH.



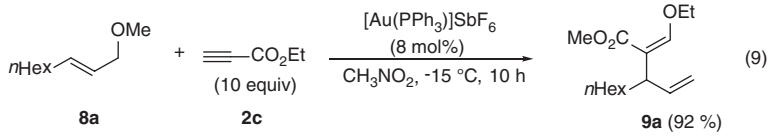
Scheme 4 Mechanistic interpretation; relative free energies (in kcal/mol, $CHCl_3$) are shown in parentheses.

Tandem alkoxylation/Claisen rearrangement of allyl ethers

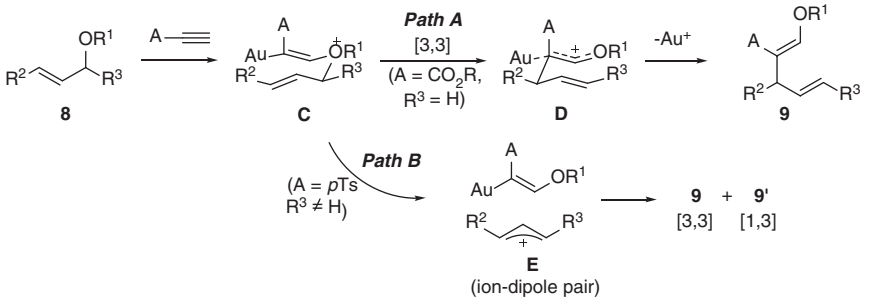
Intramolecular carboalkoxylation initiated by the alkoxy addition of allyl ethers onto triple bonds, followed by *O*-alkyl shift led to a development of various heterocycle syntheses [11]. Although allyl alcohols have been known to undergo corresponding intermolecular reaction with allyl shift [12], less nucleophilic allyl ethers have not been reported to undergo intermolecular reactions prior to our work [13, 14].

Allyl ethers have shown markedly decreased efficiency in the [4 + 2] annulation or metathesis-type reaction due to the inductive effect of oxygen atom and thus the decreased electron-density in the π-bond. Instead, the reaction of allyl ethers with propiolates occurred with *O*-addition onto alkynes and the following sigmatropic allyl 1,3-shift resulted in β-alkoxyacrylates or 2-alkoxyvinylsulfones with (Z)-stereohemistry (Scheme 5). As in the intramolecular counterpart [11], the charge-induced Claisen rearrangement occurred under an exceptionally mild condition.

In the reaction of (E)-1-methoxynon-2ene **8a** with ethyl propiolates **2c**, the effect of ligand, counter-anion and solvent was examined. The most effective catalytic system was found to be pre-formed $Au(PPh_3)SbF_6$ (5 mol%) in CH_3NO_2 and for a full conversion, 10:1 ratio of ethyl propiolate/allyl ether was required (eq. 9). Contrary to the [4 + 2] annulation or metathesis where [tBu$_2$P(*o*-biphenyl)Au]$^+$ complex was the most suitable, the allylalkoxylation was most efficient with the less bulky PPh_3 ligand, which presumably reflect the increasing steric interaction between [Au(L)] moiety and R^2 substituent in the transition state from **C** into **D** (Scheme 5).

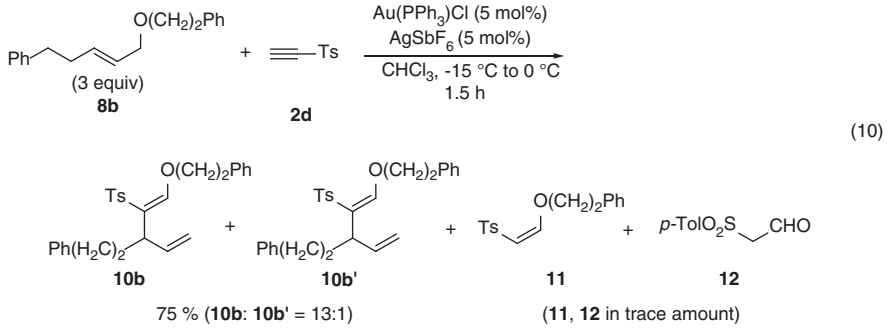


The reaction of allyl ethers with *p*-toluenesulfonylacetylene (**2d**) was much faster than that of propiolates. In this case, only 3 equiv of excess olefin gave a complete conversion of **2d**. However, depending on the allyl



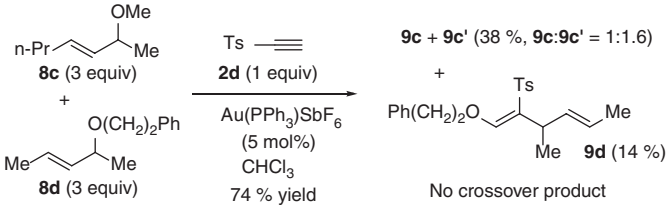
Scheme 5 Tandem alkoxylation/Claisen rearrangement

ethers used, varying amount of alkoxy addition adduct **11** and hydration product **12** was observed in the reaction mixture, which was especially severe for slower reacting allyl ethers. The alkoxy addition adduct **11** most probably formed from a premature dissociation of allyl cation from **C** before the Claisen rearrangement (Scheme 5) and the hydration product **12** resulted from the reaction of **2d** with adventitious water (eq. 10).



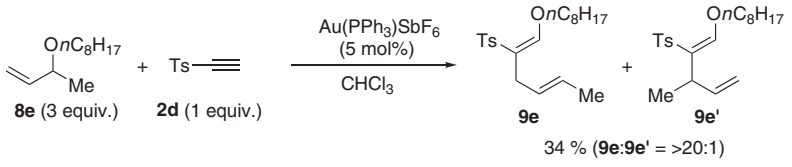
(10)

In the reaction of allyl ethers **8** with propiolates or tosylacetylene, several trends became apparent (Scheme 5). Substrates **8** having R^2 substituents (γ-substituted allyl ethers) generally provided higher yield of **9** than those without R^2. However, those with R^3 substituent (α-branched allyl ethers) were poor substrates with both **2c** and **2d**. With tosylacetylene **2d**, α-branched allyl ethers gave a low ratio of [3,3]/[1,3]-shift products (**9/9'**) in a low overall yields of **9**. The mechanism for the [1,3] shift product (**9'**) formation was inspected through cross-over experiments (eq. 11), which indicated that no cross-over occurred between α-branched allyl ethers **8c** and **8d**. Furthermore, addition of an isolated 2-alkoxyvinylsulfone **11** to the reaction mixture did not result in an incorporation of **11** in the product **9/9'**.



(11)

The ratio of **9/9'** turned out to be dependent on the steric demand at the allylic termini (R^2 and R^3). While the reaction of **8c** with **2d** gave a mixture of **9c/9c'** (1:1.6) in 40 % yield, that of **8e** (R^2 = H, eq. 12) provided a mixture of **9e/9e'** in a ratio of >20:1 favoring the apparent [3,3] shift product. The mechanistic scenario that is the most consistent with these experiments with α-branched allyl ethers and sulfonyl acetylene **2d** is shown in Path B (Scheme 5). α-Branched allyl ethers evolve to **9** and **9'** via initial dissociation into **E**. Absence of cross-over indicated the formation of a tight ion-dipole pair between vinyl gold and allyl cation. Then the ratio of **9/9'** is determined by the steric effect at the allylic termini, favoring nucleophilic attack of the vinyl gold in **E** at the less hindered allyl terminus [14]. Alternative sigmatropic [1,3]-shift seemed less likely because such a rearrangement should occur with *antara*-facial selectivity due to the orbital symmetry.



(12)

Conclusions

In summary, intermolecular transformations were scrutinized to understand and to utilize the interaction of the acceptor-substituted alkynes with olefins or allyl ethers. The three types of reactions outlined here do

not occur without the acceptor-substituted alkynes, which underscores the synergistic interaction of these substituents in bringing about the intermolecular reactions. From the mechanistic understanding gained in these processes, it should be possible to derive asymmetric variants, for example, in the [4 + 2] annulation and allylalkoxylation in the future. Such efforts are in process in this laboratory.

Acknowledgment: This work was supported by National Research Foundation of Korea through grants NRF-2010-0022936, NRF-2012-015662 and NRF-2012M3A7B4049653.

References

[1] (a) V. Michelet, P. Y. Toullec, J.-P. Genêt. *Angew. Chem. Int. Ed.* **47**, 428 (2008); (b) E. Jiménez-Núñez, A. M. Echavarren. *Chem. Rev.* **108**, 3326 (2008); (c) A. Fürstner. *Chem Soc. Rev.* **38**, 3208 (2009).
[2] For gold-catalyzed intermolecular reactions involving alkynes and alkenes: (a) A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats. *Adv. Synth. Catal.* **14**, 6672 (2008); (b) I. Braun, A. M. Asiri, A. S. K. Hashmi. *ACS Catal.* **3**, 1902 (2013). (c) R. B. Dateer, B. S. Shaibu, R.-S. Liu, *Angew. Chem. Int. Ed.* **51**, 113 (2012); (d) V. López-Carrilo, A. M. Echavarren. *J. Am. Chem. Soc.* **132**, 9292 (2010); For the role of a digold-alkyne complex in this reaction: (e) A. Grirrane, H. Garcia, A. Corma, E. Álvarez. *ACS Catal.* **1**, 1647 (2011).
[3] For use of ynamides in gold catalyzed intermolecular reactions: (a) R. B. Dateer, B. S. Shaibu, R.-S. Liu, *Angew. Chem. Int. Ed.* **51**, 113 (2012); (b) S. Kramer, Y. Odabachian, J. Overgaard, M. Rottländer, F. Gagosz, T. Skrydstrup. *Angew. Chem. Int. Ed.* **50**, 5090 (2011); (c) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem. Int. Ed.* **50**, 8931 (2011); see also ref. 3c.
[4] (a) J. Urbano, A. J. Hormigo, P. De Frémont, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez. *Chem. Commun*. 759 (2008); (b) C.-M. Ting, Y.-L. Hsu, R.-S. Liu. *Chem. Commun*. **48**, 6577 (2012); (c) A. Benito; A. Corma, H. Garcia, J. Primo, *Appl. Catal., A* **116**, 127 (1994).
[5] H.-S. Yeom, J. Koo, H.-S. Park, Y. Wang, Y. Liang, Z.-X. Yu, S. Shin. *J. Am. Chem. Soc.* **134**, 208 (2012).
[6] (a) J. -E. Kang, E.-S. Lee, S.-I. Park, S. Shin. *Tetrahedron Lett.* **46**, 7431 (2005); (b) J.-E. Kang, S. Shin. *Synlett*, 717 (2006); (c) C. Lim; J.-E. Kang, E.-S. Lee, S. Shin, *Org. Lett.* **9**, 3539 (2007).
[7] (a) A. Fürstner, P. W. Davies. *Angew. Chem. Int. Ed.* **46**, 3410 (2007); (b) A. Fürstner. *Chem Soc. Rev.* **38**, 3208 (2009).
[8] For reviews: (a) S. I. Lee, N. Chatani. *Chem. Commun.* 371 (2009); For representative examples: (b) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren. *Angew. Chem. Int. Ed.* **43**, 2402 (2004); (c) C. Nieto-Oberhuber, M. P. Muñoz, S, López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren. *Chem. Eur. J.* **12**, 1677 (2006); (d) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **46**, doi: 10.1021/ar400174p (2013).
[9] E. Hansen, D. Lee. *Acc. Chem. Res.* **39**, 509 (2006).
[10] (a) W. R. Dolbier, Koroniak, H.; K. N. Houk, C. Sheu. *Acc. Chem. Res.* **29**, 471 (1996); (b) J. M. Um, H. Xu, K. N. Houk, W. Tang. *J. Am. Chem. Soc.* **131**, 1542 (2009).
[11] For selected recent examples: (a) H. Kim, Y.-H. Rhee. *J. Am. Chem. Soc.* **134**, 4011 (2012); (b) C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, **131**, 14460 (2009); (c) M. Uemura, I. D. G. Watson, M. Katsukawa, F. D. Toste. *J. Am. Chem. Soc.* **131**, 3464 (2009); (d) I. Nakamura, C. S. Chan, T. Araki, M. Terada, Y. Yamamoto. *Adv. Synth. Catal.* **351**, 1089 (2009); (e) S, E. An, J. Jeong, B. Baskar, J. Lee, J. Seo, Y. H. Rhee. *Chem. Eur. J.* **15**, 11837 (2009); (f) P. Dubé, F. D. Toste. *J. Am. Chem. Soc.* **128**, 12062 (2006); (g) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **127**, 15024 (2005); (h) I. Nakamura, Y. Mizushima, Y. Yamamoto. *J. Am. Chem. Soc.* **127**, 15022 (2005).
[12] (a) Y. Kataoka, O. Matsumoto, K. Tani. *Chem. Lett.* **25**, 727 (1996); (b) J. M. Ketcham, B. Biannic, A. Aponick. *Chem. Commun.* **49**, 4157 (2013).
[13] S. R. Park, C. Kim, D.-g. Kim, N. Thrimurtulu, H.-S. Yeom, J. Jun, S. Shin, Y. Rhee. *Org. Lett.* **15**, 1166 (2013).
[14] J. Jun, H.-S. Yeom, J.-H. An, S. Shin. *Beilstein J. Org. Chem.* **9**, 1724 (2013).