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A New Insight into the Stereoelectronic Control of the Pd(0)-Catalyzed Allylic Substitution: Application for the Synthesis of Multisubstituted Pyran-2-ones via an Unusual 1,3-Transposition

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Abstract: Pyran-2-ones **3** undergo a novel Pd(0)-catalyzed 1,3-rearrangement to afford isomers **6**. The reaction proceeds via an η^2-Pd complex, whose pyramidalization (confirmed by quantum chemistry calculations) offers a favorable antiperiplanar alignment of the Pd-C and allylic C-O bonds (**C**), thus allowing the formation of an η^3-Pd intermediate. Subsequent rotation and rate-limiting recombination with the carboxylate arm then gives isomeric pyran-2-ones **6**. The calculated free energies reproduce the observed kinetics semi-quantitatively.

Introduction

The classical Tsuji-Trost Pd(0)-catalyzed allylic substitution[1] represents a robust, stereo- and regioselective methodology that has been frequently utilized in organic synthesis as an indispensable tool. The reaction is known to proceed via η^3-complexes[1] that are formed from allylic esters, typically with inversion of configuration, where the Pd approaches the allylic moiety from the side opposite to the leaving group (**A** in Chart 1).[2,3] Retention pathway for the formation of η^3-complexes (**B**) has also been reported, especially in those instances, where the leaving group can coordinate the approaching palladium and thus steer its approach to the C=C bond.[4,5] In all these reactions, good alignment of the π-orbitals of the double bond with the σ bond of the leaving group (X) has been regarded as a prerequisite for the reaction to occur.[1-6] In other words, the allylic leaving group should be positioned perpendicularly to the plane of the C=C bond (**A**/**B**). Herein, we show that this commonly accepted interpretation of the stereoelectronic effect requires a modification, reflecting pyramidalization of the sp^2 centers and the palladacyclic nature of the η^2-intermediate.

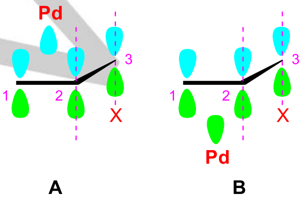
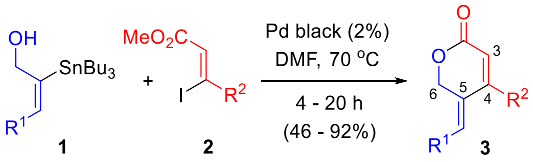


Chart 1. Stereoelectronic effects in the formation of η^3-complexes.

Results and Discussion

Construction of 4-Substituted-5-alkylidene Pyran-2-ones. The pyran-2-one moiety, occurring in a number of natural products, is known to be responsible for a wide range of biological effects, such as antifungal, antibiotic, and cytotoxic.[7] It is, therefore, of little surprise that the past decade has witnessed a considerable effort aiming at the development of an efficient and modular construction of the pyran-2-one core.[8,9] We have recently disclosed[10,11] a new method for rapid assembly of novel 4-substituted-5-alkylidene pyran-2-ones **3** through a cross-coupling of 2-tributystannyl allyl alcohols **1** and β-iodo acrylates **2**, catalyzed by the ligand-free palladium black (Scheme 1). Notably, this reaction did not proceed under homogeneous conditions with PdL_4, presumably due to the enhanced stability of the ligated products of the initial oxidative addition.[11]



Scheme 1. Synthesis of 4-substituted-5-alkylidene pyran-2-ones (for R^1 and R^2 see Table 2).

Palladium-Catalyzed 1,3-Rearrangement of 5-Alkylidene Pyran-2-ones. While screening the reaction conditions for the preparation of pyran-2-one **3a** (R^1 = Pr, R^2 = Ph; see Table 2 for R^1 and R^2), an unexpected formation of the isomeric 4,6-

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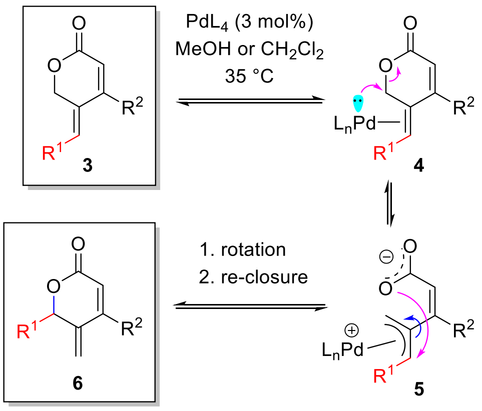
disubstituted-5-methylene pyran-2-one **6a** as a byproduct (≤11%) was observed (Scheme 2) in those cases, when the Pd black catalyst used was generated from $Pd(PPh_3)_4$ via an air oxidation of the phosphine ligand.[11] Subsequently, isomerization of **3b**, labeled at the 6-position with ^{13}C, was found to proceed under homogeneous conditions with $Pd(PPh_3)_4$ (3 mol%) in DMF at 120 °C for 60 min, which afforded **3b** and **6b** in 30% and 64% yield, respectively.[11] Since the label moved from C(6) to the *exo*-methylene, the latter reaction can be assumed to proceed via the η^3-Pd complex **5** that undergoes a partial rotation about the C(4)-C(5) bond with ensuing attack by the liberated carboxylate. Replacement of $Pd(PPh_3)_4$ with $Pd(TFP)_4$ [TFP = tris(2-furyl)phosphine][12] allowed to obtain the same **3b**/**6b** mixture (31% and 65%, respectively) at 90 °C within 210 min and the reaction mixture turned out to be cleaner.



Scheme 2. Pd-Catalyzed allylic 1,3-rearrangement.

A logical question then arose as to whether this side reaction can be enforced to proceed to completion and whether theoretical analysis can rationalize this rather anomalous behavior. Herein, we report on the development of this isomerization into a practical synthetic protocol to obtain yet another, very unusual pyran-2-one substitution pattern via a simple switch from heterogeneous to homogeneous Pd-catalysis. First elucidated was the temperature and solvent effect, employing **3d**[11] as a model compound (Table 1): MeOH and CH_2Cl_2 were found to be suitable solvents for reaching good conversions at 70 °C and even at 45 and 35 °C (Table 1, entries 1 and 2); only at 28 °C the reaction proved to be rather slow, giving 17:83 (CH_2Cl_2) and 19:81 (MeOH) ratios, respectively, over 20 h. The isomerization also proceeded in Me_2CO and MeCN but only at 70 °C (entries 3 and 4), whereas DMF, THF, and toluene turned out to be unsuitable at this temperature.

Screening of other homogeneous catalysts at 35 °C revealed that only the Pd^0L_4 type complexes were capable of promoting the isomerization. With TFP, Ph_3P, and diphos in MeOH and DIOP[13] in CH_2Cl_2, the **3d**:**6d** ratio was found to be in the range of 7:93 to 3:97 within 4 h (entries 5-7). Other ligands, such as PEPSI-iPr, oxazolines, and MeCN, proved ineffective (see also Table S2 in Supporting Information). The two isomers are at a dynamic equilibrium, since ca 5 % of **3d** was detected by ^1H NMR within 4 hrs following the exposure of pure **6d** to the optimized reaction conditions (vide infra).

Table 1. Optimization of the Pd-catalyzed pyran-2-one isomerization **3d** → **6d**.[a]

entry	catalyst	solvent	Ratio[b] **3d** : **6d**		
			70 °C	45 °C	35 °C
1	$Pd(TFP)_4$	CH_2Cl_2	4 : 96	4 : 96	-
2	$Pd(TFP)_4$	MeOH	5 : 95	5 : 95	6 : 94
3	$Pd(TFP)_4$	Me_2CO	7 : 93	68 : 32	-
4	$Pd(TFP)_4$	MeCN	9 : 91	68 : 32	-
5	$Pd(PPh_3)_4$	MeOH	-	-	7 : 93
6	$Pd(diphos)_2$	MeOH	-	-	5 : 95
7	$Pd_2(dba)_3$/(-)-DIOP	CH_2Cl_2	-	-	3 : 97

[a]The reaction was carried out on a 0.2 mmol scale in 0.5 mL of solvent with 3 mol% of PdL_n over the period of 4 h. [b]Determined by ^1H NMR spectroscopy; no other products or impurities were detected.

Subsequently, a series of lactones **3c-3u** was prepared (see the SI) and subjected to the optimized conditions with $Pd(TFP)_4$ at 35 °C in MeOH or a MeOH-CH_2Cl_2 (1:1) mixture, depending on the solubility (Table 2).

Table 2 shows broad applicability of the reaction. The presence of the hydroxymethyl group as the R^1 substituent is clearly beneficial, as documented by high yields and short reaction times for substrates **3c**-**3h** (entries 3-8); only for the thienyl derivative **3i** the yield dropped slightly (entry 9). Notably, among the rearranged products, **6h** is of particular interest, since this compound represents a substituted [3]dendralene, where two of its double bonds constitute part of the rigid pyranone ring.

Bulky R^2 substituents (aryl and Pr) also support the conversion (entries 11, 12, and 16); on the other hand, with small groups in that position (R^2 = H or Me), the reaction proceeds less efficiently (entries 10, 13, and 14). More complex substitution pattern, as in **3o** and **3p**, proved to be well tolerated (entries 15 and 16), although in the latter instance the reaction became rather slow. With R^2 = CH_2OH (**3q**, entry 17), the outcome copied that observed for other CH_2OH derivatives (entries 3-8).

The *ortho*-condensed derivatives **3r** and **3s** behaved in a similar way, giving **6r** and **6s** in high yields, though after a longer period of time. By contrast, the C(4)-unsubstituted pyran-2-ones **3t** and **3u** did not undergo the reaction. Hence, the steric congestion, exercised by the C(4)-substituent R^2, can be regarded as the driving force for the allylic transposition to occur. In its absence, the reaction either becomes very slow (**3j**, entry 10) or does not proceed at all (**3t** and **3u**).

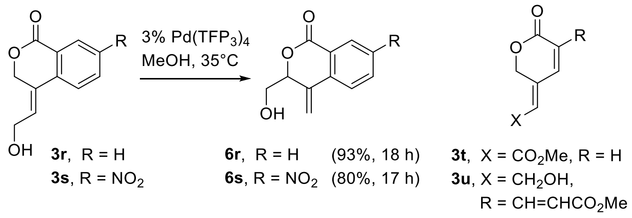
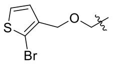


Table 2. Scope of the Pd-catalyzed pyran-2-one isomerization **3** → **6**.[a]

entry	substrate	product	R^1	R^2	Time (h)	Yield (%)[b]
1	**3a**	**6a**	Pr	Ph	4	54
2	**3b**[c]	**6b**[d]	C_5H_{11}	Ph	3.5	65[e]
3	**3c**	**6c**	CH_2OH	Ph	4	90
4	**3d**	**6d**	CH_2OH	Pr	4	91[f]
5	**3e**[g]	**6e**	CH_2OH	4-(MeO)-C_6H_4	4	84
6	**3f**	**6f**	CH_2OH	4-(NO_2)-C_6H_4	4	85
7	**3g**	**6g**	CH_2OH	4-(MeO_2C)-C_6H_4	4	86
8	**3h**	**6h**	CH_2OH	(*E*)-CH=$CHCO_2Me$	4.5	78[h]
9	**3i**	**6i**	CH_2OH	2-thienyl	3.5	69
10	**3j**	**6j**	1-hydroxycyclohexan-1-yl	H	11	53[i]
11	**3k**	**6k**	1-hydroxycyclohexan-1-yl	3,4-$Cl_2C_6H_3$	4	89[i]
12	**3l**	**6l**	CH_2N_3	Pr	4.5	74
13	**3m**	**6m**	Cl-$CH_2CH_2CH_2$	Me	18.5	74
14	**3n**	**6n**	Me	Me	10	33
15	**3o**	**6o**	BocNH-$CH_2CH_2CH_2$	3,4-$Cl_2C_6H_3$	6	53
16	**3p**	**6p**		Ph	19	60
17	**3q**	**6q**	$PhCH_2$	CH_2OH	4	75[j]

[a] The reaction was carried out on a 0.5 mmol scale in MeOH (2.0 mL) at 35 °C with Pd(TFP)$_4$ (3 mol%). [b] The **3**:**6** ratios in the crude product were ≤5:95 (unless stated otherwise) according to ^{1}H NMR; no other discrete products were isolated. [c] Labeled with ^{13}C in the CH_2O group. [d] Labeled with ^{13}C in the *exo*-methylene (ref 11). [e] Carried out in DMF at 90 °C over 120 min; the **3b**:**6b** ratio was 31:65 (ref 11). [f] Carried out on a gram scale. [g] (*E*)-isomer. [h] The product undergoes decomposition and was characterized only by NMR spectroscopy. [i] Carried out in a 1:1 MeOH-CH_2Cl_2 mixture. [j] An inseparable mixture of **3q** and **6q** (13:87).

Stereoelectronic Effects in the Palladium-Catalyzed 1,3-Rearrangement of 5-Alkylidene Pyran-2-ones. Stereoelectronic control of this 1,3-transposition[14] requires that the allylic leaving group be positioned more or less perpendicularly to the plane of the C=C bond (**A** in Chart 1). Therefore, the isomerization **3** → **6** emerged as a surprise, since lactones **3** are nearly planar molecules, which should preclude the reaction. The X-ray structure of **3c** actually shows that the allylic C-O bond is far from any alignment with the π-system in both conformations present in the crystal; here the dihedral angles deviate from the plane of the C=C bond by mere 9° and 42°, respectively, i.e., far away from the postulated ideal of 90° (see the SI).

A closer look at the reaction, which starts with η^2-coordination (**4**), suggests that the stereoelectronic considerations should be modified to reflect the actual geometry of the η^2-complex and its palladacyclic nature. It is well known that η^2-complexes are partly pyramidalized at the carbons of the original C=C bond. Thus, the Zeisse salt K[$PtCl_3(C_2H_4)$] is pyramidalized at each carbon atom by 17°, according to neutron diffraction.[15] In the rhodium complex CpRh(C_2H_4)(C_2F_2) the CH_2 and CF_2 groups are bent away from planarity by 21° and 37°, respectively,[16] while the η^2-nickel-complex of $(NC)_2C=C(CN)_2$ exhibits deviation of 38°, close to the corresponding epoxide (32°).[17]

Taking into account the Chatt-Dewar-Duncanson model,[18] it can be argued that, since the η^2 → η^3 conversion features a "nucleophilic" expulsion of the nucleofuge, it is the back-donation from Pd (**C** in Chart 2) rather than donation (**A** in Chart 1) that should play the key role. Therefore, geometry **C**, featuring donation from the d-orbital[19] to the σ*-orbital of the leaving group C-X bond, can be regarded as a more appropriate model. Naturally, some degree of deviation (θ) from ideal collinearity (**D**/**E**) should be allowed in analogy with Wagner-Meerwein rearrangements that are known to tolerate up to 30° distortion.[20-22]

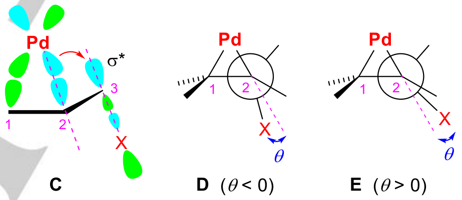


Chart 2. A new interpretation of the stereoelectronic effects in the formation of η^3-complexes: Collinearity of the C-Pd and C-X bonds in the η^2-complex. For computed orbitals, see the SI (Figure S2).

Quantum Chemical Calculations. To gain credence for the qualitative orbital considerations and to elucidate the mechanism in detail, assess the validity of the stereoelectronic arguments, and characterize the intermediates and transition states, quantum chemical calculations were carried out for three representative cases, namely a facile vs. less efficient reaction (**3d** → **6d** vs. **3j** → **6j**) and absence of reactivity (**3u** → **6u**). A computational approach similar to that employed by us previously,[23] was used (see the computational details section below) with the difference that we obtained electronic energies (E_{el}(QM) in eq. 1) of the stationary points employing both "calibration quality" coupled cluster (DLPNO-CCSD(T)/CBS-*est*) method and by "standard" DFT methods (BP-86-D3, B3LYP-D3 and TPSSh-D3). Notably, the coupled cluster and DFT-D3 values were fairly similar to each other. Thus, general conclusions are, to a large extent, independent on the method used (c.f. Figure S2 in SI for the TPSSh-D3/COSMO-RS reaction profiles) – with the exception of the Pd(TFP)$_3$/Pd(TFP)$_4$ pre-equilibrium discussed below and to a smaller extent binding of the reactant to the Pd(TFP)$_3$ catalyst. To unambiguously identify reaction coordinates, a thorough conformational search was carried out to identify the lowest-energy conformers for all species involved in the reaction.[24]

First, computations have clearly shown that the reaction, carried out in MeOH, should be slightly exergonic, with ΔG_{DLPNO-}

$_{\text{CCSD(T)/COSMO-RS}}$ = -1.9, -4.0, -1.9 kcal mol^{-1} for the **3d/6d**, **3j/6j**, and **3u/6u** reactant/product pairs, respectively. Less clear is the solution form of the Pd(TFP)$_n$ catalyst: for Pd(PPh$_3$)$_4$, ligand dissociation is known to occur in toluene almost quantitatively to yield Pd(PPh$_3$)$_3$ as the most stable species.[25] Reproducing this experimental observation computationally is not trivial, considering the large contributions from dispersion and solvation,[26] yet our B3-LYP/COSMO-RS protocol yielded $\Delta G_{\text{B3LYP-D3/COSMO-RS}}$ = -1.8 kcal mol^{-1} for the Pd(PPh$_3$)$_4$ → Pd(PPh$_3$)$_3$ + PPh$_3$ reaction in toluene (-0.2 kcal mol^{-1} in MeOH), which is in agreement with the experimental observations. The same approach suggests a less favorable dissociation process for Pd(TFP)$_4$ but the precise prediction of the associated free energy change is sensitive to the method used. Therefore, our mechanistic analysis starts with Pd(TFP)$_3$.

The isomerization commences with the replacement of the coordinated TFP ligand in Pd(TFP)$_3$ by the reactant **3** to form the initial reactant complex **4** and/or **4_Rot** (depicted for the reaction of **3d** in Figure 1). This step presumably occurs through an associative mechanism with an intermediate or TS [Pd(TFP)$_3$(**3**)] and is slightly exergonic with $\Delta G_{\text{DLPNO-CCSD(T)/COSMO-RS}}$ = -2.2, -3.6, and -1.3 kcal.mol^{-1} for **3d**, **3j**, and **3u**, respectively (Figure 2).

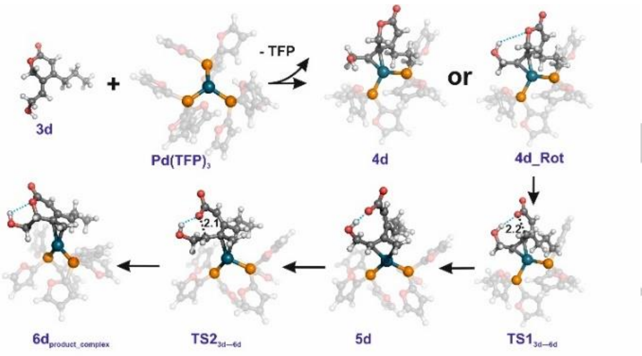


Figure 1. The reaction mechanism for the Pd(0)-catalyzed allylic isomerization **3d** → **6d**.

In the next step, the C-O bond is cleaved ($R_{\text{C-O}}$ = 2.2 Å in the transition state **TS$_1$**) and the η^3-complex **5** is formed; the computed activation free energies associated with this process are $\Delta G^{\neq}_{\text{DLPNO-CCSD(T)/COSMO-RS}}$ = 19.8, 18.5, and 22.9 kcal mol^{-1} for **3d** → **5d**, **3j** → **5j**, and **3u** → **5u**, respectively. Both **TS$_1$** and the ensuing intermediate **5** (formally an η^3-allyl zwitterionic complex) are stabilized by hydrogen bonding between the departed carboxylate and the CH$_2$OH group. It can be noticed that the free energy difference between the most stable reactant structure **4** (with a hydrogen bond between the hydroxyl and the oxygen of the furyl group) and the conformer **4_rot** (with the re-orientated hydroxyl that is now hydrogen-bonded to the lactone oxygen of the reactant) is almost negligible (~1 kcal mol^{-1}; Figure S3 in the SI). Fairly stable η^3-intermediates **5** (with free energies comparable to **4**, c.f. Figure 2) convert via the **TS$_2$** (overall activation energies of 21.4, 23.9, and 22.0 kcal mol^{-1} for **5d** → **6d**, **5j** → **6j**, and **5u** → **6u**, respectively) to the final product complexes **6$_{\text{pc}}$**, which are, again, energetically close to the reactant complexes **4** (~1 kcal mol^{-1}). This implies that the final dissociation of the product is quite close to being isoergic. Interestingly, while for **3d** → **6d** and **3j** → **6j** reactions the **TS$_2$** is involved in the rate-determining step (RDS), the RDS in the **3u** → **6u** conversion is represented by **TS$_1$**.

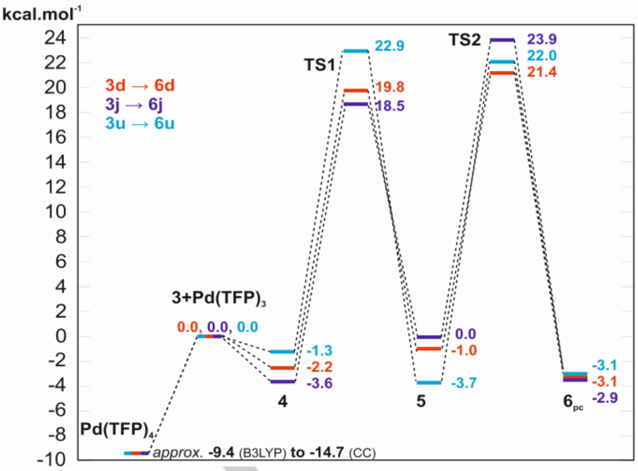


Figure 2. Reaction coordinates for the **3d** → **6d**, **3j** → **6j**, and **3u** → **6u** reactions. The (formal) addition of reactants and loses of TFP in the initial steps are omitted for clarity.

Kinetic modeling. To make quantitative comparison with the experimental reaction times (Table 2), the DLPNO-CCSD(T)/COSMO-RS and B3LYP-D3 reaction coordinates were subjected to kinetic modeling. At first sight, the standard free energies computed here are difficult to reconcile with the observed reactivity, whereby the reactants reach equilibrium with the products within a few hours. For example, analysis of entry 4 in Table 2 gives an apparent half-life of 10^2 - 10^4 s for **3d**, which corresponds to an apparent standard free energy barrier of 21-24 kcal mol^{-1}. However, the calculated standard free energy difference between Pd(TFP)$_4$ + reactant and rate-limiting **TS$_2$** is much larger, namely at +36.2 (DLPNO-CCSD(T)) and +32.2 kcal mol^{-1} (B3LYP-D3). Clearly, the difference from experiment is larger than the expected error margin.

A closer kinetic analysis, taking into account the experimental concentrations rather than the standard conditions, indicates that the calculated free energies are in fact in agreement with experiment, at least within the expected error margin. Qualitatively, this can be explained by noting that given the unfavorable dissociation equilibrium for Pd(TFP)$_4$, the steady-state concentration of TFP will be well below the standard state 1 M, so that the further loss of TFP and substrate binding equilibrium to form **4d** will be much more favorable than those expected, given the computed standard free energies.

Quantitative insight was obtained from kinetic simulations using the Tenua program,[27] with rate constants calculated from the *ab initio* data. Using the raw calculated free energies, the modelled half-life of reaction for **3d** in MeOH at 35 °C, with Pd(TFP)$_4$ at 0.0075 M and substrate 0.25 M, comes out at 5000 h, and thereby about 10^3 times slower than is observed experimentally. This large difference in rate can be interpreted in terms of an error in the apparent free energy of activation of about 4 kcal mol^{-1} – significant, but smaller than the error of 8-15 kcal mol^{-1} estimated above, based simply upon the standard free energies. This error could reflect overestimating the free energy for dissociation of Pd(TFP)$_4$, or for **TS$_1$** and **TS$_2$**, or for both. Indeed, B3LYP-D3 suggests a smaller free energy of dissociation to Pd(TFP)$_3$ (+9.4 kcal mol^{-1} instead of +14.7), but using this modified value only leads to a decrease in the half-life by a factor of thirteen: the greater degree of dissociation corresponds to a higher steady-state concentration of TFP, which inhibits further reaction, as discussed above. If, instead, we assume that theory over-predicts the free energy of **TS$_1$** and **TS$_2$**, and they are decreased by 4.5 kcal mol^{-1}, this leads to predicted kinetics broadly in line with experiment, with a half-life of 3.7 h. We note that the whole region between **TS$_1$** and **TS$_2$** involves zwitterions that are presumably stabilized by hydrogen-bonding to solvent, an effect which is only partly described by the continuum approach used here.

Obtaining reactivity *trends* is somewhat more straightforward than obtaining absolute reactivity. Indeed, in the present case, with barriers **TS$_1$** and **TS$_2$** lowered by 4 kcal mol^{-1} relative to reactants, the predicted rates for substrates **3d**, **3j**, and **3u** are in relation 200:8:1 to one another, i.e. **3j** is much less reactive than **3d**, and **3u** somewhat less reactive still, qualitatively consistent with the experimentally observed diminished reactivity for **3j** and the lack of reactivity for **3u**. Once again, even for relative reactivity, accuracy by greater than a factor of 1-2 kcal mol^{-1} remains hard to achieve, so the qualitative agreement found here is quite satisfactory.

The calculations have also corroborated the initial orbital and stereoelectronic considerations. Indeed, in the η^2-intermediates **4d** and **4j** (**4/4_rot**) the alignment of the Pd-C(5) and C(6)-O bonds deviates from collinearity by mere +18° and +16° (**E**), respectively, which is well within the 30° tolerance[20-22] proposed for the Wagner-Meerwein rearrangements (*vide supra*).[28] On the contrary, the same deviation for **4u** is as large as +49° which provides an elegant and intuitive stereoelectronic explanation for the lack of reactivity of the compound.

Conclusions

In summary, the Pd^{0}L$_4$-catalyzed allylic isomerization **3** → **6**, originally observed as a side reaction during the coupling **1 + 2** → **3**, was nurtured into a synthetically useful protocol for the preparation of pyran-2-ones with an unusual structural pattern. The latter reaction represents a [1,3] rearrangement that would normally be symmetry-allowed only in the excited state.[29] In a broader perspective, the present study demonstrates that structurally different products can be obtained from the same starting materials by marginal modification of reaction conditions. This principle, in its own right, opens interesting new opportunities, e.g., in the realm of multisubstituted heterocycles, where it is not unusual that each substitution pattern at the heterocyclic core requires its own synthetic strategy.[42]

Substrates **3** are rather flat, which may seem to preclude the formation of the required η^3-intermediate from the initially generated η^2-complex (**3** → **4** → **5**). However, a more detailed analysis of the stereoelectronic effects, based on the back donation in the η^2-complex as the decisive factor, suggests that it is the alignment of the Pd-C bond with the allylic C-O bond (**C**) that should be considered, rather than the currently accepted alignment of the C=C bond π-system with the allylic bond of the substrate (**A**). High-level quantum chemistry calculations have fully confirmed this new analysis: the deviation (θ) from the antiperiplanar arrangement of the key Pd-C and C-O bonds (**E**) in the η^2-complex **4d** has been calculated to be by mere 18°, which can be regarded as being comfortably within the tolerable range. Awareness of these effects can be expected to change the philosophy of strategic planning in organic synthesis, since our findings broaden the scope of the π-allyl chemistry to the substrates previously regarded as unlikely to react.

Experimental Section

Representative procedure for the preparation of pyran-2-one 6d. Commercial Pd black (25 mg, 0.02 equiv) was added to a solution of (*Z*)-methyl-3-iodo-3-propyl acrylate (3.000 g, 11.8 mmol) and (*E*)-2-tributylstannyl but-2-en-1,4-diol (5.570 g, 14.2 mmol, 1.2 equiv)11 in DMF (12 mL). The flask was placed into a pre-heated oil bath at 70 °C and the mixture was stirred at this temperature until TLC showed complete consumption of the iodo acrylate. The reaction mixture was then diluted with EtOAc, and the solution was washed with saturated aqueous NH$_4$Cl and 4% aqueous NaF. The precipitate was filtered off and the organic phase was dried over anhydrous Na$_2$SO$_4$. Chromatography on silica gel (hexanes:EtOAc 7:3) furnished pyran-2-one **3d** (1.460 g, 8 mmol, 68%) as a yellow oil.[11]

Compound **3d** (1.449 g, 8.23 mmol) and Pd(TFP)$_4$ (256 mg, 0.25 mmol, 3 mol%) were transferred into a dry, Ar-filled flask. The flask was evacuated and flushed with Ar (3×). Anhydrous MeOH (30 mL) was added, and the flask was placed into an oil-bath heated at 35 °C and the mixture was stirred at this temperature. When TLC analysis indicated no further change (4 h), the solvent was evaporated and the residue was purified by column chromatography (hexanes: EtOAc 8:2) to afford **6d** (1.365 g; 91%) as a yellow oil (R_f = 0.41 in hexanes: EtOAc 3:7).

4-Propyl-5-methylidene-6-hydroxymethyl-5,6-dihydro-2H-pyran-2-one **(6d)**. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 5.84 (s, 1H), 5.60 (s, 1H), 5.41 (s, 1H), 5.05 (t, *J* = 6.0 Hz, 1H), 3.92 – 3.72 (m, 2H), 2.44 – 2.31 (m, 2H), 1.65 – 1.52 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 163.5, 154.2, 136.2, 116.6, 116.1, 81.4, 65.6, 33.5, 20.8, 13.8. **IR** (ATR) ν_{max} 3367, 2962, 2962, 2934, 2874, 1675, 1407, 1363, 1247, 1080,1068 cm^{-1}. **LRMS** (RIC) *m/z* (rel. intensity) 205.1 [M+Na]$^+$ (100); 183.1 [M+1]$^+$ (19); 173.1 (49); 165.2 (15); 157.7 (12); 133.8 (24). **HRMS** (TOF-ESI) *m/z* cal for. $C_{10}H_{14}O_3^+$ 183.1016; found 183.1024.

Computational details

All DFT calculations were carried out using the Turbomole 7.2 program.[30] Geometries of all structures (minima and saddle points) were optimized employing the dispersion-corrected B-P86 functional [BP86-D3(BJ)][31,32] and the def-TZVP[33] basis set (for Pd, this basis set includes the Stuttgart-Dresden effective core potentials) in an implicit solvent with the dielectric constant of ε_r = 32.6 corresponding to methanol - using the COSMO solvation model[34] as implemented in Turbomole 7.2 program. Subsequent vibrational frequency calculations were performed at the same level of theory for all calculated structures, also in an implicit solvent with ε_r = 32.6 (methanol). All transition states thus found possess exactly one negative Hessian eigenvalue, while all other stationary points were confirmed to be genuine minima on the potential energy surface (PES). By marginal displacement of the transition state geometry towards initial and final state, it was verified that the TS connects the desired structures.

The free energy value corresponding to a particular structure can be conveniently expressed as:

$$G_S = E_{el} + \Delta G_{solv} + E_{ZPVE} - RT\ln(q_{trans}q_{rot}q_{vib}) + pV \quad \text{(eq 1)},$$

where E_{el} is the electrostatic potential energy of the molecule in vacuo (gas-phase molecular energy), ΔG_{solv} is the solvation energy, E_{ZPVE} is the zero-point vibrational energy whereas $RT\ln(q_{trans}q_{rot}q_{vib})$ are the entropic terms obtained from the rigid-rotor/harmonic oscillator (RRHO) approximation in which a free rotor model was applied for low-lying vibrational modes under 100 cm^{-1} with a smoothing function applied (sometimes denoted as quasi-RRHO, or RRFRHO approximation).

Electronic energies were obtained by performing single point calculations employing the BP-86-D3(BJ), B3-LYP-D3(BJ),[31a,35] and TPSSh-D3(BJ)[36] and def2-TZVPD basis set, in vacuum. The reference reaction and activation energies were obtained using DLPNO-CCSD(T)/aug-cc-pVDZ calculations[37,38] and ORCA 4.0 software.[39] By carrying out the MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ calculations we were able to obtain complete basis set estimates, DLPNO-CCSD(T)/CBS, that have been used throughout. We used Truhlar's extrapolation scheme[40] to obtain E(MP2/CBS) to which the ΔE_{CC} = E(DLPNO-CCSD(T)/aDZ) - E(MP2/aDZ) was added. The ΔG_{solv} was obtained using Klamt's conductor-like screening model for realistic solvation method (COSMO-RS).[41] COSMO-RS calculations were carried out using *cosmotherm* software and the recommended protocol: BP86-D3(BJ)/def2-TZVPD single point calculations in vacuo and in ideal conductor ($e = \infty$) followed by the COSMO-RS calculations in the target solvent (CH_3OH). Finally, a correction of ($1.9\cdot\Delta n$) kcal.mol^{-1} (corresponding to the difference between the concentration of the ideal gas at 298 K and 1 atm and its 1 mol.L^{-1} concentration; Δn is the change in number of moles in the reaction) has been applied in order that the computed values refer to 1 mol.L^{-1} standard state.

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Conflicts of interest

The authors declare no competing financial interest.

Keywords: allylic rearrangement • palladium • catalysis • stereoelectronic effects • quantum chemistry calculations

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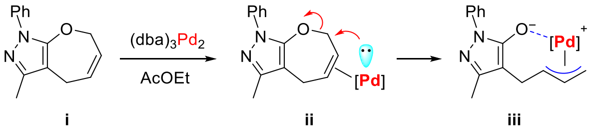

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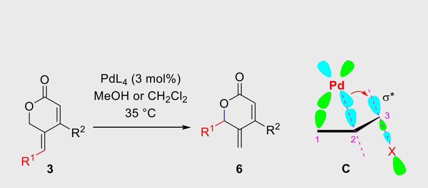

A new insight into Pd-catalyzed allylic isomerizations, exemplified by an unusual 1,3-transposition leading to multisubstituted pyranones, is presented.

Zbyněk Brůža, Dr. Jiří Kratochvíl, Prof. Dr.Jeremy N. Harvey, Dr. Lubomír Rulíšek, Dr. Lucie Nováková, Jana Maříková, Dr. Jiří Kuneš, Prof. Dr. Pavel Kočovský, Prof. Dr. Milan Pour

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A New Insight into the Stereoelectronic Control of the Pd(0)-Catalyzed Allylic Substitution: Application for the Synthesis of Multisubstituted Pyran-2-ones via an Unusual 1,3-Transposition