Assisted Tandem Catalysis

DOI: 10.1002/anie.201204251

Tandem Palladium(0) and Palladium(II)-Catalyzed Allylic Alkylation Through Complementary Redox Cycles**

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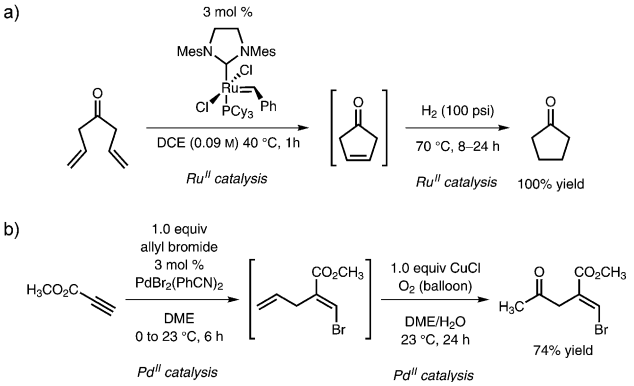
Among the strategies that seek to address the challenges inherent to performing chemical synthesis in our increasingly resource-conscious world, catalysis has provided the most significant contribution to conducting synthetic transformations in an atom-economical way, defining a paradigm in which starting materials are used efficiently and waste is minimized.[1] In the interest of further enhancing the efficiency and sustainability of the production of fine chemicals, there has been a recent focus on performing sequential catalytic operations in a single reaction vessel.[2] The application of such tandem processes has the potential to deliver important practical advantages, both with respect to the increase in material throughput and the concomitant decrease in the cost, labor, and time associated with the workup and isolation of intermediates.[3] Just as importantly, such an approach also provides an opportunity to develop new methods that orchestrate the performance of several concurrent catalytic events, allowing for the discovery of new types of reactivity and selectivity for the direct construction of molecular complexity.

Of the many types of tandem catalysis, those that employ one precatalyst to perform two mechanistically distinct bond-forming events in the presence of a reagent that triggers this change in mechanism are called "assisted tandem catalysis".[4] Strategically, these methods offer advantages over other tandem processes because they obviate the need to either begin with or subsequently add a second catalyst, making efficient use of the typically valuable precatalyst, and they eliminate the possibility for deleterious interactions between two different catalytic species.

Despite these attractive qualities, reports of assisted tandem catalysis are uncommon and the number of known chemical triggers is small.[5] A significant fraction of such processes involve a Ru–carbene-catalyzed alkene metathesis event followed by a Ru-catalyzed non-metathetic transformation.[6] For example, Grubbs and co-workers have reported that their second generation metathesis catalyst can perform a Ru^{II}-catalyzed ring-closing metathesis of hepta-1,6-dien-4-one to afford cyclopent-3-enone; addition of H_2 under high pressure generates a different Ru^{II} species that hydrogenates the newly formed alkene (Scheme 1a).[7] Similarly, Rawal and co-workers have demonstrated that a Pd^{II} catalyst which performs a bromoallylation of alkynes can also be used to conduct a subsequent Pd^{II}-catalyzed Wacker oxidation of the newly formed alkene (Scheme 1b).[8] These examples, among other analogous reports, share the requirement that each step of the tandem process be conducted with the same oxidation state of the catalyst. Reports of assisted tandem catalysis in which different catalyst oxidation states are used to effect each stage are rare,[9] and there are no known examples that employ palladium, or that form C–C bonds in both catalytic steps.



Scheme 1. a) Ring-closing metathesis followed by hydrogenation using tandem Ru^{II} catalysis. b) Bromoallylation followed by Wacker oxidation using tandem Pd^{II} catalysis. DCE = 1,2-dichloroethane, DME = dimethoxyethane, Mes = mesityl.

We became interested in the possibility of applying our recently disclosed palladium-catalyzed allylic C–H alkylation of 1,4-dienes[10] to a new assisted tandem catalytic process. In that report we demonstrated that PPh_3, a ligand that has long been employed in a wide variety of palladium-mediated allylic alkylations that proceed through leaving group ionization,[11] could also promote allylic alkylation by C–H activation. Despite the mechanistic dichotomy between these two processes, the fact that they could both be promoted by the same phosphine ligand encouraged us to consider whether it might be feasible to conduct both types of reactions in one pot with a single precatalyst. The hypothesis was that an oxidant could be used to trigger the necessary change in mechanism, thus converting a Pd^0 catalyst capable of performing allylic alkylation through leaving group ionization into a Pd^{II}

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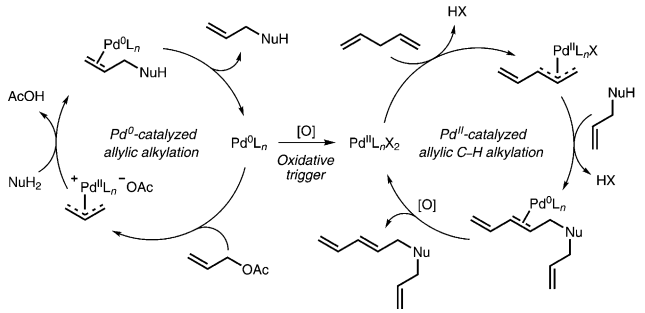
[**] We thank the NSF (CHE 0948222) for their generous support of our programs. D.A.T. acknowledges support from a Stanford Graduate Fellowship (The William K. Bowes, Jr. Foundation) and an Eli Lilly and Company Graduate Fellowship; M.M.H. acknowledges support from the Studienstiftung des deutschen Volkes and the DAAD—PROMOS scholarship.

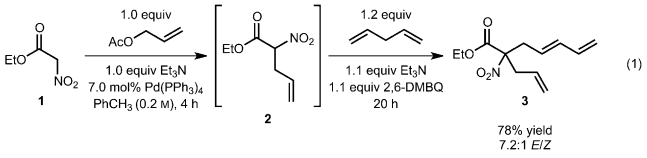
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204251.



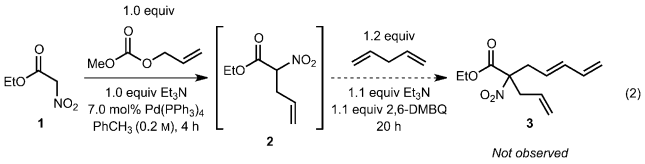
Scheme 2. Pd^0-catalyzed allylic alkylation and Pd^{II}-catalyzed allylic C–H alkylation performed in tandem with the use of an oxidative trigger. Ac = acetyl, L = ligand, Nu = nucleophile.

catalyst capable of performing allylic alkylation by C–H activation (Scheme 2). This approach might provide the first means of chemoselectively achieving two different allylic alkylations simultaneously by differentiating each event using the oxidation state of both the electrophile and the metal. Since each partner would only react in a matched sense (for example, in Scheme 2, allyl acetate with Pd^0 or 1,4-pentadiene with Pd^{II}), such a strategy would govern the introduction of otherwise indistinguishable allyl groups through complementary catalytic redox cycles. As this method accepts substrates for both Pd^0 and Pd^{II}-catalyzed allylic alkylations, it provides greater flexibility in terms of the choice of electrophile than either reaction alone. When considering the commercial availability of a desired starting material or the kind of substrate that would best fit into a synthetic sequence, an allyl group may be more efficiently installed using either the corresponding allyl acetate or the corresponding alkene; both options become available with this tandem catalysis method.

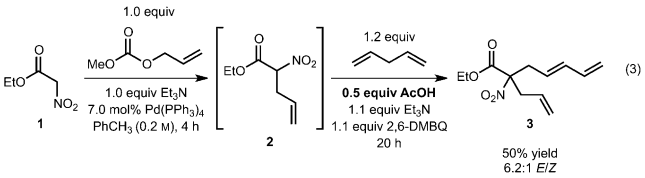
When ethyl nitroacetate (**1**) is treated with allyl acetate (1.0 equiv) in the presence of Et_3N (1.0 equiv) and $Pd(PPh_3)_4$ (7.0 mol%) in toluene at room temperature, ethyl 2-nitropent-4-enoate (**2**) is generated. In line with our hypothesis, if to this reaction 1,4-pentadiene (1.2 equiv), Et_3N (1.1 equiv), and 2,6-dimethylbenzoquinone (2,6-DMBQ; 1.1 equiv) are subsequently added, (*E*)-ethyl 2-allyl-2-nitrohepta-4,6-dienoate (**3**) can be isolated in 78% yield [Eq. (1)]. The success of



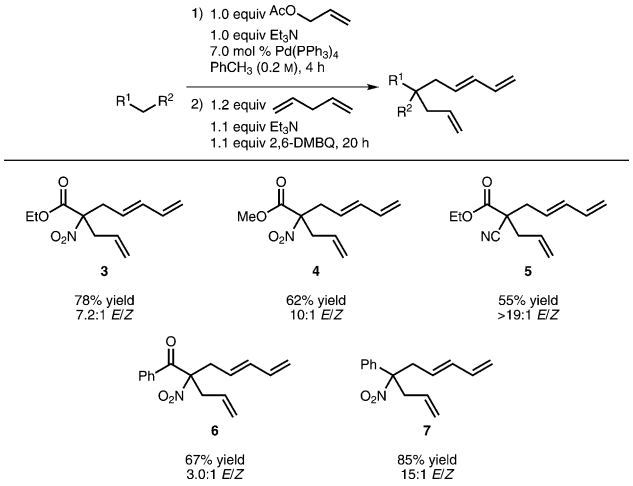
this transformation demonstrates that 2,6-DMBQ can not only be employed as the oxidative trigger to convert a Pd^0 catalyst that performs the allylic alkylation with allyl acetate into a Pd^{II} catalyst that performs the allylic alkylation with 1,4-pentadiene, but also as the oxidizing reagent necessary for converting **2** to **3**. Indeed, control experiments verify that no allylic C–H alkylation proceeds in the absence of 2,6-DMBQ. Unexpectedly, the nature of the leaving group in the first half of this tandem process is critical for the success of the second half. For example, when allyl acetate is replaced with allyl methyl carbonate, only **2** is observed, with no trace of **3** [Eq. (2)]. This result demonstrates that the acetate generated



by allylic ionization is necessary for the subsequent allylic C–H alkylation, a finding which is consistent with mechanistic work that suggests carboxylate ligands on Pd^{II} are responsible for C–H activations that proceed through concerted metalation–deprotonation pathways.[12] Indeed, when acetic acid is added to a reaction that otherwise lacks acetate, the desired allylic C–H alkylation event is restored [Eq. (3)].



We established the scope of this tandem catalytic process by systematically varying the nucleophile, the allylic acetate, and the electrophile undergoing C–H activation. When reacted with allyl acetate and 1,4-pentadiene, ethyl nitro acetate gives desired product **3** in 78% yield with a 7.2:1 *E*/*Z* selectivity (Scheme 3). With the corresponding methyl ester,

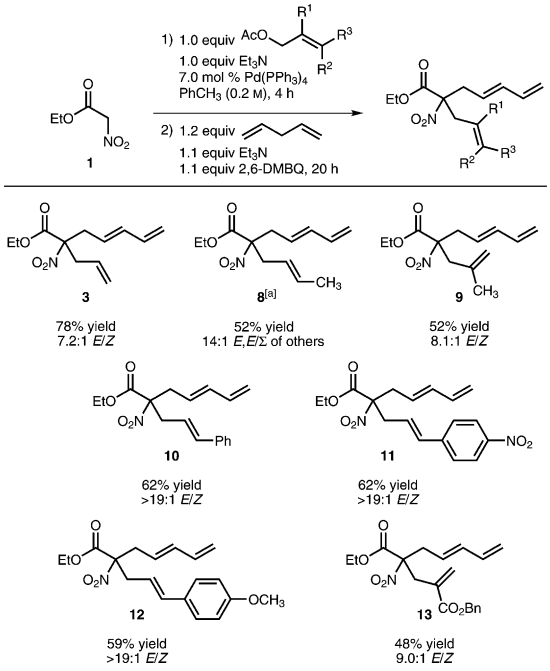


Scheme 3. Tandem Pd^0 and Pd^{II}-catalyzed allylic alkylations with stabilized nucleophiles. All yields shown are of isolated products; *E*/*Z* ratios obtained by ^1H NMR spectroscopy.

the yield of **4** moderately decreases to 62%, but the *E*/*Z* selectivity increases to 10:1. Conducting the reaction with ethyl cyanoacetate provides **5** in 55% yield and with complete control of the internal double bond geometry. Electron-withdrawing groups besides esters can also be borne by nucleophiles for the tandem catalytic reaction. For example, nitroacetophenone gives **6** in 67% yield with 3.0:1 *E*/*Z* selectivity. The success of the reaction with (nitromethyl)-

benzene to generate **7** in 85% yield with 15:1 *E*/*Z* selectivity demonstrates that, in the absence of a second strongly electron-withdrawing functionality, the nitro group alone can serve as the main nucleophilic activating group.

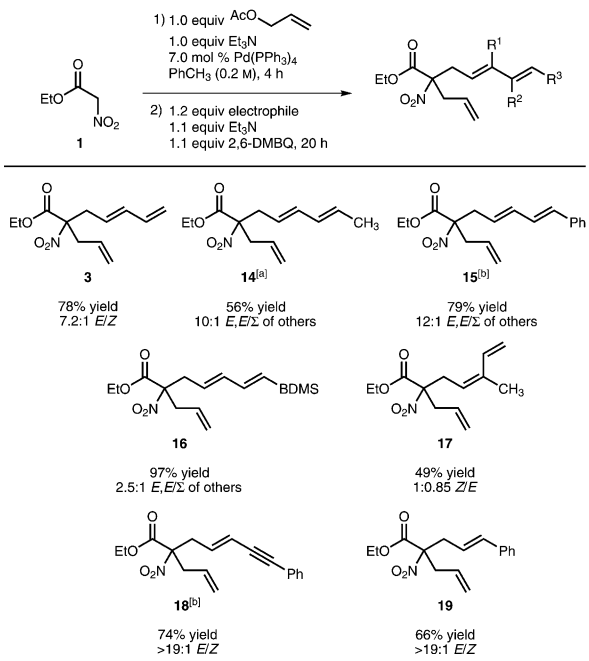
A variety of allylic acetates effectively undergo reaction with ethyl nitroacetate in concert with 1,4-pentadiene (Scheme 4). With but-3-en-2-yl acetate, which is substituted



Scheme 4. Tandem Pd^0 and Pd^{II}-catalyzed allylic alkylations with allylic acetates. All yields shown are of isolated products; *E*/*Z* ratios obtained by ^{1}H NMR spectroscopy. [a] Reaction conducted with but-3-en-2-yl acetate. Σ of others = sum of all other configurations.

on the carbon bearing the leaving group, **8** is isolated in 52% yield with a predominantly *E*,*E* configuration. When the electrophile is methallyl acetate, in which there is substitution on the central carbon of the *p*-allylpalladium intermediate, desired product **9** can be obtained in 52% yield with an 8.1:1 *E*/*Z* selectivity. In general, cinammyl-based substrates provide excellent control of the double bond geometry set in the subsequent allylic C–H alkylation. For example, reaction with cinnamyl acetate gives **10** in 62% yield with >19:1 *E*/*Z* selectivity. The corresponding electron-deficient *para*-nitro electrophile provides **11**, also in 62% yield and >19:1 *E*/*Z* selectivity, and the corresponding electron-rich *para*-methoxy electrophile gives **12** in 59% yield and >19:1 *E*/*Z* selectivity. When benzyl 2-(acetoxymethyl)acrylate is employed as the allylic acetate, **13** is isolated in 48% yield and with 9.0:1 *E*/*Z* selectivity.

Many different types of electrophiles undergo C–H activation in this tandem catalytic process (Scheme 5). When a 1:1 *E*/*Z* mixture of 1,4-hexadiene is used as a substrate, desired product **14** is isolated in 56% yield with a 10:1 ratio of the *E*,*E* configuration to the other double bond isomers. When one terminus of 1,4-pentadiene is substituted



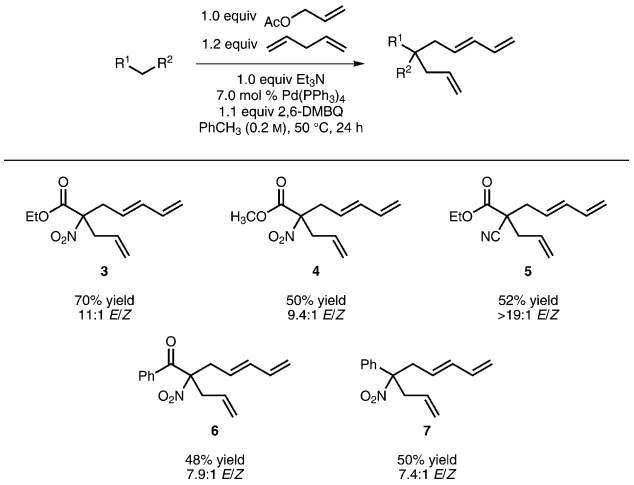
Scheme 5. Tandem Pd^0 and Pd^{II}-catalyzed allylic alkylations with electrophiles. All yields shown are of isolated products; *E*/*Z* ratios obtained by ^{1}H NMR spectroscopy. [a] Reaction conducted with a 1:1 *E*/*Z* mixture of 1,4-hexadiene. [b] The second half of the tandem catalysis was performed at 50°C; see the Supporting Information for details. BDMS = benzyl(dimethyl)silyl, Σ of others = sum of all other configurations.

with a phenyl group, the corresponding triene (**15**) can be obtained in 79% yield with almost complete stereoselectivity. The corresponding benzyl(dimethyl)silyl containing 1,4-diene gives **16** in 97% yield, but with less control over the double bond geometries. In addition to activating C–H bonds belonging to methylene groups, the catalyst can also react with methine C–H bonds. For example, when 3-methyl-1,4-pentadiene is employed as an electrophile, **17** can be obtained in 49% yield, with a slight excess of the *Z* configuration.

The allylic C–H alkylation event is not limited to 1,4-dienes. It can also be performed with 1,4-enynes, as a phenyl-substituted 1,4-enyne is smoothly converted to **18** in 74% yield and with complete control of double bond geometry. Allylbenzene, in which the adjacent π system is a phenyl group instead of a double or triple bond, reacts efficiently to give **19** in 66% yield and with >19:1 *E*/*Z* selectivity.

Because the chemical trigger used to generate the second catalyst species would interfere with the performance of the first, every example of assisted tandem catalysis requires a delay between the start of the reaction and the addition of the trigger. Although this temporal separation allows each catalytic transformation to be conducted independently, it necessitates monitoring the first reaction to determine when the second can begin, an inconvenience that decreases the operational practicality of executing multiple bond-forming steps using this strategy. Given control experiments which demonstrate that Pd^0-catalyzed allylic alkylation is more facile than the analogous Pd^{II}-catalyzed reaction, our hypothesis was that it would be possible to carry out this tandem

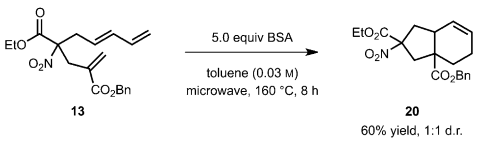
catalytic process without delaying the introduction of either the oxidant or the second electrophile. Even in the presence of the chemical trigger, the difference in relative rates should allow the Pd^0-catalyzed bond-forming event to proceed to completion before the Pd^{II}-catalyzed one. When ethyl nitroacetate, allyl acetate, 1,4-pentadiene, 2,6-DMBQ, Et_3N, and $Pd(PPh_3)_4$ are combined at the same time in toluene in a single reaction vessel and heated to 50 °C for 24 h, **3** is obtained in 70% yield and with 11:1 *E*/*Z* selectivity (Scheme 6), an achievement that marks the first example of



Scheme 6. Simultaneous tandem Pd^0 and Pd^{II}-catalyzed allylic alkylations with stabilized nucleophiles. All yields shown are of isolated products; *E*/*Z* ratios obtained by ^1H NMR spectroscopy.

assisted tandem catalysis that does not require intervention to initiate the second catalytic step. Several aspects of this success merit further comment. First, both Pd^0 and Pd^{II} catalytic cycles operate sequentially in the presence of 2,6-DMBQ, suggesting that this strong oxidant for Pd^0 is effectively out-competed by allyl acetate. Additionally, the rate of the first Pd^0-catalyzed allylation is substantially faster than the second, as significant quantities of the corresponding bis-allylated product are not detected. Notably, although there is a slight decrease in the amount of isolated material, this process is more stereoselective than the two-stage protocol (Scheme 3). In analogous reactions with methyl nitroacetate, ethyl cyanoacetate, benzoylnitromethane, and (nitromethyl)benzene, the corresponding products (**4**, **5**, **6**, and **7**, respectively) can be similarly obtained (Scheme 6).

One of the advantages of employing 1,4-dienes as substrates for this type of palladium-catalyzed allylic C–H functionalization reaction is that the resulting products contain the corresponding 1,3-dienes, which are functional groups with diverse applications in synthesis.[13] For example, **13** undergoes an intramolecular Diels–Alder reaction when heated in a microwave reactor to give bicycle **20** in 60% yield [Eq. (4); Bn = benzyl, BSA = bis(trimethylsilyl)acetamide]. This cycloaddition illustrates the efficiency with which this tandem protocol can be used assemble molecular complexity; in only two steps, four C–C bonds are formed.



(4)

In summary, we have demonstrated that two concurrent Pd-catalyzed allylic alkylation events can be independently controlled by exploiting the chemoselectivity of the catalyst in its Pd^0 and Pd^{II} states. By differentiating substrates using their oxidation level, it is possible to govern which catalyst species each engages with. Such an approach may prove to be a more general strategy for effecting two or more coupling reactions that, in the absence of another distinguishing feature, would have to be performed stepwise.

Experimental Section

General procedure for the tandem Pd^0- and Pd^{II}-catalyzed allylic alkylations: A reaction vial equipped with a stir bar was charged with $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), sealed with a septa, and then evacuated and filled with Ar three times. $PhCH_3$ (0.7 mL) was added, followed by the nucleophile (0.200 mmol), the allylic acetate (0.200 mmol), and Et_3N (27.9 μL, 0.200 mmol). A second reaction vial equipped with a stir bar was charged with 2,6-DMBQ (30.0 mg, 0.220 mmol), sealed with a septa, and then evacuated and filled with Ar three times. $PhCH_3$ (0.3 mL) was added to the second reaction vial, and after 4 h this solution was added to the reaction via syringe, followed by the alkene (0.240 mmol) and Et_3N (30.7 μL, 0.220 mmol). After 20 h, the reaction was concentrated under reduced pressure to give crude material, which was purified by column chromatography on silica gel (see the Supporting Information for details).

Received: June 1, 2012
Revised: August 6, 2012
Published online: October 10, 2012

Keywords: 1,4-dienes · allylic alkylation · C-H activation · palladium · tandem catalysis

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