Organic & Biomolecular Chemistry

Accepted Manuscript

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DOI: 10.1039/C7OB02925J

Journal Name

ARTICLE

# *E-Z* isomerization in Suzuki cross-couplings of haloenones: Ligand effects and evidence for a separate catalytic cycle.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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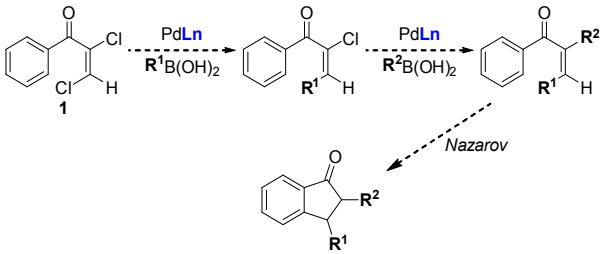
Suzuki cross-coupling of haloalkenes is generally assumed to occur with retention of the alkene stereochemistry. While studying Suzuki cross-couplings on *E*-1,2-dichlorovinyl phenyl ketone, we were surprised to observe extensive isomerization. More surprisingly, the ligand employed strongly influenced the degree of isomerization: DPEphos and Xantphos led to 96% isomerized cross-coupled product whereas reactions in the absence of a phosphine ligand, or reactions employing t-BuXantphos, gave 94% retention of stereochemistry. While *E-Z* isomerization in Pd-catalyzed vinylic couplings has previously been attributed to events within the cross-coupling catalytic cycle, we present experimental and computational evidence for a separate Pd-catalyzed isomerization process in these reactions.

## Introduction

The efficient assembly of specific geometric isomers of highly substituted alkenes remains a challenge for synthetic chemists. 1,2-Disubstituted alkenes can generally be obtained as the thermodynamically-favoured *E* isomers, while Wittig reactions and Lindlar-catalyzed hydrogenation of alkynes provide *Z* isomers. However, general approaches to stereochemically defined tri- and tetra-substituted alkenes are less well-developed. Pd-catalyzed cross-couplings generally retain the configuration of the vinylic C-X bond.[1-6] Thus, if specific geometric isomers of vinylic halides can be obtained, metal-catalyzed cross-couplings offer versatile access to alkyl- or aryl-substituted vinyl groups, as well as dienes, trienes and similar structures. The Suzuki reaction is a particularly convenient and reliable cross-coupling widely used in the total syntheses of complex natural products,[7-10] anticancer agents,[11, 12] inhibitors of tubulin polymerization,[13-15] anti-apoptotic agents,[16] insect pheromones[17] and vitamins.[18]

Our interest in modular elaboration of alkenes starting from trichloroethylene[19-21] led us to examine Suzuki reactions of *E*-1,2-dichlorovinyl phenyl ketone **1**[22]. We anticipated that the elaborated aryl vinyl ketone products might be further transformed, for example into indanones by Nazarov cyclization (Scheme 1).[23-29]




**Scheme 1.** Planned regio- and stereo-controlled modular assembly of indanones.

Suzuki couplings of **1** were expected to occur with retention of the alkene configuration.[5-19, 30-35] Further, the reactions should favour the β- over the α-position in **1**.[36-42] We indeed observed the predicted regioselectivity. However, depending on the ligand employed we obtained either nearly complete double bond isomerization, or retention of configuration.[43-47] Subsequent investigation revealed some intriguing observations regarding the mechanism of the *E-Z* isomerization process for our compounds, which were not consistent with intrinsic *E/Z* stereochemical instability of vinylpalladium intermediates,[43, 48, 49] or paths such as Pd-H catalysis[50] or reversible addition-elimination[51] that have been proposed for related cases. Our DFT model calculations support an alternative explanation for the rapid isomerization observed in Suzuki reactions of these enones.

## Results and discussion

*E*-Dichlorovinyl ketone **1** was prepared by a modification of the method of Jonczyk and Gierczak (Scheme 2).[22] Our NMR spectra of **1** differed from their data, although our results were internally consistent. An X-ray crystal structure verified the structure of its precursor **2**. Later the *Z*-isomer (**6**) of **1** became

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Electronic Supplementary Information (ESI) available: NMR spectra, X-ray crystal structures, computational results, details of survey reactions. See DOI: 10.1039/x0xx00000x

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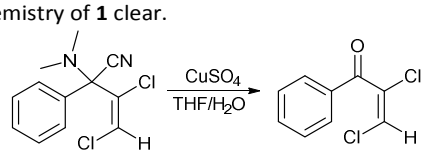
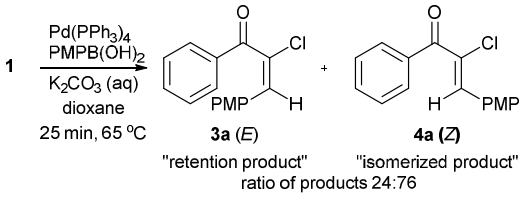
available (*vide infra*) and spectroscopic comparison made the *E* stereochemistry of **1** clear.




**2** **1**

Scheme 2 Preparation of enone 1.

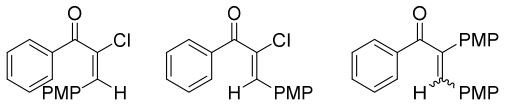
Initially we treated **1** with *p*-methoxyphenylboronic acid ($PMPB(OH)_2$) in the presence of $Pd(PPh_3)_4$ and 2M aqueous $K_2CO_3$ in dioxane at 65 °C,[52] monitoring by GC/MS (Scheme 3). Consumption of **1** was complete in 25 minutes. Two products of *m/z* 272 were obtained in a 26:74 ratio, which were separated by flash chromatography. A combination of chemical degradation and $^1H$ and $^{13}C$ NMR techniques assigned the minor product as **3a** (*E*) and the major product as **4a** (*Z*).† In particular, the $^3J_{C\text{-}H}$ between the vinylic proton and the carbonyl carbon (readily observed in an HMBC experiment) was highly diagnostic of the alkene configurations of **3** and **4**. *Z* isomers typically show $^3J_{C\text{-}H}$ around 5 Hz, whereas $^3J_{C\text{-}H}$ in *E* isomers is 8-9 Hz.[53] Eventually we were able to confirm the structures of **3a** and **4a** through X-ray crystallography.




**Scheme 3.** Stereoisomeric products of Suzuki coupling. PMP = 4-methoxyphenyl.

From a survey of conditions for the transformation shown in Scheme 3,† we determined that using $Pd_2(dba)_3$ in the presence of 3 equiv. of $Cs_2CO_3$ in dioxane at 85 °C gave full conversion to products in one hour. The effect of different phosphine ligands was the most striking feature of the reaction, however. Selected results are presented in Table 1.

**Table 1.** Effect of different phosphine ligands on product ratios




**3** (*E*) **4** (*Z*) **5** (*E/Z mixture*)

| | Ligand[a] | Product ratio **3** : **4** : **5**[b] After 1 hour | After 24 hours |
|---|---|---|---|
| 1 | DPEphos | 4 : 96 : 0 | 4 : 96 : 0 |
| 2 | Xantphos | 6.5 : 93.0 : 0.5 | 4 : 96 : 0 |
| 3 | $(Cy)_3P$ | 50 : 50 : 0 | 7 : 93 : 0 |
| 4 | *t*-BuXantphos | 93 : 5 : 2 | 5 : 89 : 4 |
| 5 | No phosphine[c] | 94:5:1 | 55 : 43 : 2 |

a. Conditions: **1** (0.25 mmol), *p*-$MeOPhB(OH)_2$ (0.25 mmol), $Pd_2(dba)_3$ (2.5 mol %); $Cs_2CO_3$ (3 equiv.); Dioxane (1.5 mL), 85 °C. Ligands: DPEphos (5.0 mol %); Xantphos (5.0 mol %); $(Cy)_3P$ (7.5 mol %); *t*-BuXantphos (5.0 mol %); b. Ratios determined by GC/MS analysis; c. $Pd_2(dba)_3$ (5.0 mol %), no phosphine ligand added.

The reaction performed without any phosphine ligand (Entry 5) formed the expected "retention" product **3**, which subsequently partly isomerized under the reaction conditions over 24 hours. In contrast, arylphosphine ligands (Entries 1 and 2) led to the rapid production of a ~4:96 ratio of **3**:**4**, which remained unchanged over time and presumably represents the equilibrium situation. The sterically bulky and electron-rich arylphosphine *t*-BuXantphos (Entry 4) gave predominantly **3**, just as the "no phosphine" reaction did. This strongly suggests that the "retention product" **3** is formed first, and the nature of the phosphine ligand (if present) influences the rate at which isomerization to **4** occurs.

Based on these observations, we were able to carry out Suzuki couplings of **1** with a range of arylboronic acids, using appropriate conditions to produce predominantly the "retention products" **3a-h** (conditions A or B) or the "isomerized products" **4a-h** (conditions C) as shown in Table 2.‡ Reactions under conditions A or B were monitored closely and stopped as soon as tlc indicated complete consumption of **1**. While timing was less critical under conditions C, we also stopped these reactions when starting material was consumed.

The reactions with relatively electron rich boronic acids (Table 2, entries 1-3) proceeded quickly in all cases. Electron deficient boronic acids reacted slowly with **1**; while *p*-fluorophenylboronic acid led to products **3d** or **4d** in 5 hours, treatment with *p*-nitrophenylboronic acid failed to produce **3e** under any conditions tested (entry 5). Benzofuran-2-yl- and thien-2-ylboronic acids reacted slowly but cleanly (entries 6 and 7). Attempted reaction of **1** with 4-(2-fluoropyridyl)boronic acid did not form any detectable products under phosphine-free conditions, while only 13% conversion leading to an 83:17 mixture favouring what we tentatively identified as **3h** was observed using *t*-BuXantphos as ligand. In contrast, in the presence of DPEphos (Conditions C) this boronic acid reacted slowly with **1** to form isomerized product **4h** in fair yield (entry 8). The results in Table 2 indicate that it is possible to obtain excellent results with either retention of the initial vinyl halide configuration, or isomerization to the thermodynamically favoured alkene isomer.

Because Pd-catalyzed cross couplings of vinylic halides are expected to be stereospecific, we next sought to understand how the *Z* arylated products were formed from the *E* halide, and if possible why the stereochemistry depended on whether a phosphine ligand was present or not.

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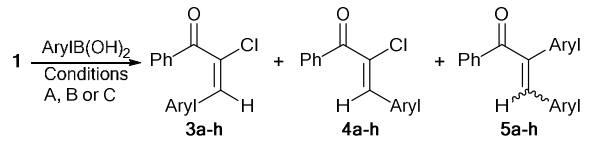
**Table 2.** Stereoselective Suzuki couplings with arylboronic acids.

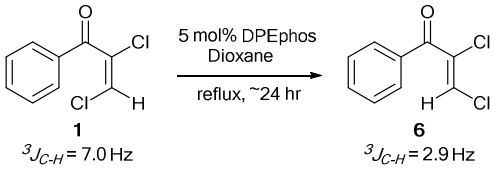



| | Aryl | Conditions[a] (hours) | 3 : 4 : 5[b] (yield %)[c] | $^3J_{C\text{-}H}$ (Hz)[d] |
|---|---|---|---|---|
| 1 | *p*-methoxyphenyl | A (1.0) | (**3a**: 78) | 8.6 |
| | | B (1.0) | (**3a**: 73) | |
| | | C (0.5) | 4:96:0 (**4a**: 80) | 4.9 |
| 2 | *p*-tolyl | A (2.0) | 90:6:4 (**3b**: 75) | 8.8 |
| | | C (0.5) | 5:92:3 (**4b**: 76) | 4.7 |
| 3 | phenyl | A (3.5) | 94:4:2 (**3c**: 69) | 8.6 |
| | | C (2.0) | 8:90:2 (**4c**: 70) | 4.7 |
| 4 | *p*-fluorophenyl | A (7.0) | 91:9:0 (**3d**: 72) | 8.3 |
| | | C (5.0) | 6:94:0 (**4d**: 78) | 4.6 |
| 5 | *p*-nitrophenyl | A, B, C (24.0) | No product | - |
| 6 | benzofuran-2-yl | A (8.0) | 90:10:0 (**3f**: 76) | 8.1 |
| | | C (2.0) | 8:92:0 (**4f**: 74) | 4.5 |
| 7 | thien-2-yl | A (24.0) | 95:5:0 (**3g**: 77) | 8.1 |
| | | C (24) | 16:80:4 (**4g**: 62) | 5.0 |
| 8 | 2-fluoropyridin-4-yl | A (24.0) | No product | - |
| | | B (24.0) | 13% conv, 83:17:0[e] | |
| | | C (24) | 4:95:1 (**4h**: 69) | 4.4 |

a. **1** (0.5 mmol), $ArylB(OH)_2$ (1 equiv), Dioxane (3.0 mL), 85 °C, $Cs_2CO_3$ (3 equiv.). Conditions A: $Pd_2(dba)_3$ (5.0 mol %). Conditions B: $Pd_2(dba)_3$ (2.5 mol %), *t*BuXantphos (5.0 mol %). Conditions C: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (5.0 mol %). b. Ratios determined by GC/MS and/or $^1$H NMR of crude reaction mixtures. c. Isolated yields of chromatographically purified major products. d. Coupling observed by HMBC between vinylic $^1$H and carbonyl $^{13}$C of the major product. e. GC/MS analysis of the crude product obtained using method B revealed two new compounds of m/z 260 in a ratio of 83:17. Presumably the major product was the *E*-isomer **3h** but this was not purified and characterized. The minor product of this reaction was identified as **4h**, by GC/MS comparison with a sample prepared by method C and fully characterized.

**Experimental mechanistic studies**

The rapid isomerization observed in the presence of DPEphos or Xantphos is striking when compared to the outcomes when no phosphine was present. A few reports of similar *E/Z* isomerization during Pd-catalyzed reactions of vinylic halides have appeared.[43, 48, 49, 54, 55] We investigated the isomerization of reactant **1** and coupling product **3a** in some detail. The thermal stereochemical stabilities of **1** and **3a** were confirmed by extended heating in dioxane at 85 °C. No isomerization of **1** could be detected, while **3a** formed only 6% of **4a** after 24 hours. Chalcones may undergo photochemical isomerization, but we verified that reactions conducted in the dark gave the same outcomes. Phosphine ligands might promote formation of **4** via Michael addition to **1** or **3**, bond rotation, and then elimination of phosphine.[51] Heating **1** with 5 mol% DPEphos led to 8% isomerization in 1 hour, while similar treatment of **3a** gave 3% of **4a**. The slow isomerization of **1** in the presence of phosphines did allow us to obtain its *Z* isomer **6** after either very long reaction times (Scheme 4), or in the presence of large excesses (ca. 500 mol%) of phosphine. Comparison of **1** and **6** by NMR confirmed the *E* stereochemistry of **1**. However, these processes were too slow to account for the observed level of isomerization under the conditions of our Suzuki couplings.




Scheme 4 Slow isomerization of **1** occurs on heating with DPEphos or other phosphines.

Compounds **1** and **3a** were each heated separately with each component of the cross-coupling reaction, individually and in combination. No detectable isomerization of **1** occurred within a time window comparable to the cross-coupling reaction time, but these studies revealed that **3a** easily isomerized to **4a** in the presence of *both* $Pd_2(dba)_3$ and DPEphos Neither the Pd source nor the phosphine alone promoted significant isomerization of **3a**, but NMR monitoring showed that substantial isomerization took place within minutes of exposing **3a** to the ligand/catalyst mixture (Figure 1).†

The predominant formation of **3a** in reactions employing t-BuXantphos as ligand (see Table 1 and conditions B in Table 2) was noteworthy. The Suzuki couplings in the presence of DPEphos and t-BuXantphos proceeded at comparable rates, but the rate of isomerization of **3a** in the presence of t-BuXantphos was much slower than that observed when DPEphos was used. *These experiments confirmed that loss of stereochemical integrity was independent of the actual Suzuki coupling process, and reflected isomerization of the initially-formed product **3a**.*

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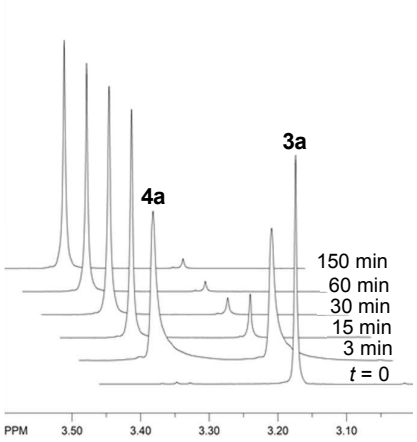
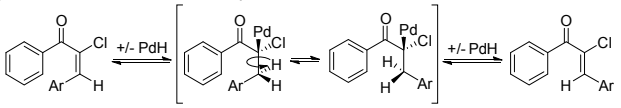



Figure 1 Isomerization of **3a** to **4a** in the presence of $Pd_2(dba)_3$/DPEphos monitored by $^1H$ NMR in toluene-$d_8$ at 350 K ($OCH_3$ region shown). More than 50% isomerization has occurred during the addition and mixing of the catalyst.

Further evidence supporting this interpretation came from reducing the catalyst concentrations in the Suzuki coupling reactions. If loss of stereochemistry took place within the cross-coupling catalytic cycle, then changing catalyst loadings would cause parallel changes in the rates of cross-coupling and isomerization. Instead, isomerization rates (judged by extent of conversion at specific time points) declined much faster than did cross-coupling rates as the catalyst concentration was lowered.

**A role for palladium hydride species?** It seemed possible that traces of Pd-H species might be present in our reactions and might promote isomerization (Scheme 5). For instance, Skrydstrup et al. reported[50] that many types of alkenes undergo positional and/or geometric isomerization in the presence of $PdL_2HX$ compounds.




Scheme 5 Possible palladium hydride-mediated isomerization pathway.

In particular, they found that $PdL_2HX$ mediated the equilibria of dimethyl maleate/fumarate and *Z*/*E*-stilbene.[50] When we exposed dimethyl maleate by itself to cross-coupling conditions C, 80% isomerization to dimethyl fumarate was observed in 1 hour. We then added varying amounts of dimethyl maleate to Suzuki cross couplings of **1** with 4-methoxyphenylboronic acid under conditions C, again for 1 hour. The product ratio **3a**:**4a** formed in these reactions depended on the concentration of dimethyl maleate (Figure 2). However, in the reactions shown in Figure 2 it did not appear that maleate was undergoing significant isomerization to fumarate, nor did maleate undergo any isomerization when treated with $Pd_2dba_3$ and DPEphos in toluene-$d_8$ at 350 K (77 °C).

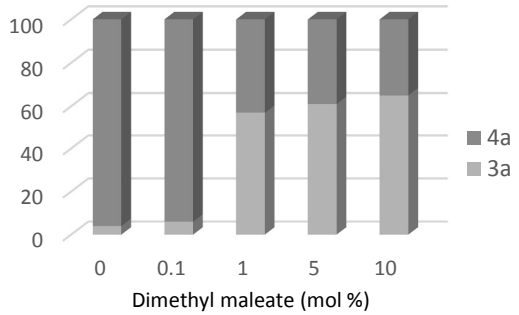



Figure 2 The product ratio **3a**:**4a** from the Suzuki couplings of **1** under conditions C (after 1 hour) is influenced by the presence of dimethyl maleate.

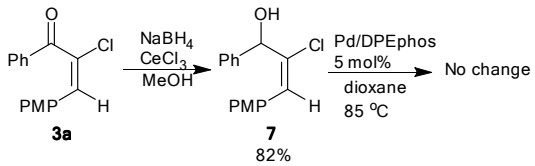
NMR monitoring of the isomerization of **3a** to **4a** in toluene-$d_8$ with 5 mol% of Pd/DPEphos in the presence of 2 mol% of dimethyl maleate showed that the process was greatly slowed.† Furthermore, when **3a** was heated in toluene with 5 mol% Pd/DPEphos and 1 equivalent of dimethyl maleate, neither **3a** nor maleate isomerized at all.

On the other hand, *Z*-stilbene was not isomerized under our cross-coupling conditions, nor did it have any effect on the isomerization of **3a** to **4a** in the presence of 5 mol% Pd/DPEphos.

Hills and Fu showed that $L_2PdHX$ species undergo reductive elimination when exposed to tertiary amines and other relatively strong bases.[56] We observed that replacing $Cs_2CO_3$ by $Et_3N$ had no effect on the isomerization of **3a**. We also found no effect when benzoquinone or TEMPO were added, both of which are known to destroy Pd-H species.[57, 58]

*The results of our experiments with dimethyl maleate and Z-stilbene, as well as those using triethylamine, benzoquinone or TEMPO are inconsistent with a role for a palladium hydride species in the isomerization process. Instead, our experiments suggested that dimethyl maleate and product **3a** might be competing for a Pd species that promoted their isomerization, but that Z-stilbene cannot compete in this way.*

**Is the carbonyl necessary for isomerization?** The failure of *Z*-stilbene to participate in the isomerization raised the question of whether the conjugated carbonyl was essential for the isomerization we were observing. We therefore carried out a Luche reduction[59] of **3a** to form the allylic alcohol **7**. When **7** was treated with 5 mol% Pd/DPEphos, it did not undergo any detectable isomerization (Scheme 6). This indicates that the conjugated carbonyl is necessary for the isomerization to occur under these conditions.




Scheme 6 Allylic alcohol **7** does not isomerize under conditions that would isomerize the enone **3a**.

**Computational model studies.**

*E*/*Z* isomerization during Pd-catalyzed cross coupling reactions of isolated haloalkenes has been attributed to intrinsic

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*zwitterionic metal carbene character* in a vinylpalladium intermediate within the catalytic cycle (Figure 3).[43, 48] This argument was originally developed to rationalize the results of Rh- and Pd-catalyzed carbometallation reactions of alkynes.[60-63] It suggests that the C-C π-bond is weakened sufficiently in these structures to permit thermal *E/Z* isomerization,[64] assuming that isomerization happens within the cross-coupling catalytic cycle. This assumption is inconsistent with the isomerization of **3a**, which cannot undergo oxidative insertion to form a vinylpalladium intermediate of this type.

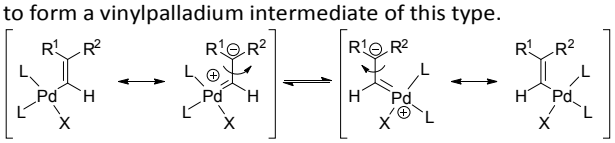
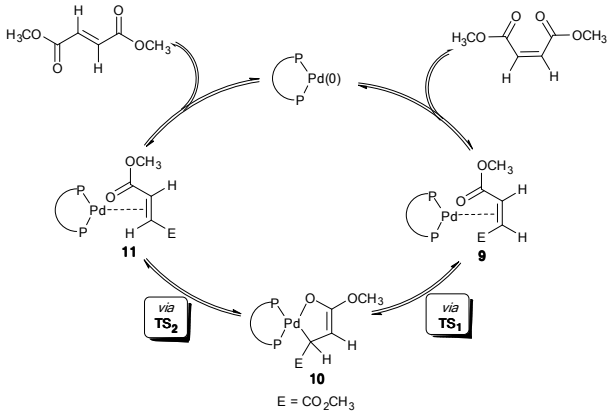


Figure 3. Proposed[43, 48] zwitterionic metal carbene character of the vinylpalladium intermediate leading to a weakened π bond and thermal isomerization during the Suzuki catalytic cycle.

A DFT computational model for the equilibrium in Figure 3 revealed that the lengths and angles of the C=C and C-Pd bonds were not perturbed as the zwitterion model suggests. The calculations also indicate that forced rotation of the vinylpalladium moiety around the C=C bond has a barrier similar to the case of a hydrogen atom at the same position, and Pd=C double-bond character does not develop during forced rotation.

**Metallacycle pathway.** Canovese and Visentin studied the geometric isomerization of electron-poor alkenes (including dimethyl maleate/fumarate) in the presence of Pd(0)/ligand complexes both experimentally and computationally.[65, 66] Their proposed mechanism involves reversible isomerization of a Pd(0) $\eta^2$-enone fragment to a cyclic Pd(II) enolate (Scheme 7). Isomerization was found to be particularly easy with a "hard/soft" P/N ligand at Pd, where the Pd-C bond of the enolate intermediate develops *trans* to the N donor group. While these authors only report results for symmetrically substituted alkenes, the mechanism requires no more than a single carbonyl or similar group conjugated to the C=C bond. The Canovese/Visentin mechanism was recently invoked to explain the stereochemical outcomes in tandem Pd-catalyzed syntheses of diarylallylidene oxindoles,[67] and in direct C-H functionalization of simple acrylamides.[68] Thus, it seemed plausible that a version of this mechanism could describe our situation as well but we sought some computational support for this hypothesis.



Scheme 7 The Canovese/Visentin mechanism for Pd-catalyzed fumarate/maleate isomerization via a metallacycle intermediate.

DFT methods (TPSSh/def-TZVPP//B-LYP/def-SV(P)) were used to compare the energetics of Scheme 7 for enone and maleate/fumarate substrates. As a simple, generic model for a diphosphine ligand we used DMPE. The three minima and two transition states corresponding to Scheme 7 were located for **3a**/**4a** as well as for the maleate/fumarate system studied by Visentin. The results are summarized in Figure 4. They confirm that enones are capable of following the same isomerization path as maleate/fumarate. In fact, the calculated barrier for isomerization is somewhat lower, and the enolate intermediate for the enone substrate is more stable, in agreement with our observations. Furthermore the calculations suggested that the π-complexes from dimethyl maleate or fumarate would be much more tightly bound than those from either **3a** or **4a**, which is consistent with our experimental observation that added maleate had an inhibitory effect on the **3a**/**4a** isomerization (Figure 2).

Computations were also performed to seek a pathway

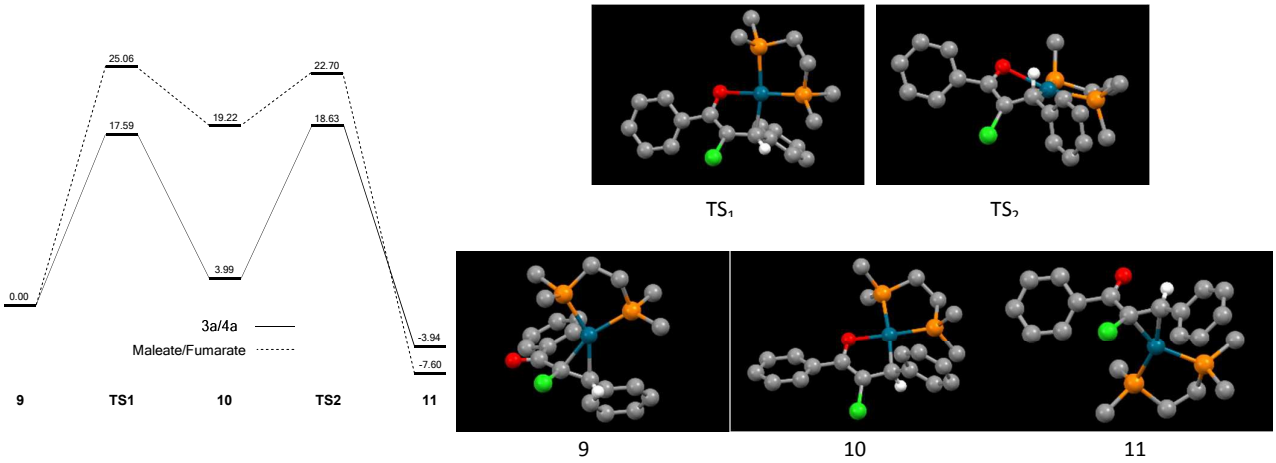



Figure 4 DFT calculations support the Canovese/Visentin isomerization pathway depicted in Scheme 7. Energies (kcal $mol^{-1}$) relative to the initial π-complexes are indicated for each calculated stationary state. The calculated structures for the stationary states in the **3a**/**4a** interconversion are depicted at right.

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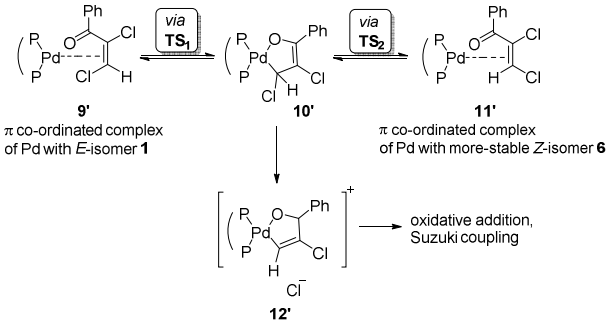
DOI: 10.1039/C7OB02925J




analogous to that in Scheme 7 for isomerization of the dichloro compound **1**. Such a pathway was in fact identified (Scheme 8), and for the simplified catalyst model it appeared to be energetically reasonable. However, our calculations produced a clearly elongated Cβ-Cl bond for enolate intermediate **10'** (1.98 - 3.80 Å) indicating a tendency to directly eliminate $Cl^-$ and so form **12'**, the equivalent of a Cβ-Cl oxidative addition product. A proper analysis of the reaction path in Scheme 8 would require inclusion of solvation in the geometry optimizations, which goes beyond the scope of this work.




Scheme 8 Calculated reaction path for Pd-catalyzed isomerization of **1**/**6** is potentially interrupted by elimination of chloride from **10'**, leading to the oxidative addition step in the Suzuki catalytic cycle.

## Conclusions

The stereochemical outcome of Suzuki cross couplings of vinyl chloride **2** can be controlled by the appropriate choice of ligand, to form either the kinetic "retention" product or the thermodynamically-favoured "isomerization" product. Reactions in which no phosphine ligand is present strongly favour retention of the vinyl halide configuration, as do reactions using t-BuXantphos ligands. In contrast, DPEphos or Xantphos ligands lead to rapid E/Z isomerization of the kinetic product.

Our experimental and computational studies seem to be inconsistent with several mechanistic rationales proposed in the literature for related isomerizations. Instead, the results are best explained by a mechanism first proposed by Canovese and Visentin[65, 66] for maleate and bis(sulfonyl)ethene. These authors noted that their calculations "emphasized the crucial role exercised by the conjugate C=O group for the outcome of the whole process. This evidence seems to reduce significantly the spectrum of olefins fit for this mechanism of rearrangement." Our observation that a single conjugated carbonyl group is sufficient to induce easy isomerization is significant because enones are by no means rare as reaction partners in Pd/phosphine catalyzed chemistry.

## Experimental

**(3*E*)-3,4-Dichloro-2-(dimethylamino)-2-phenylbut-3-enenitrile (2).**

This compound was prepared as described by Jonczyk and Gierczak.[22] Yield: 40%; White solid (mp 113.8-114.2 °C); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 6H), 6.35 (s, 1H), 7.39-7.43 (AA'BB'C, 3H), 7.76-7.79 (AA'BB', 2H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 40.92, 74.42, 113.23, 117.45, 126.74, 128.85, 129.58, 132.75, 135.96 ppm; HRMS: Calculated for $C_{12}H_{12}N_2Cl_2$: 254.0378, Found: 254.0366.

Crystal data. $C_{12}H_{12}Cl_2N_2$, M = 255.14, monoclinic, a = 13.368(5), b= 7.287(2), c = 14.142(5) Å, α= 90.0, β= 113.436(8), γ= 90.0, U = 1264.0(7) Å$^3$, T = 293 K, space group P21/c, Z = 4, 9000 reflections measured, 2353 unique (Rint = 0.0128). The final wR(F2) was 0.1369 (all reflections).

**(2*E*)-2,3-Dichloro-1-phenylprop-2-en-1-one (1).**

Compound **1** was made using a modification of a procedure reported by Jonczyk and Gierczak.[22] The $^1$H NMR data obtained for our product did not match the reported data but was consistent with the results of COSY, HSQC and HMBC experiments. Yield: 85%; Yellow oil; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.69 (s, 1H), 7.51-7.54 (AA'BB', 2H), 7.64-7.67 (AA'BB'**C**, 1H), 7.96-7.97 (AA'BB', 2H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$) δ 118.89, 127.73, 129.03, 129.83, 133.50, 134.66, 188.25 ppm; HRMS: Calculated for $C_9H_6OCl_2$: 199.9796, Found: 199.9798

**General procedures for Suzuki couplings with retention of configuration (Table 2, conditions A or B, compounds 3a-g).**

For reactions under conditions **A**, **1** (1 eq.), the appropriate boronic acid (1 eq.), $Pd_2(dba)_3$ (5 mol%) and $Cs_2CO_3$ (3 eq.) were placed in a glass tube with a screw cap.

For reactions under conditions **B**, **1** (1 eq.), the appropriate boronic acid (1 eq.), Pd2(dba)3 (2.5 mol%), t-BuXantphos (5 mol%) and Cs2CO3 (3 eq.) were employed.

In either case, anhydrous dioxane (to make a final concentration of **1** of 0.166 M) was added to the glass tube. The stirred solution was heated at 85 °C until consumption of **2** was complete. The reaction mixture was then cooled to room temperature and ice-cold water was added. The reaction mixture was extracted with ethyl acetate (ca. 5 mL × 3). The combined organic extract was washed with brine (ca. 15 mL) and dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated and the product (**3a-g**) was isolated from the residue by silica-gel chromatography, eluting with 97:3 hexanes:ethyl acetate.

**(2*E*)-2-Chloro-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (3a).**

Conditions **A**: 78%; Conditions **B**: 73%; Yellow solid (mp 91.7-93.1 °C); $^1$H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.69-6.72 (AA'BB', 2H), 7.09-7.12 (AA'BB', 2H), 7.14 (s, 1H), 7.40-7.44 (AA'BB', 2H), 7.53-7.57 (AA'BB'**C**, 1H), 7.96-7.98 (AA'BB', 2H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$) δ 55.19, 114.03, 124.76, 125.95, 128.81, 129.90, 129.95, 132.52, 134.12, 134.15, 159.84, 191.79 ppm; HRMS: Calculated for $C_{16}H_{13}O_2Cl$: 272.0604, Found: 272.0605.

Crystal data. $C_{16}H_{13}ClO_2$, M = 272.71, monoclinic, a = 14.28(2), b= 9.823(14), c = 9.912(14) Å, α= 90.0, β= 98.27(2), γ= 90.0, U = 1376(3) Å$^3$, T = 293 K, space group P21/c, Z = 4, 9855 reflections measured, 2549 unique (Rint = 0.0164). The final wR(F2) was 0.1976 (all reflections).

**(2*E*)-2-Chloro-3-(4-methylphenyl)-1-phenylprop-2-en-1-one (3b).**

Conditions **A**: 75%; Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 6.97-7.07 (AA'BB', 4H), 7.15 (s, 1H), 7.39-7.45 (AA'BB', 2H), 7.52-7.58 (1H, AA'BB'**C**), 7.95-7.98 (AA'BB', 2H) ppm; $^{13}$C

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NMR (75 MHz, $CDCl_3$) δ 21.23, 125.96, 128.33, 128.84, 129.35, 129.99, 130.50, 132.73, 134.04, 134.19, 138.80, 191.66 ppm; HRMS: Calculated for $C_{16}H_{13}OCl$: 256.0655, Found: 256.0653.

**(2*E*)-2-Chloro-1,3-diphenylprop-2-en-1-one (3c).**

Conditions **A**: 69%; Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.17-7.20 (m, 6H), 7.39-7.45 (AA'BB', 2H), 7.52-7.58 (AA'BB'C, 1H), 7.95-7.98 (AA'BB', 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 127.06, 128.37, 128.63, 128.67, 128.85, 129.98, 132.77, 133.33, 133.98, 134.25, 191.43 ppm; HRMS: Calculated for $C_{15}H_{11}OCl$: 242.0498, Found: 242.0492.

**(2*E*)-2-Chloro-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (3d).**

Conditions **A**: 72%; Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.84-6.91 (AA'BB', 2H), 7.13-7.18 (m, 3H), 7.40-7.46 (AA'BB', 2H), 7.54-7.59 (AA'BB'**C**, 1H), 7.93-7.97 (AA'BB', 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 115.60, 115.89, 127.01, 127.04, 128.91, 129.50, 129.56, 129.94, 130.17, 130.28, 131.63, 133.89, 134.39, 161.00, 164.32, 191.35 ppm; HRMS: Calculated for $C_{15}H_{10}OClF$: 260.0404, Found: 260.0402.

**(2*E*)-3-(Benzofuran-2-yl)-2-chloro-1-phenylprop-2-en-1-one (3f).**

Conditions **A**: 76%; Yellow solid (mp 104-105.5 °C); $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.70 (s, 1H), 7.02 (s, 1H), 7.10-7.22 (m, 3H), 7.45-7.50 (m, 3H), 7.56-7.61 (m, 1H), 8.03-8.06 (m, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 108.16, 111.17, 120.08, 121.35, 123.23, 125.53, 127.92, 127.96, 128.86, 129.73, 134.15, 134.33, 149.86, 155.10, 190.57 ppm; HRMS: Calculated for $C_{17}H_{11}O_2Cl$: 282.0448, Found: 282.0445.

Crystal data. $C_{17}H_{11}ClO_2$, M = 282.71, monoclinic, a = 8.087(4), b= 6.124(4), c = 13.998(7) Å, α= 90.0, β= 91.490(9), γ= 90.0, U = 693.0(6) $Å^3$, T = 293 K, space group P21, Z = 2, 5162 reflections measured, 2586 unique (Rint = 0.0168). The final wR(F2) was 0.0866 (all reflections).

**(2*E*)-2-Chloro-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (3g).**

Conditions **A**: 77%; Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.90-6.93 (m, 1H), 7.03-7.05 (m, 1H), 7.22-7.28 (m, 2H), 7.47-7.52 (m, 2H), 7.59-7.65 (m, 1H), 8.01-8.05 (m, 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 124.81, 126.07, 127.34, 128.00, 128.87, 129.99, 130.02, 134.09, 134.29, 135.66, 191.19 ppm; HRMS: Calculated for $C_{13}H_9OSCl$: 248.0063, Found: 248.0057.

**General procedure for Suzuki couplings with inversion of configuration (Table 2, conditions C, compounds 4a-h).**

Compound **1** (1 eq.), the appropriate boronic acid (1 eq.), $Pd_2(dba)_3$ (2.5 mol%), DPEphos (5 mol%) and $Cs_2CO_3$ (3 eq.) were placed in a glass tube with a screw cap. Anhydrous dioxane (to make a final concentration of **1** of 0.166 M) was added to the glass tube. The stirred solution was heated at 85 °C until tlc analysis indicated complete consumption of **1**. The reaction mixture was then cooled to the room temperature and ice-cold water was added. The reaction mixture was extracted with ethyl acetate (ca. 5 mL × 3). The combined organic extract was washed with brine (ca. 15 mL) and dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated and the product (**4a-h**) was isolated from the residue by silica-gel chromatography, eluting with 97:3 hexanes:ethyl acetate.

**(2*Z*)-2-Chloro-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4a).**

Yield: 80%; White solid (mp 58.2-60.0 °C); $^1H$ NMR (500 MHz, $CD_3OD$) δ 3.84 (s, 3H), 6.99-7.01 (AA'BB', 2H), 7.49 (s, 1H), 7.50-7.54 (AA'BB', 2H), 7.60-7.64 (AA'BB'**C**, 1H), 7.72-7.73 (AA'BB', 2H), 7.87-7.89 (AA'BB', 2H) ppm; $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 54.51, 113.79, 125.25, 127.55, 128.22, 128.94, 132.07, 132.71, 137.27, 140.59, 161.84, 191.75 ppm; HRMS: Calculated for $C_{16}H_{13}O_2Cl$: 272.0604, Found: 272.0604.

Crystal data. $C_{16}H_{13}ClO_2$, M = 272.71, orthorhombic, a = 8.858(3), b= 11.306(5), c = 27.121(11) Å, α= 90.0, β= 90, γ= 90.0, U = 2716.0(19) $Å^3$, T = 293 K, space group Pbca, Z = 8, 18717 reflections measured, 2525 unique (Rint = 0.0144). The final wR(F2) was 0.1230 (all reflections).

**(2*Z*)-2-Chloro-3-(4-methylphenyl)-1-phenylprop-2-en-1-one (4b).**

Yield: 76%; Yellow solid (mp 58.2-58.4 °C); $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.28-7.29 (AA'BB', 2H), 7.48-7.53 (m, 3H), 7.58-7.64 (AA'BB'**C**, 1H), 7.77-7.82 (AA'BB', 4H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 21.59, 128.45, 129.40, 129.50, 129.67, 130.17, 130.84, 132.38, 137.14, 140.12, 141.17, 191.40 ppm; HRMS: Calculated for $C_{16}H_{13}OCl$: 256.0655, Found: 256.0655.

Crystal data. $C_{16}H_{13}ClO$, M = 256.71, orthorhombic, a = 8.8054(8), b= 11.6093(11), c = 26.7629(15) Å, α= 90.0, β= 90, γ= 90.0, U = 2735.8(4) $Å^3$, T = 293 K, space group Pbca, Z = 8, 18840 reflections measured, 2543 unique (Rint = 0.0144). The final wR(F2) was 0.1132 (all reflections).

**(2*Z*)-2-Chloro-1,3-diphenylprop-2-en-1-one (4c).**

Yield: 70%; Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.42-7.53 (m, 6H), 7.57-7.63 (1H, AA'BB'**C**), 7.79-7.87 (AA'BB', 4H) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 128.47, 128.62, 129.54, 130.42, 130.44, 130.67, 132.53, 132.91, 136.86, 139.69, 191.28 ppm; HRMS: Calculated for $C_{15}H_{11}OCl$: 242.0498, Found: 242.0493.

**(2*Z*)-2-Chloro-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (4d).**

Yield: 69%; Yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.02-7.06 (AA'BB', 1H), 7.41 (s, 1H), 7.48-7.53 (AA'BB', 2H), 7.59-7.65 (AA'BB'**C**, 1H), 7.78-7.82 (AA'BB', 2H), 8.46-8.52 (AA'BB', 2H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 109.52, 110.02, 127.25, 127.31, 128.67, 129.60, 132.25, 132.28, 133.04, 133.94, 136.13, 141.89, 142.00, 150.32, 150.53, 162.18, 165.42, 190.46 ppm;

HRMS: Calculated for $C_{14}H_9NOFCl$: 261.0357, Found: 261.0362.

**(2*Z*)-3-(Benzofuran-2-yl)-2-chloro-1-phenylprop-2-en-1-one (4f).**

Yield: 74%; Yellow solid (mp 62.5-65 °C); $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.27-7.32 (m, 1H), 7.37-7.42 (m, 1H), 7.47-7.54 (m, 3H), 7.58-7.65 (m, 2H), 7.67-7.71 (m, 1H), 7.77-7.80 (m, 3H) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 111.48, 113.33, 122.38, 123.68, 127.0, 128.34, 128.60, 128.88, 129.42, 130.93, 132.58, 136.64, 150.26, 155.14, 190.11 ppm; HRMS: Calculated for $C_{17}H_{11}O_2Cl$: 282.0448, Found: 282.0454.

Crystal data. $C_{17}H_{11}ClO_2$, M = 282.71, orthorhombic, a = 6.1663(8), b= 12.6929(11), c = 17.4233(15) Å, α= 90.0, β= 90, γ= 90.0, U = 1363.7(2) $Å^3$, T = 293 K, space group P212121, Z = 4, 10108 reflections measured, 2540 unique (Rint = 0.0282). The final wR(F2) was 0.0853 (all reflections).

**(2*Z*)-2-Chloro-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (4g).**

Yield: 62%; Yellow oil; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.15-7.17 (AA'BB', 1H), 7.46-7.52 (AA'BB', 3H), 7.58-7.61 (AA'BB'C, 1H), 7.67-7.68 (AA'BB', 1H), 7.74-7.78 (m, 3H) ppm; $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 127.24, 127.98, 128.48, 129.24, 132.22, 132.33,

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134.19, 134.83, 136.70, 137.22, 190.48 ppm; HRMS: Calculated for $C_{13}H_9OClS$: 248.0063, Found: 248.0054.

**(2*Z*)-2-Chloro-3-(2-fluoropyridin-4-yl)-1-phenylprop-2-en-1-one (4h).**

Yield: 69%; Yellow oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.02-7.06 (AA'BB', 1H), 7.41 (s, 1H), 7.48-7.53 (AA'BB', 2H), 7.59-7.65 (AA'BB'**C**, 1H), 7.78-7.82 (AA'BB', 2H), 8.46-8.52 (AA'BB', 2H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 109.52, 110.02, 127.25, 127.31, 128.67, 129.60, 132.25, 132.28, 133.04, 133.94, 136.13, 141.89, 142.00, 150.32, 150.53, 162.18, 165.42, 190.46 ppm; HRMS: Calculated for $C_{14}H_9NOFCl$: 261.0357, Found: 261.0362.

**(2*Z*)-2,3-Dichloro-1-phenylprop-2-en-1-one (6).**

Compound **1** (100.0 mg, 1 mmol), DPEphos (13.5 mg, 0.025 mmol) and anhydrous dioxane (3.0 mL) were boiled under reflux for 24 hr, at which time tlc indicated complete conversion. The reaction mixture was then cooled to room temperature and ice-cold water was added. The reaction mixture was extracted with ethyl acetate (ca. 6 mL × 3). The combined organic extract was washed with brine (ca. 20 mL) and dried over anhydrous sodium sulphate. After filtration, the filtrate was concentrated and the product **6** was obtained from the residue by silica-gel chromatography. Yield: 78%; Yellow oil; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.48-7.51 (AA'BB', 2H), 7.60-7.63 (AA'BB'**C**, 1H), 7.74-7.75 (AA'BB', 2H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$) δ 128.68, 129.45, 133.27, 133.60, 135.45, 135.90, 187.64 ppm; HRMS: Calculated for $C_9H_6OCl_2$: 199.9789, Found: 199.9796.

**(2*E*)-2-Chloro-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol (7)**

Compound **3a** (100.0 mg, 0.37 mmol) was dissolved in MeOH (1 mL) in a test tube. $CeCl_3.7H_2O$ (136.7 mg, 0.37 mmol) was added to the tube. $NaBH_4$ (13.9 mg, 0.37 mmol) was carefully added. The test tube was agitated from time to time as the reaction was allowed to proceed until tlc indicated complete conversion of **3a**. Aqueous 0.5 M HCl was then added to the test tube. The mixture was then extracted with ethyl acetate (ca. 5 mL × 3). The combined organic extract was washed with brine (ca. 20 mL) and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvents, the product **7** (82.7 mg, 82%) was isolated from the residue by silica-gel chromatography as a colourless, viscous oil.

$^1$H NMR (500 MHz, $CDCl_3$) δ 2.53 (1H, s), 3.81 (3H, s), 5.95 (1H, s), 6.88 – 6.90 (2H, m), 7.01 (1H, s), 7.21 – 7.23 (2H, m), 7.32 – 7.35 (1H, m), 7.38 – 7.41 (2H, m), 7.47 – 7.48 (2H, m) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$) δ 55.31, 70.90, 114.16, 126.13, 127.02, 127.94, 128.51, 129.67, 130.87, 136.07, 140.22, 159.42 ppm; HRMS: Calculated for $C_{16}H_{15}O_2Cl$: 274.0761, Found: 274.0773.

**Computational methods.**

All calculations were carried out with the program Turbomole[69] coupled to an external optimizer.

For the study of forced C=C rotation, geometries were optimized at the TPSSh level,[70] using the def-TZVP basis set[71, 72] (Stuttgart ECP for Pd[73]). BOptimize[74] was used to constrain the values of H-C1-C2-C3 and H-C1-C2-Cl dihedral angles in steps of 15° while relaxing all other degrees of freedom; see the SI for energies and further details.

For the study of enone/enolate interconversion, geometries were fully optimized (with PQS OPTIMIZE[75, 76]) at the b-lyp level[77-79] with the RI approximation,[80, 81] using the def-SV(P) basis set;[82, 83] vibrational analyses were used to check the nature of all stationary points. Improved single-point energies were evaluated at the TPSSh[70]/def-TZVPP[84] level, and these energies were combined with thermal corrections (enthalpy and entropy, 298 K, 1 bar) and a DFT-D dispersion correction[85] (zero damping) to obtain final free energies.

## Acknowledgements

We thank the Faculty of Science and the Department of Chemistry at the University of Manitoba for financial support of this work. We also acknowledge the vital assistance of Dr. Kirk Marat (NMR), Dr. Tom Ward (GC/MS) and Mr. Mark Cooper (X-ray crystallography).

## Notes and references

† Details are provided in the supplementary information.

‡ The *E*/*Z* geometries of all compounds in this study were determined using the $^3J_{C\text{-}H}$ method. The results were confirmed from X-ray crystal structures obtained for compounds **3a**, **4a**, **4b**, **3f** and **4f**. Full details are in the supplementary information.

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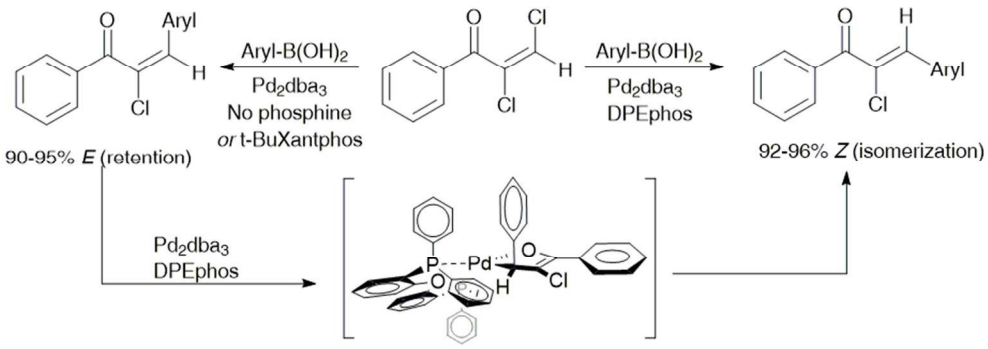
View Article Online
DOI: 10.1039/C7OB02925J



We present evidence for a palladocyclic enolate-like pathway for isomerization of enones occurring during Suzuki cross-coupling reactions.

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