Contemporaneous Dual Catalysis by Coupling Highly Transient Nucleophilic and Electrophilic Intermediates Generated in Situ

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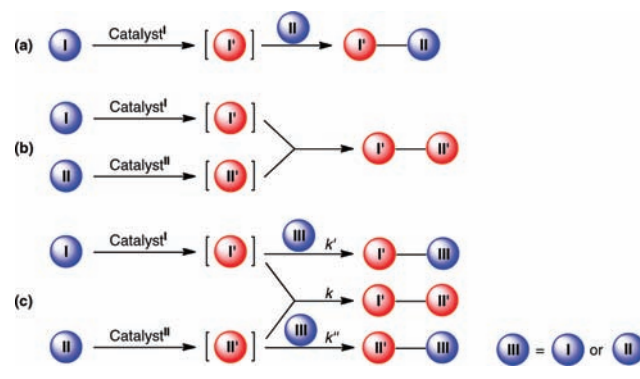
S *Supporting Information*

ABSTRACT: We report herein a new process, which we call contemporaneous dual catalysis, that selectively couples two highly reactive catalytic intermediates while overcoming competing trapping by stoichiometric reactive species also present in the reaction. The reaction proceeds via the convergence of a vanadium-catalyzed propargylic rearrangement and a palladium-catalyzed allylic alkylation. It generates a variety of α-allylated α,β-unsaturated ketones, which are not readily accessible by other means. Notably, this dual catalysis is achieved using low catalyst loadings (1.0 mol % [Pd], 1.5 mol % [V]) and gives good to excellent yields (up to 98%) of the desired products.

Scheme 1. (a) Conventional Catalysis; (b) Typical Dual Catalysis; (c) Contemporaneous Dual Catalysis

The development of new catalytic methods has been an area of intense research in both industrial and academic laboratories over the last century. During this time, thousands of catalytic reactions have been invented,[1,2] driven in part by the growing demands of the pharmaceutical, agrochemical, petrochemical, flavors, fragrances, and materials industries for rapid access to complex chemical structures. As the global demand for fine chemicals continues to grow, minimization of the environmental impact of these chemical manufacturing processes has become increasingly important. To facilitate the continuous advancement of our society and sustainability of our planet, it is vital to design and implement new modes of catalysis that enable previously inaccessible chemical processes while minimizing the waste generated and energy required for their production.

In general, catalytic transformations rely on the principle of capturing the small amount of catalyst-activated intermediate with a coupling partner present in the reaction. To date, the majority of catalytic reactions have been developed by activating a substrate (**I**) with a substoichiometric amount of a catalyst and trapping the resulting activated species with a second reactant (**II**), which is generally present in stoichiometric or superstoichiometric quantities (Scheme 1a).[3] A significant drawback of this approach is that if the second reagent **II** requires activation for the reaction to occur, it is done so stoichiometrically. Recently, dual catalysis has been a popular target for many research groups.[4] This strategy employs the selective activation of two substrates (**I** and **II**) by two different catalysts (catalyst[I] and catalyst[II]) to generate **I'** and **II'**, which are subsequently coupled to afford **I'**−**II'** with concomitant regeneration of both catalysts (Scheme 1b).[5] One advantage of this approach is that it allows reactions to proceed without the addition of stoichiometric activating reagents. Furthermore, these reactions have been shown to have novel reactivity, generating products that are difficult or impossible to obtain by the traditional one-catalyst and/or one-reaction approach.

Despite their advantages, the number of dual-catalyzed reactions that have been developed is dramatically less than those where a single catalyst is employed. One factor that contributes to this disparity is that the in situ-generated reactive intermediates are not necessarily chemoselective. They can be intercepted with stoichiometric amounts of reactant (**I** or **II**) prior to the desired reaction. In theory, if the relative rate constants (k, k', and k'') for the trapping of catalytic species **I'** with either catalytic species **II'** or substrate **I** or **II** are similar, the activated intermediate **I'** is more likely to react with **I** or **II** because they are present in higher concentrations than the relatively small amount of **II'**. Therefore, an important goal is the development of contemporaneous dual catalysis, where the two intermediates **I'** and **II'**, formed irreversibly in situ, selectively react with each other in the presence of large excesses of competing reagents (Scheme 1c). To conquer this challenge, it is critical to control the relative rates of formation of each reactive intermediate (such that $k \gg k'$ and $k \gg k''$), thereby enhancing their affinity toward each other relative to the starting materials. While this approach is attractive in theory, its practical implementation remains elusive.

A central theme of the research in our laboratories is the development of transition-metal-catalyzed reactions.[6] As part of these studies, we have demonstrated that electrophilic π-allyl—palladium intermediate **1** can be generated from a variety of alkenes containing allylic leaving groups in the presence of a palladium(0) catalyst (Figure 1a). Upon its formation, **1** can react with a wide range of nucleophilic coupling partners,
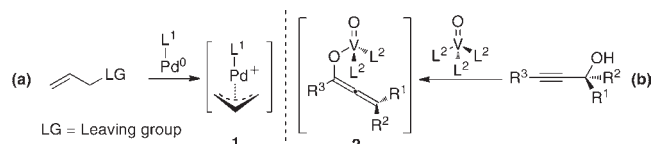
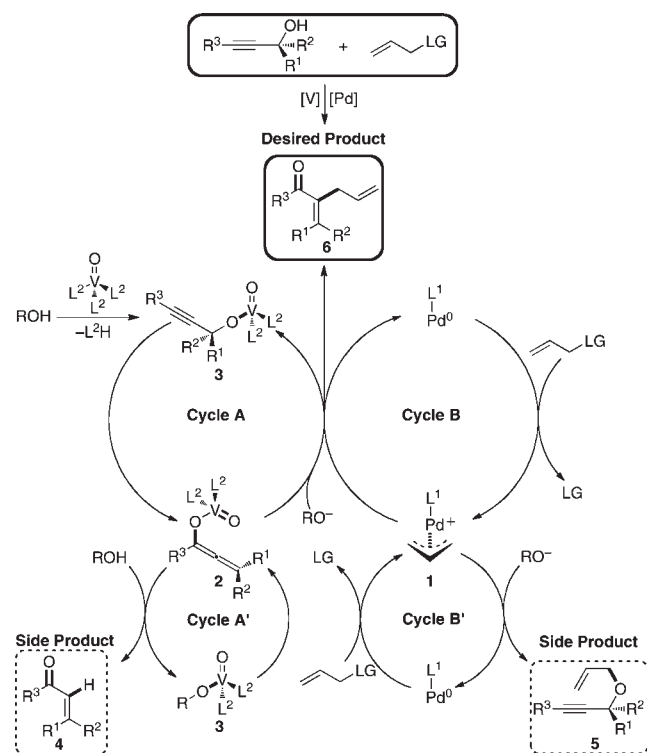**Figure 1.** Catalytic formation of (a) π-allyl–palladium **1** and (b) vanadium–allenoate **2**.

Figure 2. Design blueprint for the contemporaneous dual catalysis.

including alcohols, amines, enolates, and malonates, to generate new allylic C–O, C–N, or C–C bonds.[7] In a similar pursuit, we have demonstrated that oxyvanadium catalysts can perform a 1,3-transposition of propargylic alcohols to generate nucleophilic vanadium–allenoate intermediate **2** (Figure 1b). We have shown that **2** can be intercepted in an intermolecular fashion by aldehydes or imines rather than simple protonation, which affords the Meyer–Schuster rearrangement product.[8] In our efforts to develop a contemporaneous dual catalysis process and to expand the utility of the vanadium-catalyzed rearrangement, we wondered whether the catalytic generation of the nucleophilic vanadium–allenoate **2** could be coupled with the catalytic generation of the electrophilic π-allyl–palladium complex **1** to generate a 1,4-diene product faster than trapping of either **1** or **2** with the propargylic alcohol could occur via nucleophilic attack or protonation, respectively (see below).

A detailed description of the proposal is shown in Figure 2. To enter cycle **A**, the vanadium catalyst undergoes transesterification with the propargylic alcohol (ROH) to generate vanadium ester **3**. The ester then undergoes a 1,3-transposition to generate vanadium–allenoate **2**. Subsequently, in a dual catalysis manifold, the reactive allenoate intermediate **2** can be intercepted by the π-allyl–palladium intermediate **1** that is generated in the parallel cycle **B** to give the desired product **6**. Alternatively, intermediate **2** could undergo protonation to generate enone **4**
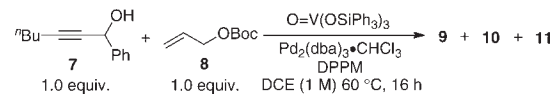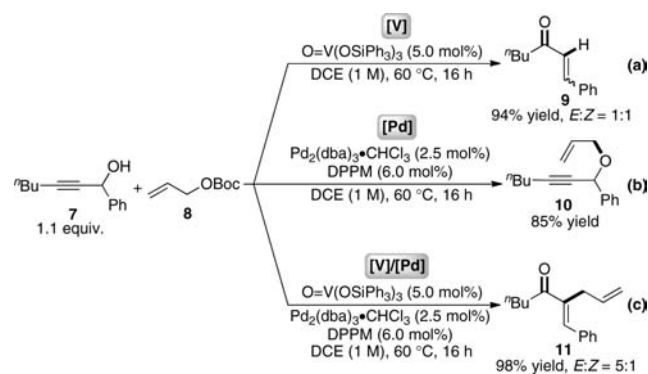
(cycle **A'**). Intermediate **1** also has the potential to undergo nucleophilic attack by the propargylic alcohol to generate O-allylated alcohol **5** (cycle **B'**). The challenge, therefore, is to find conditions under which the selective reaction between intermediates **1** and **2** to afford the desired enone **6** proceeds faster than the alternative processes involving stoichiometric partners that produce the undesired **4** and/or **5**. In order to accomplish this, we set out to identify both the ligands and the V and Pd catalyst ratio ([V]/[Pd]) that would selectively promote cycles **A** and **B** rather than **A'** and **B'**. The daunting challenge of identifying two catalysts that are compatible and chemoselective is a critical prerequisite for this type of dual catalysis. In addition, the proposed dual catalysis would result in the formation of α-allyl-substituted α,β-unsaturated ketone products **6**, which are not readily accessible by other means.

To test this new dual catalysis concept, we began by choosing propargyl alcohol **7** and allyl carbonate **8** as the coupling partners along with a catalyst combination of O=V(OSiPh$_3$)$_3$ and Pd$_2$-(dba)$_3$·CHCl$_3$ (dba = *trans,trans*-dibenzylideneacetone) complexed with the phosphine ligand 1,1-bis(diphenylphosphino)-methane (DPPM).[9] As both vanadium and palladium catalysts have the potential to react with substrates **7** and/or **8** independent of the other catalyst,[10,11] three parallel reactions were conducted under identical conditions using [V], [Pd], and both [Pd] and [V] as catalyst(s), respectively. When only the vanadium catalyst was employed, α,β-unsaturated ketone **9**,[12] the Meyer–Schuster rearrangement product, was isolated in 94% yield with complete recovery of allylic carbonate **8** (Scheme 2a). When the palladium complex was used as the sole catalyst, O-allylated alcohol **10**[13] was isolated in 85% yield as the only product (Scheme 2b). Much to our delight, when both the vanadium and palladium catalysts were employed simultaneously, the desired allylated enone **11** was isolated in high yield.[14] These preliminary studies revealed that the successful execution of our contemporaneous dual catalysis gives α-allylated enone **11** with excellent yield (98%) and good stereoselectivity (E:Z = 5:1) (Scheme 2c) by outcompeting both of the two side reactions (Meyer–Schuster rearrangement and O-allylation). We hypothesized that enone **11** might result from rearrangement of **10** by the vanadium catalysis in a tandem catalytic process. However, when **10** was subjected to the reaction conditions with either [V] or [V]/[Pd] catalyst(s), **11** was not observed. This control reaction indicated that contemporaneous dual catalysis had occurred and that the reaction did not proceed through two stepwise transformations.

To further test the validity of our method involving two parallel catalytic cycles, we performed a study that varied the

Table 1. Studies of [V]/[Pd] Ratio Variations in Dual Catalysis

entry	[V] (mol %)	[Pd] (mol %)[a]	Conv. (%)[b]	9:10:11[c]	E:Z for 11[c]
1	5.0	5.0	100	3:1:47	3:1
2	1.0	5.0	93	1:12:17	3:1
3	5.0	1.0	96	30:1:16	6:1
4	1.5	1.0	62	5:1:65	6:1
5[d]	1.5	1.0	100	1:0:5	7:1

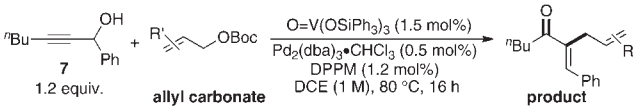[a] $Pd_2(dba)_3 \cdot CHCl_3$/DPPM = 1:2.4. [b] Determined by ^1H NMR spectroscopy by observing consumption of **7**. [c] Determined by ^1H NMR spectroscopy. [d] Reaction was performed by using 1.2 equiv of **7** at 80 °C for 16 h to give a 98% isolated yield of **11**.

[V]/[Pd] ratio of the reaction shown in Scheme 2c. The results of these studies are summarized in Table 1. As expected, the dual catalysis was extremely sensitive to the [V]/[Pd] ratio, and the proper ratio was critical for the promotion of cycles **A** and **B** relative to **A′** and **B′**. In general, when an excess of the palladium catalyst with respect to the vanadium catalyst was used, formation of the O-allylated alcohol product **10** began to compete with that of product **11** (entry 2). Similarly, when vanadium was in excess relative to palladium, the generation of the Meyer–Schuster rearrangement product **9** occurred at an elevated rate (entry 3). In the optimized reaction, more than 1.0 equiv of propargyl alcohol **7** was required in order to obtain complete consumption of the allyl carbonate **8** (entry 5). In this way, this reaction proceeded smoothly to give rise to an excellent isolated yield of **11** (98%) with very good E:Z stereoselectivity (7:1).

From the viewpoint of organic synthesis, the α-alkylation of carbonyl compounds is one of the most fundamental carbon–carbon bond-forming reactions. Conventionally, α-alkylated carbonyl compounds are obtained by deprotonation of an α-proton followed by addition to an electrophile, such as an alkyl halide. However, these reactions are often limited to carbonyl-containing compounds that can be regioselectively deprotonated by a base or reacted with an amine to afford the metal enolates or enamines, respectively.[15] Since it is not possible to generate allenoates by deprotonation of α,β-unsaturated carbonyl compounds, the α-alkylations of α,β-unsaturated carbonyl compounds are rare.[16] Excitingly, the dual-catalytic method offers a new disconnection and allows access to these synthetically valuable α-alkylated α,β-unsaturated carbonyl compounds in one step from a propargyl alcohol and an allyl carbonate, both of which are readily available. Importantly, our attempts to trap the vanadium–allenoate **2** with a variety of allyl halides were unsuccessful (no amount of allylated product was observed). We suggest that the allylating agent in the Pd-catalyzed reaction, being positively charged, enhances its ability to intercept the vanadium enolate.

Having identified conditions for the vanadium- and palladium-catalyzed coupling of propargylic alcohols with allylic carbonates, we sought to examine the scope of this new transformation. The results of varying the allylic carbonate coupling partner are shown in Table 2. These results demonstrate that the reaction conditions are general and that the products can be obtained in moderate to excellent yields (57−98% yield) with high

Table 2. Survey of Allyl Carbonate Scope in Dual Catalysis

[a] Using 1.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 3.6 mol % DPPM, and 4.5 mol % $O=V(OSiPh_3)_3$. [b] Using 1.5 equiv of **7** and a reaction time of 48 h.

stereoselectivity (E:Z up to 12:1). More specifically, both alkyl and aryl substituents can be incorporated at the terminal position of the olefin (entries 2, 3, and 8), including heterocycles (entries 5 and 6). Additionally, substitution on the internal carbon of the olefin is tolerated (entry 7), as well as substitution adjacent to the oxygen (entries 4 and 8). Notably, the observed reactivity difference among these allyl carbonates tested is consistent with the rate of formation of the π-allyl–palladium intermediate; carbonates, which are known to undergo slow oxidative addition, afforded lower yields of the coupled products. Thus, the choice of a suitable palladium catalyst aids in improving the efficiency of the overall reaction by tuning the rate of π-allyl–palladium formation.

Next, we sought to expand the scope of the propargyl alcohols. A variety of propargyl alcohols were synthesized and subjected to the reaction conditions (Table 3). Gratifyingly, alcohol substrates bearing various substituents, including those with electron-rich and electron-poor aromatics, heterocycles, vinyl groups, and alkyl groups at the propargylic position participated well in the reaction and provided the α-alkylated enone products in moderate to excellent yields (61−96% yield) with up to >19:1 E:Z stereoselectivity. Additionally, a wide range of substituents with various steric and electronic properties located on the terminus of the carbon–carbon triple bond were accommodated.

Overall, our new contemporaneous dual catalysis methodology has proven to be applicable to a wide variety of substrates, including both highly functionalized allyl carbonates and propargyl alcohols. These general reaction conditions, although not optimized except for the initial example, generally provided promising levels of both yield and stereoselectivity. Accordingly, α-allylated enones were always the predominant products, with little to no amount of O-allylated product observed. As this dual-catalytic transformation is performed by a combination of vanadium and palladium catalysts, its efficiency and selectivity

Table 3. Survey of Propargyl Alcohol Scope in Dual Catalysis

a Run for 48 h. b Using 1.5 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 3.6 mol % DPPM, and 4.5 mol % O=V(OSiPh$_3$)$_3$. c *tert*-Butyl cinnamyl carbonate was used instead of **8**. d The reaction used 1.5 equiv of propargyl alcohol and was run at 100 °C for 48 h.

are affected not only by the catalyst loading but also by the ratio of the two catalysts with respect to each other. To highlight the importance of the proper [V]/[Pd] ratio, we conducted several experiments that demonstrate its impact. For example, when catalyst loading ([V]/[Pd]) was increased from 4.5/3.0 mol % to 5.0/5.0 mol % while maintaining other conditions constant for entry 7 in Table 2, the yield of desired product was increased to 97% (vs 88%) without erosion of stereoselectivity. When only the palladium catalyst loading was increased from 1.0 to 2.0 mol % for entry 3 in Table 3, the yield of desired product was dramatically decreased (<5 vs 67%), whereas the O-allylated product was obtained in 83% yield. When only the vanadium catalyst loading was decreased from 4.5 to 3.0 mol % for entry 5 in Table 3, the yield of desired product was significantly increased to 87% (vs 78%) without decrease of stereoselectivity. These examples demonstrate the important nature of the relative catalyst loadings and the potential to further optimize individual reactions.

In conclusion, we have established the feasibility of coupling two highly reactive catalytic intermediates while omitting the competing side reactions with stoichiometric reagents. This transformation was achieved through the use of a combination of a vanadium-catalyzed 1,3-transposition of propargylic alcohols and a palladium-catalyzed alkylation of allylic carbonates. To our knowledge, this is the first example of trapping a catalytic amount of a highly reactive metal intermediate with a second catalytically generated metal intermediate in the presence of stoichiometric amounts of competitive reagents. We anticipate that this new tactic will provide access to a wide range of new chemical processes for generating important compounds. Further studies

of the scope and mechanism of this contemporaneous dual catalysis are in progress.

■ ASSOCIATED CONTENT

⑤ Supporting Information. Complete experimental details and characterization 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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(14) This result represents the first example of dual catalysis where two reactive intermediates generated irreversibly in situ react with each other in the presence of large excesses of competing reagents. It is important to note that the previous examples of dual catalysis have employed a catalytically generated enamine intermediate that is formed reversibly and is much more stable under the reaction conditions in comparison with our case, where the protonation of the vanadium—allenoate is much more facile and irreversible (see ref 4.)

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