#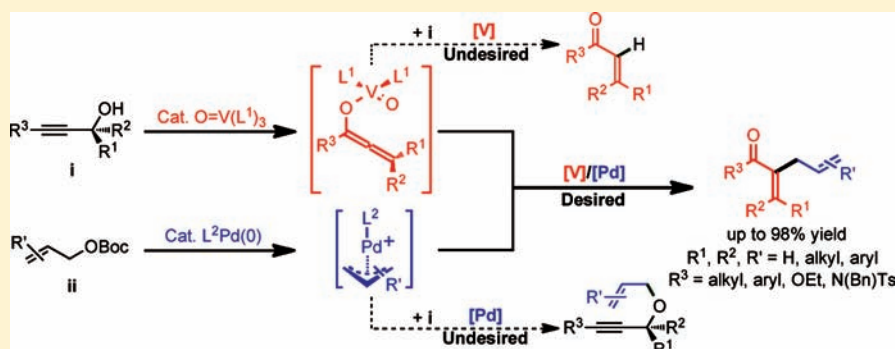 Contemporaneous Dual Catalysis: Chemoselective Cross-Coupling of Catalytic Vanadium–Allenoate and π-Allylpalladium Intermediates

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S *Supporting Information*

ABSTRACT:

This paper presents a detailed investigation of a dual catalytic system that combines a vanadium-catalyzed Meyer–Schuster rearrangement and a palladium-catalyzed allylic alkylation. The implementation of this novel reaction relies on matching the formation rates of vanadium–allenoate and π-allylpalladium intermediates with their bimolecular coupling rate in order to minimize the undesired protonation or *O*-alkylation of the catalytically generated intermediates. Chemoselectivity in this dual catalytic process was successfully achieved by adjusting ligand structure and catalyst loading ratios of the vanadium and palladium catalysts. A great range of coupling partners for both the propargyl alcohol and allyl carbonate components are readily accommodated in this new transformation, which in turn provides a novel avenue to a variety of α-allylated α,β-unsaturated ketones, esters, and amides in moderate to excellent isolated yields.

INTRODUCTION

Inspired by the finite nature of chemical feedstocks and the growing global demand for fine chemicals, the development of new synthetic processes that proceed with high efficiency, low energy consumption, and minimal waste has become an important area of research.[1] Our research group is particularly interested in improving synthetic efficiency following two specific principles: (1) the development of reactions where the maximum number of atoms of reactants appear in the products (atom economy)[2] and (2) the use of reactions that occur only at the desired functional groups in a molecule (chemoselectivity).[3] The goal is to prepare complex molecules in the smallest possible number of steps, while high efficiency and chemoselectivity are maintain in each step. To date, chemists have unimpeachably witnessed much success employing the principles of atom economy and chemoselectivity in a great number of practical applications.[4]

The hallmark of atom economical processes are simple addition reactions where two or more versatile building blocks are brought together by a catalyst without the need for additional stoichiometric reagents.[5] Our laboratory has a rich history of pursuing and developing these types of atom

economic processes.[4b] In the course of our recent studies, we became interested in coupling two catalytically generated intermediates in order to access a certain reactivity pattern and structural motif. Reactions catalyzed by two catalysts cooperatively are of great interest universally because they can exhibit reactivity and selectivity not observed in a single-catalyst system.[6] Although some studies have been conducted on the design and utilization of bifunctional catalysis systems in organic synthesis,[7] the number of dual-catalyzed reactions that have been developed is still dramatically lower than that of single catalyst systems. The paucity of dual catalytic processes arises in part from issues regarding the compatibility of the two catalysts with each other, the additional complexity of operating two separate catalytic cycles concurrently, and the low concentrations of the two reactive intermediates that must undergo a bimolecular addition to each other.

Contemporaneous dual catalysis may exemplify efficient synthesis by effectively employing the principles of atom economy and chemoselectivity. A general description of the concept
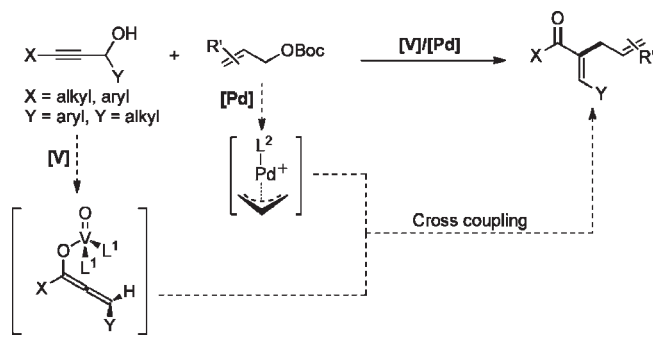
**Scheme 1. General Description of Contemporaneous Dual Catalysis**
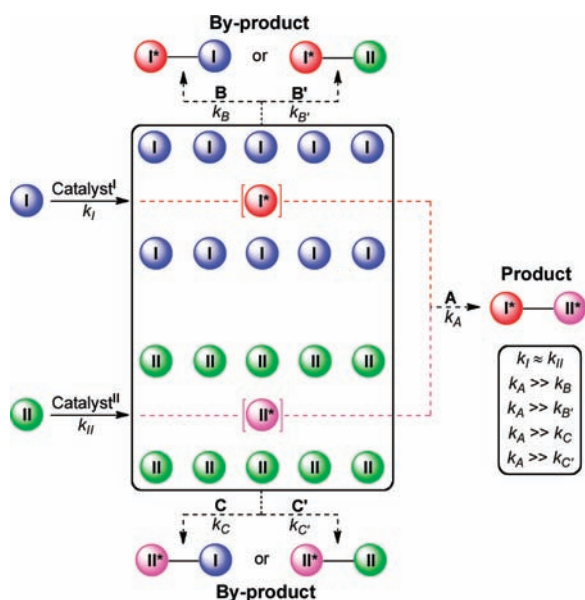
Scheme 2. Palladium and Vanadium Contemporaneous Dual Catalysis

of dual catalysis is depicted in Scheme 1. Double activation of both substrates (**I** and **II**) by two independent catalysts (catalyst[I] and catalyst[II]) would selectively generate the corresponding reactive intermediates (**I*** and **II***) catalytically. Subsequent bimolecular coupling of **I*** and **II*** would then produce the desired product **I***−**II*** (pathway A). It is noteworthy that each intermediate is surrounded by a large excess of reactive starting materials and therefore can be easily intercepted via pathways B (or B′) and C (or C′) to generate undesired byproducts. In such a system, intermediates **I*** and **II*** are present in low concentrations and will not undergo efficient bimolecular coupling unless the rate of formation of product (k_A) is significantly faster than the rates of formation of the undesired byproducts (k_B, $k_{B'}$, k_C, and $k_{C'}$). Consequently, the rapid formation of even a single undesired byproduct would prevent formation of the dual-catalyzed product. To conquer this challenge, it is critical to enhance the affinity between the two transient intermediates (**I*** and **II***) in order to increase the reaction rate of pathway A to such an extent that it could largely outcompete the potential side

Scheme 3. Formation of Ester and Amide Products via Contemporaneous Dual Catalysis
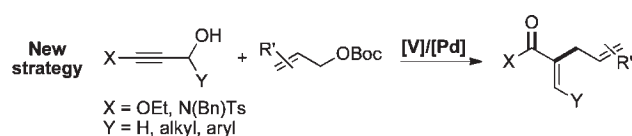
reactions. Moreover, the formation rates of **I*** and **II*** must be relatively similar ($k_I \approx k_{II}$) so that overgeneration of one intermediate does not facilitate side reactions. Thus, the execution of contemporaneous dual catalysis relies on careful design of a compatible catalyst system, the appropriate choice of the substrates, and a high affinity of the two reacting intermediates for each other.

Recently, we reported in a preliminary communication an effective example of contemporaneous dual catalysis that merges a vanadium-catalyzed Meyer−Schuster rearrangement reaction and a palladium-catalyzed allylic alkylation reaction to generate α-allylated α,β-unsaturated ketones (Scheme 2).[8] In this reaction, a vanadium−allenoate, which cannot be obtained directly by simple deprotonation of a α,β-unsaturated carbonyl compound, is generated in situ by rearrangement of a propargylic alcohol.[9] Instead of undergoing simple protonation to form the enone product, the allenoate is sufficiently reactive to intercept the π-allylpalladium intermediate, which is also generated catalytically in the reaction. The reaction proceeds efficiently despite the potential side reactions for each intermediate (protonation and O-allylation).

In the development of this dual catalytic process, certain substituents (i.e., aromatic groups) at the propargylic position of the propargylic alcohol were necessary for the reaction to occur. For example, when Y was an alkyl substituent, the reaction did not proceed at all under various conditions (see Scheme 2). We believe this result is due to the inability of the vanadium catalyst to promote the required Meyer−Schuster rearrangement with these nonactivated substrates. With this challenge in mind, we decided to further explore the substrate scope of the dual catalytic reaction because of the potential synthetic applications and because of the possibility of getting a deeper insight into the possible mechanism. We hypothesized that placement of an electron-donating heteroatom (oxygen or nitrogen) at the terminus of the alkyne would sufficiently activate the propargyl alcohol for Meyer−Schuster rearrangement to occur,[10−12] allowing us to employ alkyl groups at the propargylic position (Scheme 3). Such a variation should enable the formation of a highly reactive ketene acetal or ketene aminal intermediate and further promote the synthesis of corresponding α-allylated α,β-unsaturated ester and amide. However, there are no previous reports on the interception of these Meyer−Schuster rearrangement intermediates with an eletrophile to form new carbon−carbon bonds. In this report, we will describe the full investigation of our dual catalytic reaction involving two metal-catalyzed processes which, to our knowledge, represents the first example of contemporaneous dual metal catalysis. Furthermore, we will also propose a plausible mechanism for this transformation.

■ **RESULTS AND DISCUSSION**

Experimental Plan. The development of catalytic methods employing propargyl alcohols as latent allenoate precursors represents a facile practical entry to enolates that cannot be

Table 1. Optimization of the Ligand Structure
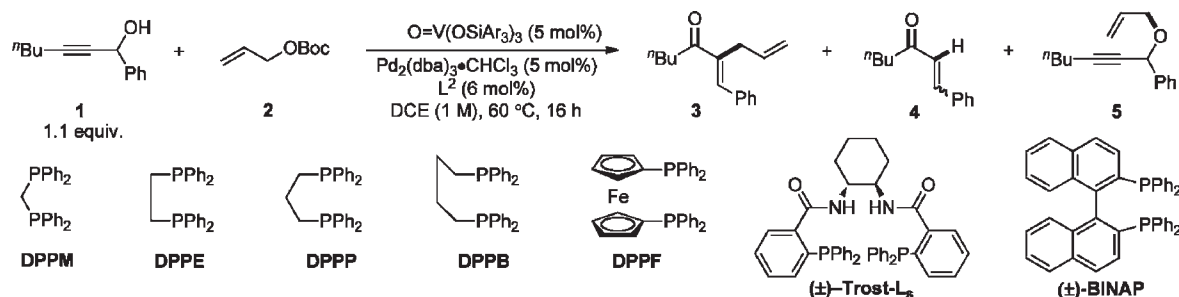
entry	Ar	L^2	conv (%)[a]	3:4:5[b]	E:Z of 3[b]	entry	Ar	L^2	conv (%)[a]	3:4:5[b]	E:Z of 3[b]
1	Ph	DPPM	100	100:9:1	5:1	5	Ph	DPPF	85	13:2:1	5:1
2	Ph	DPPE	91	6:91:1	4:1	6	Ph	Trost-L_S	48	15:72:1	2:1
3	Ph	DPPP	53	1:13:11	4:1	7	Ph	BINAP	77	6:85:1	10:1
4	Ph	DPPB	96	2:1:89	4:1	8	4-Cl-Ph	DPPM	82	19:1:6	4:1

[a] Determined by ^{1}H NMR spectroscopy by observing consumption of **1**. [b] Determined by ^{1}H NMR spectroscopy.

Table 2. Optimization of Solvent
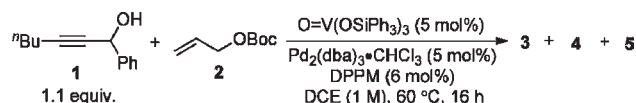
entry	solvent	conv (%)[a]	3:4:5[b]	E:Z of 3[b]
1	DCE	100	100:9:1	5:1
2	THF	100	32:5:1	2:1
3	DME	98	38:4:1	2:1
4	dioxane	14	40:2:1	2:1
5	toluene	60	17:1:8	7:1

[a] Determined by ^{1}H NMR spectroscopy by observing consumption of **1**. [b] Determined by ^{1}H NMR spectroscopy.

Table 3. Studies of the [V]/[Pd] Catalyst Ratios

entry	[V] (mol %)	[Pd] (mol %)[a]	conv (%)[b]	3:4:5[c]	E:Z of 3[c]
1	5.0	5.0	100	47:3:1	3:1
2	1.0	5.0	93	17:1:12	3:1
3	5.0	1.0	6	16:30:1	6:1
4	1.5	1.0	62	65:5:1	6:1
5[d]	1.5	1.0	100	5:1:0	7:1

[a] Pd$_2$(dba)$_3$·CHCl$_3$/DPPM = 1:2.4. [b] Determined by ^{1}H NMR spectroscopy with the consumption of **1**. [c] Determined by ^{1}H NMR spectroscopy. [d] Reaction was performed with 1.2 equiv of **1** at 80 °C for 16 h to give 98% isolated yield of **3**.

generated by simple deprotonation. Capturing this enolate with eletrophilic partners such as aldehydes and imines has proven possible.[13] Encouraged by the success of these aldol-like processes, we wondered what other carbon−carbon bond forming reactions could be accessed by trapping this nucleophilic allenoate intermediate. An alternative possible eletrophile is a π-allylpalladium cationic species, which is obtained from an alkene containing an allylic leaving group and a zerovalent palladium catalyst. Nucleophiles such as alcohols, amines, enolates, and malonates have been successfully employed in the palladium-catalyzed allylic alkylation reactions to generate new allylic C−O, C−N, or C−C bonds.[14] The challenge, however, is to favor the intermolecular reaction between these two catalytically generated intermediates, while disfavoring the two potential competing side reactions: (1) simple protonation[9] of the vanadium allenoate and (2) nucleophilic attack[15] on the π-allylpalladium unit by the starting propargyl alcohol. Herein, we describe our findings related to the development of a novel vanadium- and palladium-catalyzed coupling of propargyl alcohols and allylic carbonates.

Standard Reaction Optimization. To test the feasibility of this new proposal, we began by choosing propargyl alcohol **1** and allyl carbonate **2** as the standard coupling partners, along with a catalyst combination of O=V(OSiAr$_3$)$_3$ and a palladium(0)−phosphine

complex. The results indicated that the ligands played an important role in the successful execution of the desired contemporaneous dual catalysis reaction. In the preliminary examination (Table 1), triphenylsilanol and DPPM (diphenylphosphinomethane) were found to be the most effective ligands for the vanadium and palladium catalysts, respectively. In the presence of 5 mol % O=V(OSiPh$_3$)$_3$ and 2.5 mol % Pd$_2$-(dba)$_3$·CHCl$_3$ with 6.0 mol % DPPM, the anticipated product **3** was isolated in 98% yield with good stereoselectivity (E:Z = 5:1) (entry 1). In contrast, all other phosphine ligands screened in the reaction resulted in either low conversions or undesired byproducts **4**[16] and **5**.[17] For example, when phosphine ligands were employed that retard the rate of π-allyl formation or the rate of alkylation of the electrophile, enone **4** became the predominant product of the reaction (entries 2, 6, and 7). On the other hand, when DPPP and DPPB were employed, the O-alkylation process became much faster than the desired dual catalytic transformation, affording the desired product **3** in low yield (entries 3 and 4). Furthermore, the more electron poor vanadium catalyst did not perform as well as the original vanadium catalyst. In this case, the unwanted allylated alcohol **5** was generated in larger amounts (entry 8).
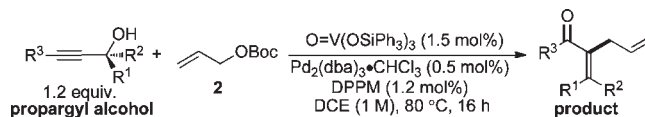
Table 4. Survey of the Allyl Carbonate Scope

entry	allyl carbonate	product	yield (%)
1		$E:Z = 7:1^a$	98
2		$E:Z = 7:1^a$	92
3		$E:Z = 7:1^a$	85
4		$E:Z = 7:1^a$	57
5[b]		$E:Z = 10:1^a$	94
6[b]		$E:Z = 6:1^a$	76
7[b]		$E:Z = 7:1^a$	88
8[b,c]		$E:Z = 12:1^a$	66

[a] Double bond geometry was assigned by analogy with compound **3**, and E/Z ratio was determined by ^{1}H NMR spectroscopy. [b] 1.5 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 3.6 mol % DPPM, and 4.5 mol % O═V(OSiPh$_3$)$_3$ were used. [c] 1.5 equivalent of **1** was used and the reaction run for 48 h.

Having determined the optimal catalyst structures for the reaction, we next studied the effects of solvent on the efficiency and selectivity of the reaction (Table 2). Although several solvents were suitable for this new process, 1,2-dichloroethane (DCE) turned out to be the best solvent, giving the product in higher yield and stereoselectivity with regard to double bond geometry.

We next determined the effect of catalyst ratios and catalyst loadings on the overall efficiency of the process. The results summarized in Table 3 revealed that the performance of the dual catalytic system was affected dramatically by the vanadium to palladium ratio. For example, when an excess of the palladium catalyst with respect to the vanadium catalyst was employed, the O-allylated byproduct **5** was formed in greater amounts along

Table 5. Survey of the Propargyl Alcohol Scope for Making α,β-Unsaturated Ketones

entry	propargyl alcohol	product	yield (%)
1		$E:Z = 6:1^a$	80
2		$E:Z = 3:1^a$	96
3[b]		$E:Z > 19:1^a$	67
4[b]		$E:Z = 4:1^a$	63
5[c,d]		$E:Z = 9:1^a$	78
6[c]		$E:Z > 19:1^a$	82
7[c]		$E:Z = 4:1^a$	72
8[b]		$E:Z = 1.1:1^a$	79
9[c,e]			61
10[c,e]			< 5

[a] Double bond geometry was assigned by analogy with compound **3**, and E/Z ratio was determined by ^{1}H NMR spectroscopy. [b] Run for 48 h. [c] 1.5 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 3.6 mol % DPPM, and 4.5 mol % O═V-(OSiPh$_3$)$_3$ were used. [d] tert-Butyl cinnamyl carbonate was used instead of **2**. [e] 1.5 equiv of propargyl alcohol was used and the reaction run at 100 °C for 48 h.

**Scheme 4. A Comparison of the Two Standard Reaction Conditions**
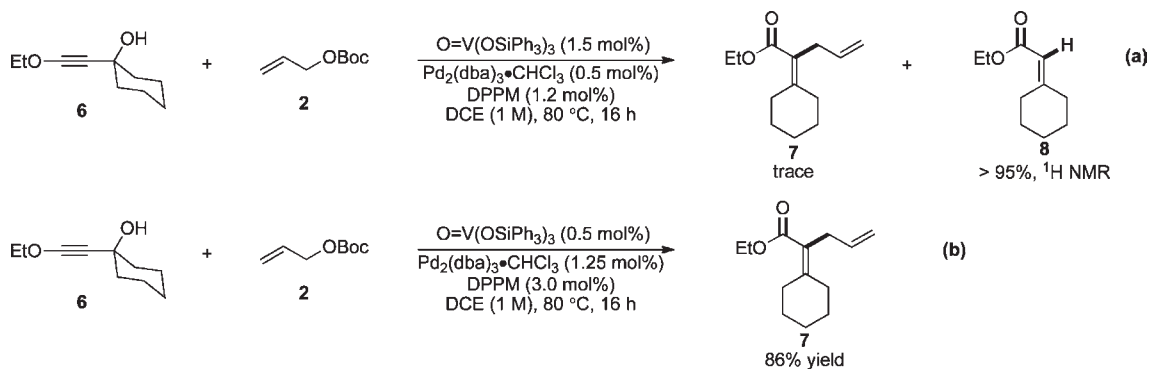
with the formation of product **3** (entry 2). Similarly, when the vanadium catalyst was present in excess relative to palladium catalyst, Meyer–Schuster rearrangement product **4** is generated as the major product (entry 3). Further optimization revealed that the reaction could proceed smoothly at fairly low catalyst loadings (1.5% vanadium and 1% palladium) to yield **3** with excellent isolated yield (98%) and double bond stereoselectivity (*E:Z* = 7:1) (entry 5). The stereochemistry of compound **3** was confirmed by ^{1}H NMR nuclear Overhauser enhancement (NOE) study. When irradiation was performed on the *β*-proton in the major isomer of *α,β*-unsaturated ketone **3**, no NOE was observed for the allylic protons, so the major product was assigned as *E*-configuration; when irradiation was performed on the same *β*-proton in the minor isomer, +2.0% NOE was observed for the allylic protons, so the minor product was then assigned as the *Z*-configuration.

Reaction Scope of Allyl Carbonates. With the optimized reaction conditions in hand, the reaction scope was examined by varying the substitution patterns on both coupling partners. First, various allylic carbonate substrates were tested in the reaction using propargyl alcohol **1** as a model substrate (Table 4). These studies confirmed that a broad range of substitution patterns on the allylic carbonates were tolerated, wherein the products were obtained in moderate to excellent yields (57–98% yield) with high stereoselectivity (*E:Z* up to 12:1). Aryl (entries 2 and 3), heteroaryl (entries 5 and 6), and alkyl (entry 8) substituents could be present at the terminal position of the olefin. In addition, substitution on the internal carbon of the olefin was tolerated (entry 7), as well as substitution on the carbon atom adjacent to the oxygen (entries 4 and 8).

Reaction Scope of Propargyl Alcohols (Preparation of α-Allylated α,β-Unsaturated Ketones). Our next goal was to investigate the scope of the reaction with regards to the propargylic alcohol (Table 5). Overall, most of the desired α-allylated α,β-unsaturated ketones were prepared successfully, affording good yields (up to 98%) with up to >19:1 (*E:Z*) stereoselectivity. Remarkably, a wide range of substituents, with varied steric and electronic properties, on the acetylene terminus were allowed. Meanwhile, substrates bearing various conjugated functional groups, including electron-rich and electron-poor arenes (entries 2–4), heterocycles (entries 1 and 7), and olefins (entry 4), on the propargylic position participated quite well in the reaction. A tertiary propargylic alcohol was also employed, and the corresponding product was isolated in good yield, albeit with no stereocontrol of the double bond geometry (entry 8).

The reaction efficiency decreased significantly, however, when the conjugated stabilizing groups were absent from the propargylic position. For instance, when both substituents on the tertiary propargylic alcohol were alkyl groups, the reaction only proceeded at higher temperature (100 °C) to give a moderate yield of the product (entry 9). When just a single aliphatic group was present at the alcohol center, only a trace amount of the desired product was obtained under a variety of reactions conditions (entry 10).
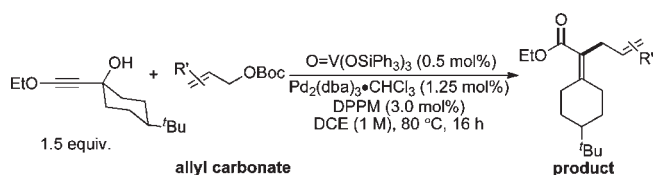
Reaction Scope of Propargyl Alcohols (Preparation of α-Allylated α,β-Unsaturated Esters). One limitation of our current methodology described above is the low reactivity of propargylic alcohols lacking an aryl or vinyl group at the propargylic center. As a solution to this problem, we envisioned that introduction of a heteroatom such as oxygen atom at the alkyne terminus of propargyl alcohol could activate the alcohol toward Meyer–Schuster rearrangement. In addition, this simple variation would allow us to obtain α-allylated α,β-unsaturated esters as products. In order to test this hypothesis, we synthesized propargyl alcohol **6**, with the challenging double alkyl substitution pattern on the propargylic position, from commercially available ethoxy acetylene and cyclohexanone via a one-step addition reaction.[11] Under the standard reaction conditions, the desired α-allylated α,β-unsaturated ester **7** was obtained only in trace amounts due to the rapid formation of enone **8** via a Meyer–Shuster rearrangement of alcohol **6** (Scheme 4a). As a result, a preliminary optimization of the catalysts' ratio and loadings were performed. To our delight, the optimal condition was identified quickly; in the presence of 0.5 mol % vanadium and 2.5 mol % palladium, product **7** was prepared in excellent isolated yield (86%) (Scheme 4b). Due to the rapid rate of Meyer–Shuster rearrangement of alcohol **6**, it was necessary to decrease the loading of the vanadium catalyst and increase the palladium catalyst loading in order to obtain the desired coupling product in good yield. Most importantly, the vanadium catalyst must be added after the solvent was charged into the reaction vessel, otherwise the high concentration neat propargyl alcohol **6** would be converted into side product **8** in a few minutes once it is exposed to the vanadium catalyst. Significantly, these observations demonstrated that the interception of this vanadium ketene acetal intermediate with electrophilic π-allylpalladium is far more challenging than the previous cases. To the best of our knowledge, this is the first example of a ketene acetal, generated from the Meyer–Schuster rearrangement of the corresponding propargyl acohol, being trapped by an electrophile to form a new carbon–carbon bond.[11,18]

Table 6. Survey of the Propargyl Alcohol Scope for Making α,β-Unsaturated Esters
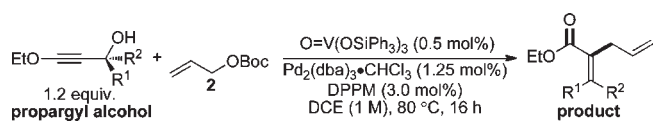
entry	propargyl alcohol	product	yield (%)
1			86
2			78
3			75
4			87
5[a]			85
6[a]		E:Z = 3:1[b]	88
7[a]		E:Z = 3:1[b]	94
8		E:Z = 4:1[b]	91

[a] 2.0 equiv of propargyl alcohol was used. [b] Determined by ^{1}H NMR spectroscopy.

Table 7. Survey of the Allyl Carbonate Scope for Making α,β-Unsaturated Esters

entry	allyl carbonate	product	yield (%)
1			47
2			77
3			82
4			56

Encouraged by these positive findings, we next tested a variety of propargylic alcohols bearing the terminal ether functionality (Table 6). The dual catalytic transformation is competent across a wide range of propargyl alcohols, including those substituted with alkyl, aryl, and vinyl groups at the propargylic position. For example, the five-, six-, and seven-membered ring systems could be incorporated (entries 1–4). Furthermore, a noncyclic substrate with disubstitution at the propargylic center (entry 5) and substrates bearing aryl and vinyl groups reacted in high yield (entries 6 and 7). Finally, the previously unreactive substrate bearing a single alkyl substituent reacted successfully, and the corresponding product was isolated in extremely high yield (91%) (entry 8). The product in entry 6 is a known compound, and its stereochemistry was assigned according to literature data.[19] The double bond geometries of products in entries 7 and 8 were then given by analogy with this compound.

Next, we explored the scope of the ester-forming reaction with respect to the allyl carbonates (Table 7). Gratifyingly, the allylic carbonate coupling component could be substituted at the terminus (entry 1) or the internal carbon (entry 4) of the olefin. In addition, alkyl, aryl, and heteroaryl substituents are tolerated on the terminus of the olefin (entries 1–3).

To exemplify the utility of the protocol, cholestane-derived substrate **9** and estrone-derived substrate **11** were tested (Scheme 5). We were pleased to find that these complex substrates readily reacted when a combination of 0.5 mol % vanadium and 5.0 mol % palladium catalysts was utilized at 80 °C for 16 h. From this result, we believe that the current methodology could be an additional tool for the structural modification of steroids and related natural products. In addition, the geometry of the carbon–carbon double bond in product **12** was tentatively assigned as Z-configuration by using a combination of two-dimensional NMR experiments COSY, NOSY, HSQC, and HMBC.

Reaction Scope of Propargyl Alcohols (Preparation of α-Allylated α,β-Unsaturated Amides). The generality of this reactivity pattern was further explored using a nitrogen atom in place of the oxygen atom on the terminus of the acetylene in the propargyl alcohols under the same catalytic conditions described above. Ynamide **13** was prepared by copper-catalyzed coupling of N-benzylsulfonamide with 1-bromo-2-triisopropylsilylethyne, followed by desilylation, deprotonation with LDA, and addition to 3-phenylpropanal.[20,21] Illustrative examples of combining the substrate **13** with three different allyl carbonates

## Scheme 5. Structural Modification of Steroid Derivatives

(a) 80% yield, E:Z = 1:1

(b) 47% yield, only Z isomer
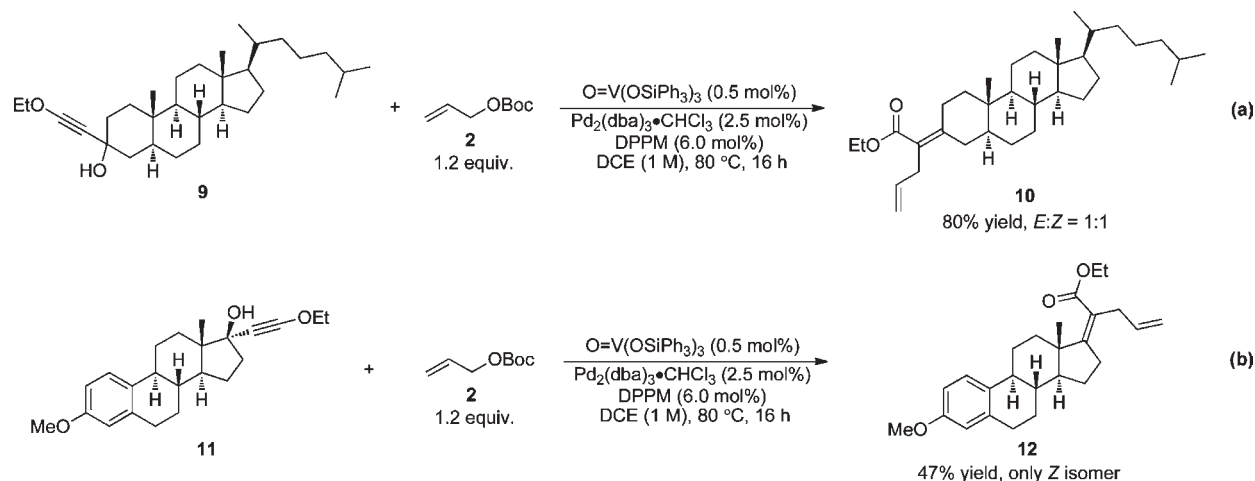
Table 8. Survey of the Propargyl Alcohol Scope for Making α,β-Unsaturated Amides
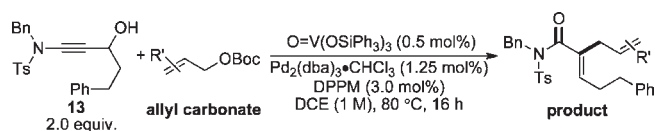
entry	allyl carbonate	product	yield (%)
1		E:Z = 2:1[a]	85
2		E:Z = 2:1[a]	82
3		E:Z = 2:1[a]	84

[a] Determined by ^{1}H NMR spectroscopy.

are shown in Table 8. The catalytic results proved to be promising, and all of the desired α-allylated α,β-unsaturated amides were prepared in high yields. The stereochemistry of the product in entry 1 was revealed by NOE study. When irradiation was performed on the β-proton in the major isomer of this α,β-unsaturated amide compound, no NOE was observed for the allylic protons, so the major product was assigned the E-configuration; when irradiation was performed on the same β-proton in the minor isomer, +1.8% NOE was observed for the allylic protons, so the minor product was then assigned the Z-configuration. The double bond geometries of products in entries 2 and 3 were then given by analogy with this compound. To the best of our knowledge, this is the first example of a ketene aminal generated from the Meyer—Schuster rearrangement of the corresponding properly alcohol being trapped by an electrophile to form a new carbon—carbon bond.[12] Moreover, the reaction scope was significantly expanded when a

Scheme 6. A Successful Example of Employing a Primary Propargylic Alcohol

15
79% yield
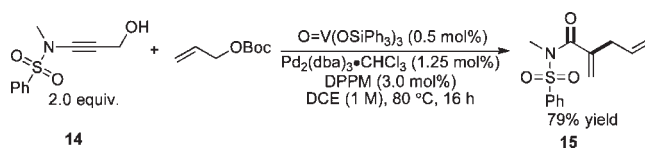
primary propargylic alcohol 14 was examined. Compound 14 was obtained by copper-catalyzed coupling of N-methylsulfonamide with ((3-bromoprop-2-yn-1-yl)oxy)(tert-butyl)diphenylsilane followed by desilylation.[20,22] Under the standard reaction condition, substrate 14 underwent efficient Meyer—Schuster rearrangement and coupling with the π-allylpalladium intermediate to generate the β,β-unsubstituted α,β-unsaturated amide 15 in good yield (Scheme 6).

As demonstrated in the above sections, a large family of α-allylated α,β-unsaturated ketones, esters, and amides were successfully prepared by using a novel contemporaneous dual catalytic system that employs both vanadium and palladium catalysts. The unsaturated carbonyl compounds are versatile building blocks for the synthesis of biologically active natural products, pharmaceuticals, agrochemicals, fragrances, and other useful fine chemicals. Our method offers a new one-step disconnection that uses propargyl alcohols and allyl carbonates that could be accessed from widespread industrial raw materials like alkynes, aldehydes, ketones, and allylic alcohols. Moreover, our approach also exemplifies a high level of atom economy and is more environmentally benign, generating tert-butanol and carbon dioxide as the only byproducts.

The value of the dual catalytic process is further amplified by the control experiments using allyl halides as eletrophiles (Scheme 7). When we attempted to trap the vanadium—allenoate derived from various propargyl alcohols with allyl bromide or allyl iodide, none of anticipated α-allylated unsaturated carbonyl compounds were observed. This observation demonstrates the need for both catalysts in the reaction, and we believe that the π-allylpalladium intermediate, being positively charged, is exclusively able to trap the vanadium allenoate.

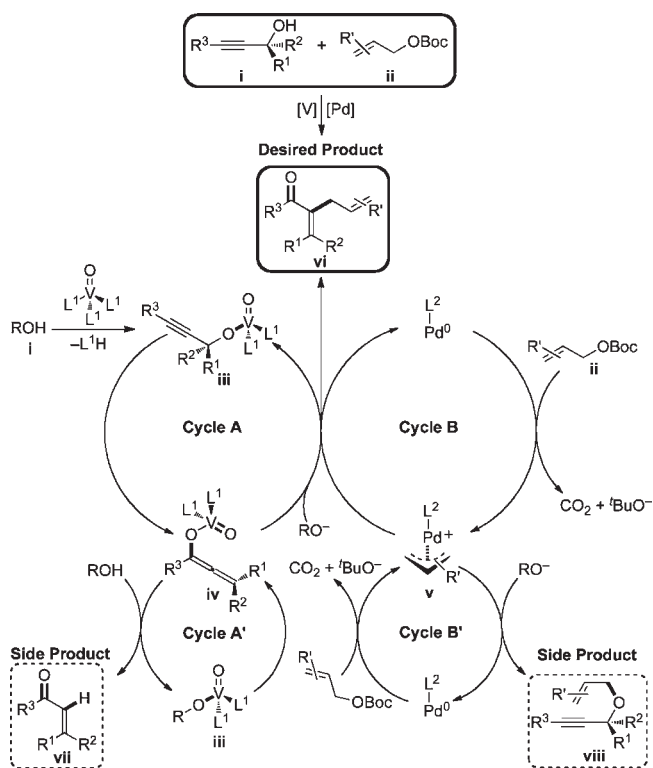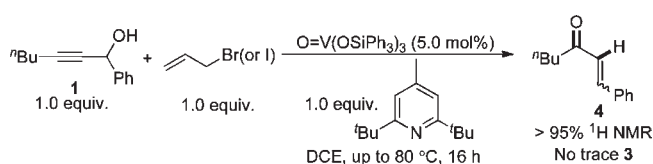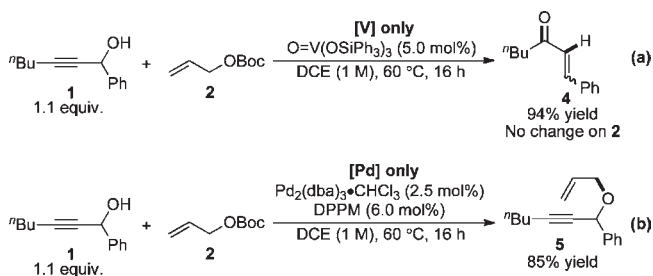**Scheme 7. Attempts To Trap Vanadium—Allenoate by Allyl Halides**

Scheme 8. Formation of Competing Side Products

Figure 1. Proposed mechanism for the contemporaneous dual catalysis.

Scheme 9. Survey of Byproducts 4 and 5 as Potential Intermediates

O-allylated alcohol (**viii**) (cycle B′). These concerns were supported by experimental results from the reactions in which a single vanadium or palladium catalyst was employed (Scheme 8). Under the standard reaction conditions, and in the presence of only the vanadium catalyst, alcohol **1** underwent Meyer—Schuster rearrangement to produce enone **4** exclusively (Scheme 8a). In contrast, when only the palladium catalyst was employed, *O*-allylated alcohol **5** was isolated in 85% yield (Scheme 8b). Significantly, neither of the two reactions resulted in even a trace amount of desired product **3**.

We next considered the possibility that the dual catalytic system might be proceeding through a consecutive two-step process. In order to preclude this possibility, several control experiments were conducted (Scheme 9). We found that enone **4** resulting from vanadium-catalyzed rearrangement of the propargylic alcohol was not converted to the desired α-allylated α,β-unsaturated ketone **3** by the palladium catalyst (Scheme 9a). In addition, the vanadium catalyst was not able to facilitate the rearrangement of allylated alcohol **5** to product **3**. Therefore, we concluded that the contemporaneous dual catalysis indeed involves the coupling of the in situ generated vanadium—allenoate and π-allylpalladium intermediates.

Once we had established that contemporaneous dual catalysis was indeed responsible for product formation, we set out to establish some general guiding principles for maintaining efficiency in the reaction across substrate classes. It is critical to harmonize the palladium and vanadium catalysts in order to favor coupling of the two reactive intermediates. The O=V(OSiPh₃)₃ catalyst was sufficiently reactive to promote the Meyer—Schuster rearrangement of propargyl alcohols containing certain functional groups, including those substituted with an aromatic group at the propargylic position or with a heteroatom at the terminus of the triple bond. Importantly, the latter propargyl alcohols could undergo rearrangement more readily and their corresponding reactions were achieved with extremely low vanadium catalyst loading (0.5 mol % V). On the other hand, the differences
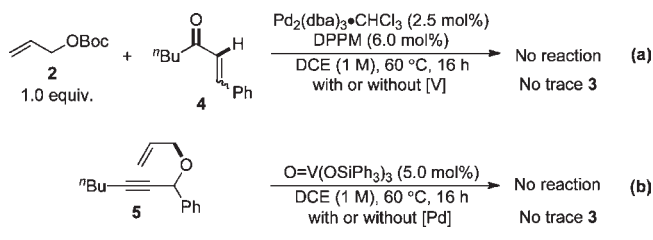
Mechanistic Discussion. The proposed reaction mechanism is outlined in Figure 1. The combination of vanadium catalysis cycle (cycle A) and palladium catalysis cycle (cycle B), in a dual catalysis manifold, leads to the formation of α-allylated α,β-unsaturated carbonyl products **vi** via coupling of the reactive intermediates from each cycle. For cycle A, the vanadium catalyst enters by transesterification with the propargylic alcohol (ROH) to generate vanadium ester **iii**. Ester **iii** is then rearranged via a 1,3-transposition of the oxygen atom to give vanadium—allenoate (**iv**). For cycle B, initial binding of palladium to the olefin of the substrate, followed by ionization of the allylic carbonate, leads to π-allylpalladium intermediate **v**. These two in situ generated intermediates then intercept each other to yield the desired product (**vi**) and regenerate the active vanadium and palladium catalysts.

The challenge of contemporaneous dual catalysis is that the coupling of the two reactive intermediates must occur in preference to two competing side reactions. On one hand, vanadium allenoate (**iv**) could be quenched via protonation by propargyl alcohol (**i**) to generate enone (**vii**) (cycle A′). On the other hand, π-allylpalladium intermediate (**v**) also has the potential to be attacked by the propargylic alcohol to generate

Scheme 10. Comparative Trials of the Variations on the Vanadium and Palladium Loadings and Ratios
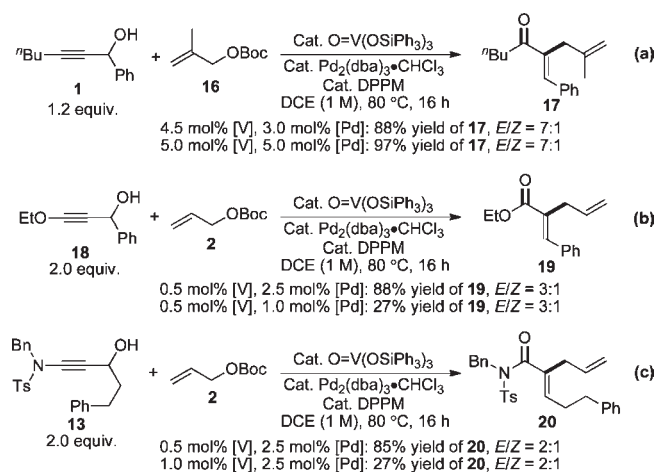
in reactivity of the allyl carbonates are consistent with the difficulties of the formation of the corresponding π-allylpalladium species. If an allyl carbonate is difficult to activate, higher palladium catalyst loadings were generally required. For example, the sterically more demanding substrate 1,3-dimethylallyl carbonate needed 3 mol % palladium (Table 4, entry 8), in contrast to the parent standard substrate allyl carbonate that required only 1 mol % palladium (Table 4, entry 1). On the basis of the appropriate adjustments of catalysts loading and ratio, a large number of interesting α-allylated α,β-unsaturated ketones, esters, and amides were prepared. The importance of these parameters was further emphasized by a series of comparative trials (Scheme 10). When catalyst loading ([V]/[Pd]) was increased from 4.5/3.0 to 5.0/5.0 mol % while maintaining other condition constants for substrates **1** and **16**, the yield of desired product was increased to 97% from 88% without erosion of stereoselectivity (Scheme 10a). Alternatively, when the palladium catalyst loading for substrate **18** was decreased from 2.5 to 1.0 mol %, the yield of desired product **19** was strikingly decreased (88% versus 27%) (Scheme 10b). Also, when the vanadium catalyst loading was increased from 0.5 mol % to 1.0 mol % for substrate **13**, the yield of desired product **20** was dramatically reduced to 10% (versus 85%) (Scheme 10c). These results establish the need to balance the catalyst loadings and ratios, depending on the inherent reactivity of the allylic carbonate or propargylic alcohol starting materials.

CONCLUSION

In conclusion, we have disclosed a new mode of catalysis, which we call contemporaneous dual catalysis. This catalytic method features two reactive chemical intermediates, which are generated by two independent catalysts from their respective substrates. These reactive intermediates then preferentially undergo bimolecular coupling in the presence of stochiometric reagents that are able to quench both active moieties. The current example was carried out via a combination of a vanadium-catalyzed 1,3-transposition of propargylic alcohols and a palladium-catalyzed alkylation of allylic carbonates. Two competing side reactions, including trapping the vanadium−allenoate and π-allylpalladium intermediates with a large excess of propargyl alcohol, were effectively overcome. An important aspect for

success is the need to control the relative catalyst loading for each process. In addition, in spite of the need for a bimolecular process between two catalytic intermediates, low catalyst loadings are still possible. To the best of our knowledge, this is the first case of contemporaneous dual catalyst being effected by two separate metal catalysts. The ability of allenoates to function as suitable nucleophiles toward π-allylpalladium complexes is also noteworthy. Furthermore, the results reported herein represent the first cases of using ester and amide enolates as nucleophiles in Pd-catalyzed allylic alkylation. It also represents the first examples of such enolates being intercepted in a Meyer−Schuster type process.

EXPERIMENTAL SECTION

Representative Procedure for the Preparation of α-Allylated α,β-Unsaturated Ketones. To a dry V-shaped vial fitted with a stirring bar were added allyl *tert*-butyl carbonate (31.6 mg, 0.20 mmol), 1-phenylhept-2-yn-1-ol (45.2 mg, 0.24 mmol), and O=V(OSiPh$_3$)$_3$ (2.7 mg, 0.003 mmol), and the vial was flushed with argon. In another vial, Pd$_2$(dba)$_3$·CHCl$_3$ (1.0 mg, 0.001 mmol) and DPPM (0.9 mg, 0.0024 mmol) were dissolved in dry DCE (0.2 mL) and stirred for 10 min. The freshly made palladium catalyst solution was transferred into the V-shaped vial through a cannula. The vial was then sealed with a Teflon cap under an argon stream and heated at 80 °C for 16 h. The crude reaction mixture was then subjected to a silica gel column using dichloromethane/petroleum ether (1:2) as an eluent to afford 4-benzylidenenon-1-en-5-one (44.8 mg, 98% yield, E:Z = 7:1). The sample for analytical data was obtained by using preparative TLC. E-isomer: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (s, 1H), 7.44−7.32 (m, 5H), 6.01−5.92 (m, 1H), 5.09−5.00 (m, 2H), 3.28 (t, J = 4.0 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H), 1.73−1.63 (m, 2H), 1.43−1.34 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 202.05, 139.80, 139.09, 135.95, 135.58, 129.33, 128.77, 128.53, 115.59, 37.61, 30.83, 27.06, 22.55, 14.02. IR: 2956, 1667, 1447, 1170, 915, 753, 698. HRMS (ESI): *m/z* calculated for C$_{16}$H$_{21}$O [M + 1]$^+$ 229.1592, observed 229.1587. Z-isomer: Colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34−7.16 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 6.64 (s, 1H), 5.91−5.80 (m, 1H), 5.17−5.12 (m, 2H), 3.10 (dd, J = 6.8, 1.2 Hz, 2H), 2.24 (t, J = 7.2 Hz, 2H), 1.47−1.43 (m, 2H), 1.16−1.11 (m, 2H), 0.76 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 210.20, 142.94, 136.39, 134.70, 130.48, 128.50, 128.42, 127.98, 117.69, 42.88, 39.52, 26.06, 22.12, 13.82. IR: 2957, 1689, 1377, 920, 754, 699.

Representative Procedure for the Preparation of α-Allylated α,β-Unsaturated Esters. To a dry V-shaped vial fitted with a stirring barwere added allyl *tert*-butyl carbonate (31.6 mg, 0.20 mmol) and 1-(ethoxyethynyl)cyclohexanol (40.4 mg, 0.24 mmol), and the vial was flushed with argon. In another vial, Pd$_2$(dba)$_3$·CHCl$_3$ (2.6 mg, 0.0025 mmol) and DPPM (2.3 mg, 0.006 mmol) were dissolved in dry DCE (0.2 mL) and stirred for 10 min. The freshly made palladium catalyst solution was transferred into the V-shaped vial through a cannula. Catalyst O=V(OSiPh$_3$)$_3$ (0.9 mg, 0.001 mmol) was added, and the vial was then sealed with a Teflon cap under an argon stream and heated at 80 °C for 16 h. The crude reaction mixture was then subjected to a silica gel column using dichloromethane/petroleum ether (1:2) as an eluent to afford ethyl 2-cyclohexylidenepent-4-enoate (36.0 mg, 86% yield) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.80−5.76 (m, 1H), 5.06−4.97 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.05 (d, J = 6.0 Hz, 2H), 2.45 (t, J = 4.8 Hz, 2H), 2.21 (t, J = 4.8 Hz, 2H), 1.62−1.52 (m, 6H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 170.10, 149.33, 135.99, 122.59, 115.16, 60.23, 33.60, 32.78, 31.38, 28.34, 28.14, 26.55, 14.36. IR: 2977, 2926, 2853, 1712, 1637, 1446, 1281, 1198, 1137, 1097, 1028, 992, 911. HRMS (ESI): *m/z* calculated for C$_{13}$H$_{21}$O$_2$ [M + 1]$^+$ 209.1542, observed 209.1536.

Representative Procedure for the Preparation of α-Allylated α,β-Unsaturated Amides. To a dry V-shaped vial fitted with a stirring bar were added allyl *tert*-butyl carbonate (31.6 mg, 0.20 mmol) and *N*-benzyl-*N*-(3-hydroxy-5-phenylpent-1-yn-1-yl)-4-methylbenzenesulfonamide (167.8 mg, 0.40 mmol), and the vial was flushed with argon. In another vial, $Pd_2(dba)_3 \cdot CHCl_3$ (2.6 mg, 0.0025 mmol) and DPPM (2.3 mg, 0.006 mmol) were dissolved in dry DCE (0.2 mL) and stirred for 10 min. The freshly made palladium catalyst solution was transferred into the V-shaped vial through cannula. Catalyst O=V-$(OSiPh_3)_3$ (0.9 mg, 0.001 mmol) was added, and the vial was then sealed with a Teflon cap under an argon stream and heated at 80 °C for 16 h. The crude reaction mixture was then subjected to a silica gel column using dichloromethane/petroleum ether (2:1) as an eluent to afford 2-allyl-*N*-benzyl-5-phenyl-*N*-tosylpent-2-enamide (78.0 mg, 85% yield, *E:Z* = 2:1) as a colorless oil. Due to the existence of two isomers, two sets of NMR signals were observed. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.22−7.09 (m, 20H), 7.03 (dd, *J* = 7.8, 0.8 Hz, 2H), 6.94−6.93 (m, 2H), 5.95 (t, *J* = 7.2 Hz, 1H), 5.55−5.47 (m, 2H), 5.33−5.30 (m, 1H), 4.93−4.78 (m, 6H), 4.69 (s, 2H), 2.83−2.81 (m, 2H), 2.55 (t, *J* = 7.7 Hz, 4H), 2.44 (t, *J* = 7.8 Hz, 2H), 2.37−2.33 (m, 8H), 1.87−1.86 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 172.58, 171.24, 144.49, 140.95, 139.50, 136.31, 135.22, 134.84, 134.28, 133.99, 131.13, 129.49, 129.36, 128.80, 128.67, 128.61, 128.58, 128.55, 128.49, 128.45, 128.43, 128.40, 128.36, 128.14, 127.78, 127.73, 126.25, 117.88, 116.53, 50.88, 50.14, 37.2, 35.07, 34.55, 32.51, 31.02, 30.07, 21.73, 21.71. IR: 3064, 3029, 2918, 2850, 1685, 1357, 1166, 1088, 699, 664. HRMS (ESI): *m/z* calculated for $C_{28}H_{30}NO_3S$ [M + 1]$^+$ 460.1946, observed 460.1942.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information.   Experimental procedures and analytical data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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