Pd-Catalyzed [3+2]-Dehydrogenative Annulation Reactions

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Dedicated to Professor Maurizio Prato on the occasion of his 70th birthday

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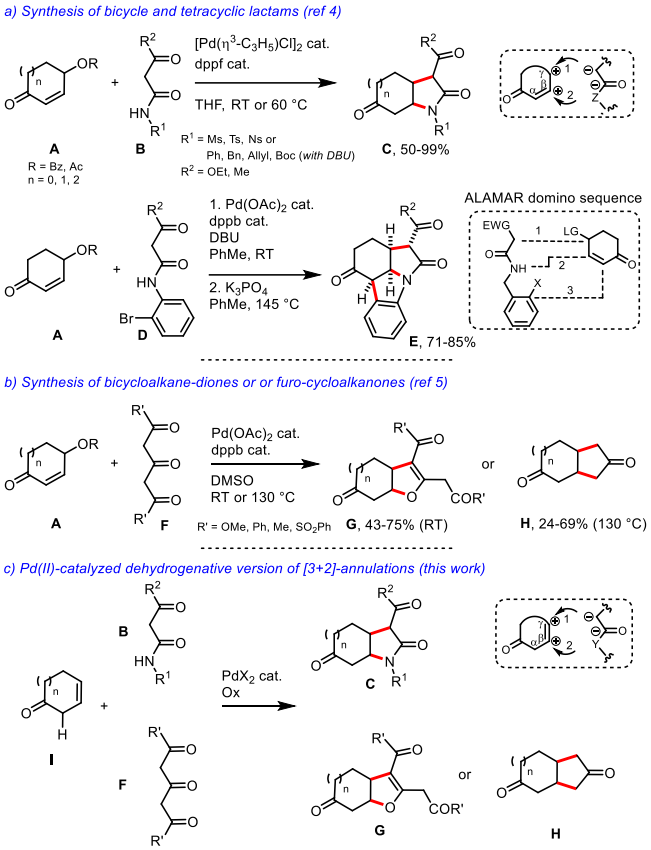
Abstract: The significance of cross dehydrogenative couplings has increased considerably in recent years. This article revisits the [3+2]-C−C/N−C, C−C/O−C and C−C/C−C annulation strategy, recently reported by our group, according to a Pd(II) catalyzed dehydrogenative variant. Our original report relied on Pd(0) catalysis, using α,β-unsaturated-γ-oxy carbonyls as bis-electrophiles and resonance-stabilized acetamides or 3-oxoglutarates as C/N and O/C or C/C bis-nucleophiles, respectively. In this more modern and straightforward Pd(II)-catalyzed dehydrogenative approach, β,γ-unsaturated carbonyl derivatives replace α,β-unsaturated-γ-oxy carbonyls as bis-electrophiles. Our study includes experimental optimization and showcases the synthetic versatility in the formation of diverse heterocyclic structures, such as bicyclic lactams, furo-cycloalkanones and bicycloalkane-diones. Furthermore, a mechanism is proposed to elucidate the underlying processes involved in these reactions.

Introduction

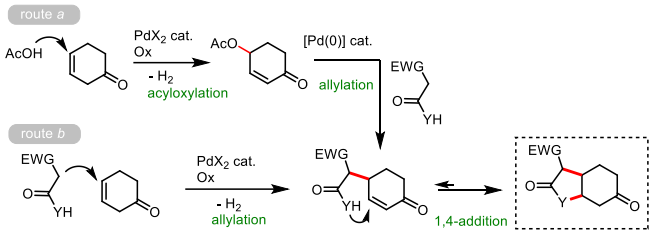
Heteropolycyclic structures are of major interest in chemistry due to their wide range of applications, including pharmaceutical, materials, catalysis and agrochemistry.[1] Synthesizing these structures in the most sustainable way, with atoms and steps economy, is therefore essential for their large-scale application.[2] In 2018, we developed a method for the synthesis of bicyclic lactams **C** *via* a Pd(0)-catalyzed [3+2]-C−C/N−C annulations,[3] using cyclic α,β-unsaturated-γ-benzyloxy-carbonyls **A** as bis-electrophiles and resonance-stabilized acetamides **B** as bis-nucleophiles (Scheme 1a, top).[4] This selective method involves an intermolecular allylation/intramolecular 1,4-addition sequence. Furthermore, in the presence of an *ortho*-haloaryl group at the nitrogen substituent (compounds **D**), an allylation/aza-Michael/arylation (ALAMAR) domino sequence can be elicited to generate more complex tricyclic structures **E** (Scheme 1a, bottom). We have also successfully extended this synthetic method to the selective formation of furo-cycloalkanone **G** or bicycloalkane-dione **H** structures using 3-oxoglutarates **F** as C/C or C/O bis-nucleophiles, depending of the experimental conditions (Scheme 1b).[5] Although these strategies are of interest in terms of efficiency, selectivity, and step economy, with the creation of two, or even three, C–C bonds in a single synthetic operation, we thought that switch from a Pd(0)-catalyzed redox neutral coupling to a dehydrogenative Pd(II)-catalyzed coupling might represent an interesting and modern variant.



Scheme 1. Pd-catalyzed [3+2]-annulation strategies: *previous works and this work*.

Building on our knowledge on transition-metal-catalyzed allylic C−H activation strategies,[6] we considered for this new project the use of β,γ-unsaturated carbonyl derivatives **I** instead of the more oxidized α,β-unsaturated-γ-oxy carbonyls **A** as bis-electrophiles, and the change from a redox neutral Pd(0) to an oxidative Pd(II) catalysis (Scheme 1c).[7] In particular, two possible reaction pathways were anticipated: the former involving a direct oxidative Pd(II)-catalyzed C-allylation (Scheme 2 top, route *a*), and the latter based on a direct Pd(II)-catalyzed acyloxylation followed by an *in-situ* Pd(0)-catalyzed C-allylation (Scheme 2, bottom, route *b*). We present here our results in the Pd(II)-catalyzed C−C/N−C, C−C/O−C and C−C/C−C dehydrogenative [3+2] annulation reactions using bis-electrophiles **I** and bis-nucleophiles **B** or **F**. In addition, *ad hoc*

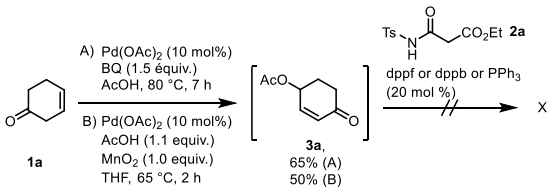
experiments enabled us to propose the reaction mechanism of the transformation under study.



Scheme 2. Mechanistic routes for the planned Pd(II)-catalyzed dehydrogenative [3+2]-annulations.

Results and Discussion

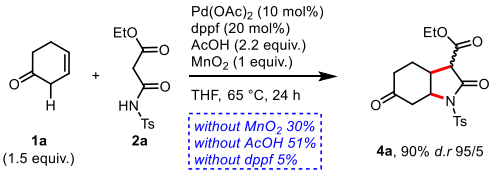
Taking the coupling between bis-electrophile **1a**[8] and bis-nucleophile **2a**[9] as our model [3+2] annulation, preliminary tests considered the sequential route Pd(II)-catalyzed allylic acyloxylation / C-allylation / 1,4-addition sequence (Scheme 2, top). As the allylation step needs a Pd(0) catalysis, we envisioned to add, after successful detection of the allyl acyloxylation step, a phosphine ligand, capable of *in-situ* Pd(II)-to-Pd(0) reduction.[10] Our first tests were quite promising. Indeed, selective γ-acyloxylation of **1a** could be successfully performed either using benzoquinone as oxidant in acetic acid, or using MnO_2 in THF, in the presence of 1.1 equivalents of AcOH (Scheme 3). To our knowledge, the γ-acyloxylation of cyclic β-γ-unsaturated cycloalkenones has not been previously reported.[6e,11] Unfortunately, any attempt to perform the other steps of the planned annulation along route *a* by *in situ* addition of a phosphine ligand (dppf, dppb or PPh_3) and of the bis-nucleophile met with failure.[12] Incompatibility between the oxidant and the phosphine, and/or activity loss of the palladium salt after the first step, was suspected to be the likely reason of the failure.[13]



Scheme 3. First attempts at the sequential process: allylic acyloxylation of **1a**, followed by C-allylation/1,4-addition sequence.

After much experimentation along route *b*, we serendipitously found that by reacting **1a** with **2a** in the simultaneous presence of MnO_2, AcOH, $Pd(OAc)_2$, and dppf, in a sealed tube, gave the desired bicyclic lactam **4a** without traces of intermediate **3a** (Scheme 4). The best result gave **4a** in 90% isolated yield after optimization of several parameters (SI, table S1).[14] With such a striking result, the planned dehydrogenative version of [3+2]-C-C/N-C annulation was thus reached.

However, some aspects of the mechanism needed a rational explanation, as the essential role of acetic acid (no reaction takes place in its absence) and well as that of the oxidant and of the phosphine (Scheme 4). ^{31}P NMR analysis at 300 K of a $Pd(OAc)_2$/dppf combination allowed to detect the formation of $[Pd(OAc)_2dppf]$ complex, without generation of Pd(0).[15] We also confirmed by ^{31}P NMR that MnO_2 did not oxidize the free-phosphine, thereby not interfering with the formation of the $[Pd(OAc)_2dppf]$ complex (see SI). Then, the influence of acetic acid on the bis-nucleophile **2a** was studied. ^{1}H-NMR analysis of a sample of **2a** in $CDCl_3$ showed that addition of one equivalent of AcOD induced a 25% decrease of the integration of the signal corresponding to the two H–C acidic atoms, and a 79% decrease after 24 h (see SI). Such integration decrease unambiguously confirms that **2a** is in equilibrium with the corresponding nucleophilic enol form.

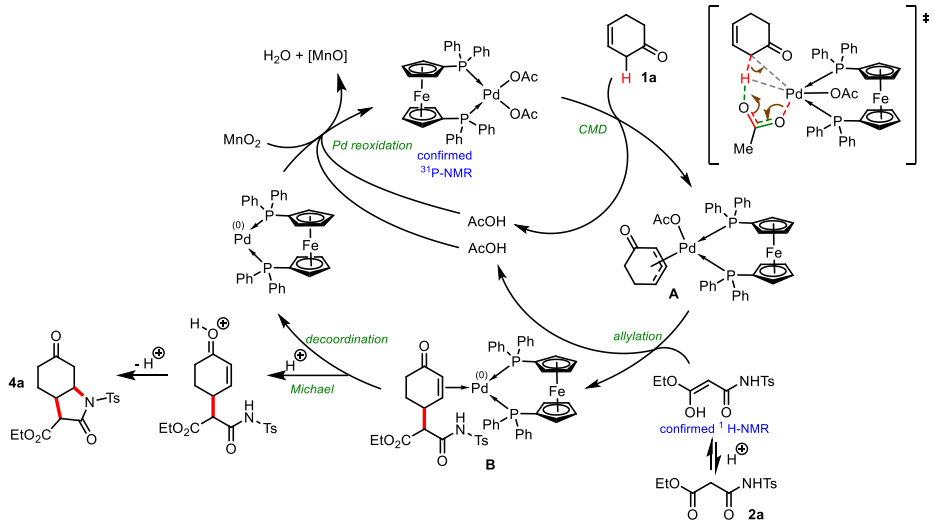


Scheme 4. Dehydrogenative C-allylation/1,4-addition: "one-pot" protocol.

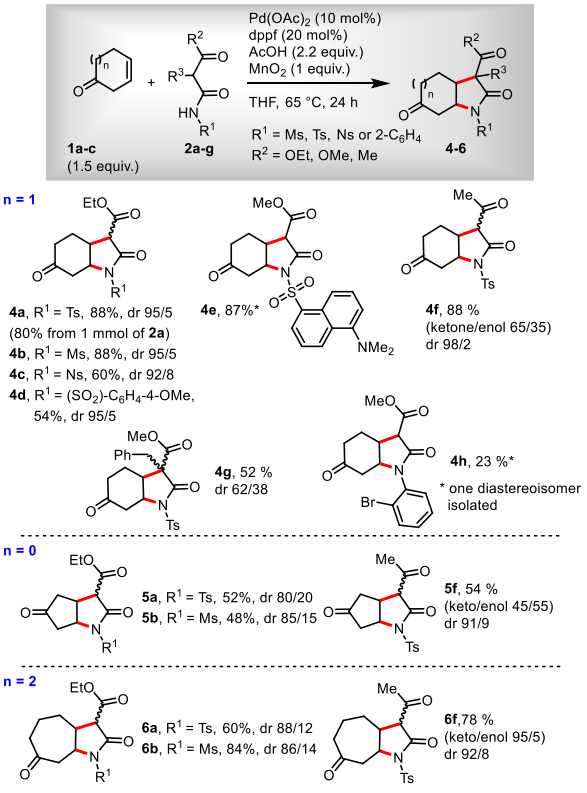
The above experimental observations allow to propose the following mechanism for the direct oxidative [3+2] annulation (Scheme 5 and Scheme 2 bottom). Interaction between the catalytic complex κ^2 P,P $[Pd(OAc)_2dppf]$ and the bis-electrophile **1a** takes place via a likely concerted-metalation-deprotonation (CMD) pathway[16] mechanism, generating the η^3-allylpalladium **A** complex and one equivalent of acetic acid. Subsequently, **A** undergoes nucleophilic attack at the γ-position by the enol form of **2a**, creating a C−C bond with release of an additional equivalent of acetic acid. Alkene decoordination from the metal in **B**, followed by aza-Michael addition leads to the final product **4a** and the release of Pd(0) complex. The latter is then reoxidized by MnO_2 in the presence of acetic acid to regenerate the catalytically active Pd(II) species. The presence of acetic acid may have an additional notable influence in this reoxidation step.[17] The generation of **4a** in 30% NMR yield in the experiment performed without MnO_2 (Scheme 4), may be accounted for by assuming that **1a**, present in excess, might act as an H_2 acceptor.

We next investigated the scope of the dehydrogenative [3+2]-annulation. To overcome the volatility problem of **1a**, as well as its partial undesired oxidation to phenol, the use of 1.5 equivalents of the β,γ-unsaturated carbonyl component was found advantageous for achieving better yields. Formation of phenol is very likely due to β-elimination of the δ-H from cyclic η^3-allylpalladium complex **A**, which competes with the allylation step, followed by keto-enol tautomerization.[18] Scheme 6 shows the annulation reactions between bis-electrophile **1a** and various *N*-sulfonyl protected acetamides (**2a-g**), which give the corresponding lactams (**4a-g**) in moderate to excellent yields and a high level of diastereoselectivity. Consistent with our previous study, the bis-nucleophile **2f** produced the desired lactam **4f** as a keto/enol mixture, while the presence of a benzyl group on the malonic position in bis-nucleophile **2g** resulted in a more moderate yield, likely due to increased steric hindrance impeding nucleophilic attack. In contrast, attempts with non-sulfonylated bis-nucleophiles (NBn, NBoc) were unsuccessful, except for *N*-aryl compound **1h**, which provided the desired product in a low yield. Subsequently, we evaluated the synthetic potential of the five-membered bis-electrophile **1b**[19] and the seven-membered one **1c**.[20] Despite encountering substantial volatility issues with

1b, we managed to obtain the bicyclic lactams **5a-b,f** in moderate yields. Conversely, the seven-membered bis-electrophile **1c** allowed better yields of the final annulated compounds **6a-b,f**.



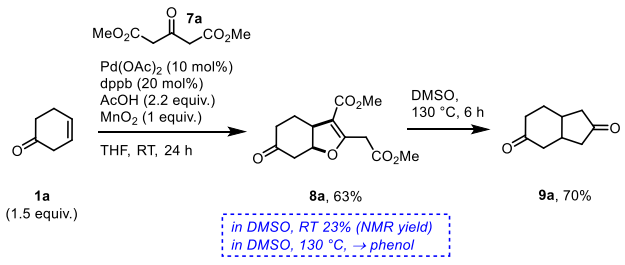
Scheme 5. Proposed mechanism for the [3+2]-dehydrogenative annulation.



Scheme 6. Scope of Pd-catalyzed dehydrogenative [3+2]-C−C/N−C bond-forming annulation.

We subsequently turned our attention to the O/C (or C/C) bis-nucleophiles, namely 3-oxoglutarates **F**. In our previous study, we observed that starting from the same γ-benzyloxycyclohexenone **A** and using the same catalytic system [$Pd(OAc)_2$/dppb in DMSO], dihydrofuran **G** or bicyclo[4.3.0]nonane **H** could be synthesized at will, simply by changing the reaction temperature (Scheme 1c). Indeed, a reversible intramolecular *O*-1,4-addition to the intermediate allylation product at room temperature affords the kinetic product, while an irreversible *C*-1,4-addition followed by demethoxycarbonylation takes place at 130°C.

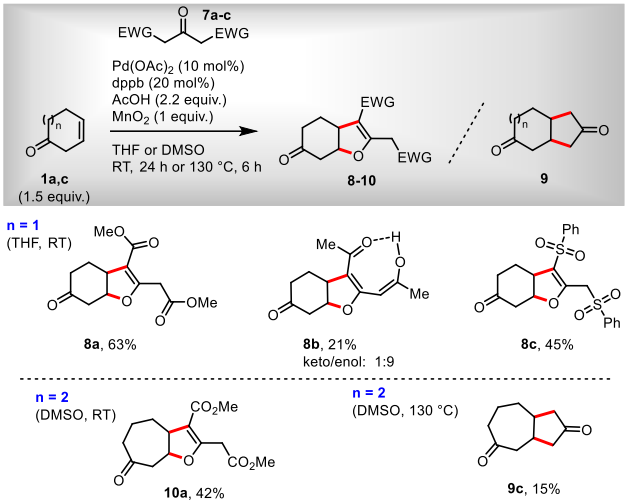
The reaction between the bis-nucleophile **7a** and the bis-electrophile **1a** was chosen as model reaction to develop a dehydrogenative version of the above [3+2]-C−C/O−C and/or C−C/C−C annulation reactions, optimizing the ligand, the solvent, and the temperature (SI, Table S2). The most favorable outcome, which gave the bicyclic dihydrofuran derivative **8a**, was achieved by using the dppb ligand in THF at room temperature (Scheme 7). Heating at 65 °C in THF lowered the yield of **8a**. In addition, use of DMSO led to poorer yield of **8a** at room temperature, or significant amount of phenol at elevated temperatures. Thus, in the case of this dehydrogenative variant, it was not possible to reverse the selectivity of the sequence (from C–C/O–C to C–C/C–C annulation), by playing on the temperature, as done in the previous study. Not unexpectedly, heating isolated **8a** at 130°C in DMSO gave **9a** in 70% yield.



Scheme 7. [3+2] annulation between **1a** and dimethyl 3-oxoglutarate **7a**.

Putting to react 1,3,5-triketone **7b**[21] with bis-electrophile **1a** gave the expected annulated product **8b** in a modest yield as a keto/enol mixture in a 1:9 ratio (Scheme 8). The use of 1,3-bis-sulfonylpropan-2-one **7c**[22] as a bis-nucleophile proved to be more effective, leading to the formation of furo-cycloalkanone **8c** with a yield of 45%. While experiments with the five-membered

bis-electrophile **1b** resulted in degradation, or formation of the Diels-Alder cycloadduct of the cyclopentadienone by-product,[23] the seven-membered bis-electrophile **1c** provided the desired heterocycle **10a** in 42% yield. The best result was obtained with DMSO as solvent, at room temperature. In this case, the kinetic-to-thermodynamic switch by increasing the reaction temperature to 130 °C, allowed the expected bicyclo[3.3.0]octane-dione **9c** to be obtained, albeit in very low yield.



Scheme 8. Scope of Pd-catalyzed dehydrogenative [3+2] C−C/O−C and C−C/C−C bond-forming annulations.

Conclusion

In summary, we have developed a new [3+2]-annulation strategy by the Pd(II)-catalyzed coupling between resonance-stabilized acetamides (or 3-oxoglutarates) and β,γ-unsaturated cyclic carbonyl derivatives. These dehydrogenative couplings enable the efficient construction of a range of heteropolycyclic structures such as bicyclic lactams, furo-cycloalkanones and bicycloalkano-diones, and they represent a more atom- and step-economical version than the corresponding Pd(0)-catalyzed redox-neutral couplings previously studied by our group. With the support of *ad hoc* experiments, it was possible to propose a plausible mechanism for this new annulation.

Experimental Section

General procedure for synthesis of 4,5-fused bicyclic pyrrolidin-2-ones 4-6: In a sealed microwave tube $Pd(OAc)_2$ (0.10 equiv.), dppf (0.20 equiv.), MnO_2 (1.0 equiv.) and the bis-nucleophile **2** (1.0 equiv.) were introduced under an argon atmosphere. Anhydrous THF (0.15 M) and bis-electrophile **1** (1.5 equiv.) were then added. After 2 minutes stirring, AcOH (2.2 equiv.) was added and the reaction allowed to stir for 24 to 30 h at 65°C until total consumption of the bis-nucleophile **2**. The mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding 4,5-fused bicyclic pyrrolidin-2-one **4-6**.

General procedure for synthesis of 4,5-fused bicyclic dihydrofurans 8 and 10: In a sealed microwave tube $Pd(OAc)_2$ (0.10 equiv.), dppb (0.20 equiv.), MnO_2 (1.0 equiv.) and the bis-nucleophile **7** (1.0 equiv.) were introduced under an argon atmosphere and solubilized in freshly distilled THF or DMSO (0.15M). After 5 minutes, the bis-electrophile **1** (1.5 equiv.) and AcOH (2.2 equiv.) were added. After 24 h stirring at RT, the mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding 4,5-fused bicyclic dihydrofurans **8**.

Supporting Information

Additional references cited within the Supporting Information.[24-27]

Acknowledgements

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Keywords: Annulation • Heterocycle • Dehydrogenative Coupling • Palladium • Mechanism

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[13] The addition of a catalytic amount of palladium/ligand system in the second step provides the desired compound **4a** in good to moderate yields.

[14] In the experiment carried out in absence of MnO_2 (30% yield, see scheme 4), the enone could partially behave as the formal H_2 acceptor. We recently met an analogous scenario in a Ru(0)-catalyzed alkenylation of 2-carboxaldimineheterocyclopentadienes: R. Sala, G. Kiala, L. F. Veiros, G. Broggini, G. Poli, J. Oble*, J. Org. Chem.* **2022**, *87*, 4640−4648.

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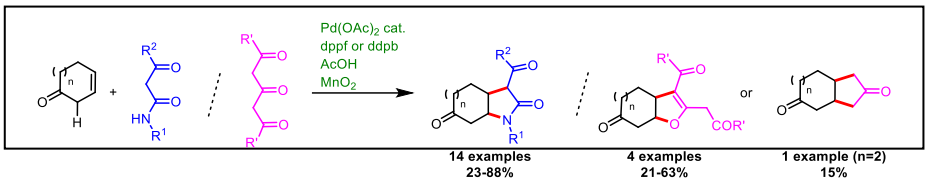

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Pd-catalyzed [3+2]-dehydrogenative annulation reactions

Pd-catalyzed [3+2] annulations go dehydrogenative: a new protocol enables the Pd(II)-catalyzed [3+2] annulation between resonance-stabilized acetamides (or 3-oxoglutarates) and β,γ-unsaturated cyclic carbonyl derivatives. This dehydrogenative strategy represents a more atom- and step- economical version than the corresponding Pd(0)-catalyzed redox-neutral couplings previously studied by our group, enabling the straightforward construction of a number of heteropolycyclic structures.

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