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Isomerisation versus carbonylative pathways in the hydroxy-carbonylation, methoxy-carbonylation, and amino-carbonylation of *N*-tosyl 3-pyrroline.

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Abstract:
The reactivity of *N*-tosyl-3-pyrroline is significantly lower than that of mono-substituted alkenes in Pd catalysed methoxycarbonylation reactions. For example, most bulky diphosphine/ Pd catalysts, including the well-known Pd catalyst derived from 1,2-bis(Di-*Tert*-ButylPhosphinoXylene (DTBPX), were found to give no product at all in the methoxycarbonylation of *N*-tosyl-3-pyrroline. The competing pathways in methoxycarbonylation of *N*-methane-sulfonyl-3-pyrroline using Pd/ DTBPX were studied using DFT calculations; these show that the coordination of the alkene is unfavourable, and once coordinated, isomerisation is a lower energy pathway that ultimately leads to an alternative product. Experimentally a side product resulting from alkene isomerisation and addition of methanol is formed slowly (if CO is present), and rapidly if CO is not. A less bulky derivative of DTBPX forms the required alkene complex with much lower barriers.
A study has been made of the enantioselective carbonylation of *N*-tosyl-3-pyrroline using water, methanol or aniline as nucleophile. This revealed that there is a range of possible products with most of these initiated by a Pd-catalysed isomerisation of the alkene. Using less bulky members of the Pd/Phanephos family of catalysts, it is possible to produce the methoxycarbonylation product from this poorly reactive alkene with reasonably good chemoselectivity and around 80% e.e. at higher pressures of CO.

Introduction

Palladium catalysed alkene carbonylation is a very important reaction in industrial synthesis, since it uses very cheap reagents in a very atom efficient manner.[1-6] Applications that have been practiced at commercial scale include: polymer synthesis by co-polymerisation, methyl propionate synthesis by ethylene methoxycarbonylation and formation of racemic fine chemicals by hydroxycarbonylation of vinyl arenes (sometimes generated in situ from alcohols).[1,2] A stand-out catalyst is the Pd complex formed from 1,2-*bis*(Di-*Tert*-ButylPhosphinoXylene (DTBPX from this point forward), which gives very high rates in ethylene methoxycarbonylation,[1b, 1l, 1o] and has also been used for some other applications.[5] The potential for enantioselective hydroxycarbonylation and alkoxycarbonylation to be a useful method for large scale asymmetric synthesis has been appreciated for a long time.[2-4] However, this is a challenging reaction and despite many important contributions, high enantioselectivity is rare especially for the intermolecular reaction; further research is needed. Catalysts which do give good enantioselectivity, combined with high regioselectivity in the methoxycarbonylation of styrene are Pd catalysts derived from the bulkier members of the Phanephos ligand family (shown in Scheme 1),[3,4] providing impetus to seek to evaluate and increase substrate scope for alkene carbonylation. In the literature, there are very sparse examples, even using achiral catalysts. Most examples of methoxycarbonylation of internal alkenes have led to tandem isomerisation-linear selective methoxycarbonylation reactions.[5] There is also a relevant report of an attempted methoxycarbonylation of a 2-pyrroline derivative that gave none of the desired ester.[6] As part of a programme aiming to increase scope in this class of reaction, we have studied carbonylation of *N*-

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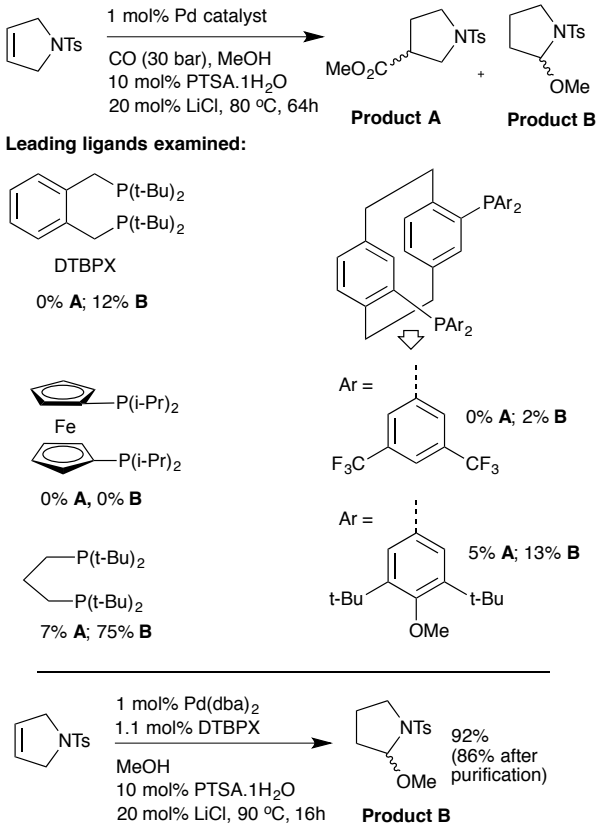
tosyl-3-pyrroline. Interest in the catalytic asymmetric synthesis of β-Proline derivatives is exemplified by a recent study reporting enantioselective hydroformylation of *N*-Boc-2-pyrroline,[7] while we recently reported the related transfer hydroformylation of *N*-tosyl pyrroline with around 70-75% e.e.[8] To access β-Proline requires oxidation and deprotection. Hydroxycarbonylation can give protected β-Proline derivatives in one step, while alkoxycarbonylation, also called hydroesterification and more formally hydro-alkoxycarbonylation, gives esters directly. Enantioselective intermolecular hydro-aminocarbonylation would give amides directly, but hydro-aminocarbonylation of alkenes has been barely studied in the published literature, despite its potential.[9, 2f] In this paper, we report hydroxy-, alkoxy- and amino-carbonylation of *N*-tosyl-3-pyrroline. An interesting competition is observed between a novel domino (Pd catalysed) isomerisation- (acid catalysed) addition process and the carbonylation to give chiral carboxylic acid derivatives.

Results and discussion

Scheme 1 shows the results from testing a range of bulky diphosphines known to form active alkene carbonylation catalysts in the methoxycarbonylation of *N*-tosyl pyrroline (Ts-3-Py). The conditions were generally similar to our previous reports and others, with the exception of longer reaction times to maximise the chances of forming some carbonylation product. None of the catalysts examined give useful amounts of the desired ester as product. The Pd/DTBPX catalyst is known to give incredibly high rates of reaction in the methoxycarbonylation of ethene.[1b,1c] However, in methoxycarbonylation of Ts-3-Py, none of the desired methyl ester, **A** was formed. A small amount of the *N,O*-acetal, **B** is formed. This arises from isomerisation of the alkene to *N*-tosyl-2-pyrroline (Ts-2-Py), followed by protonation and methanol addition. If the reaction is repeated in the absence of carbon monoxide, this isomerisation-addition product is formed in high yield using this catalyst. This implies that the isomerisation process is inhibited by CO.



Scheme 1. Attempted methoxycarbonylation of N-tosyl-3-pyrroline using a range of established ligands for Pd catalysed carbonylation; the *N,O*-acetal formed by alkene isomerisation followed by acid catalysed addition of methanol is the major product (PTSA = Para-Toluene-Sulfonic Acid). (See ESI for details)

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These poor results prompted us to use DFT calculations to study the formation and fate of the Pd-alkyl species formed from Pd/ DTBPX in methoxycarbonylation of the very closely related substrate, N-methanesulfonyl-3-pyrroline, Ms-3-Py (chosen since it has less conformational isomers that are not relevant to catalysis, but are time consuming to calculate). The Pd/ DTBPX catalyst was chosen since it is the most established and most important of alkene carbonylation catalysts to date.

Effect of CO on the formation of the Pd-alkyl intermediate from *N*-(methanesulfonyl)-3-pyrroline and [(DTBPX)Pd(CO)(H)]$^+$

The resting state of the system under CO pressure is found to be the [(DTBPX)Pd(CO)(H)]$^+$, complex **1** (Scheme 2). The strong back-bonding interaction afforded through the carbonyl ligand makes this species considerably more favourable than either the substrate bound complex [(DTBPX)Pd(H)(Ms-3-Py)]$^+$, **2** (by ΔH = 9.8 kcal/mol and ΔG = 12.6 kcal/mol), or the solvent coordinated hydridopalladium complex [(DTBPX)Pd(H)(MeOH)]$^+$, **3** (by ΔH = 13.5 kcal/mol and ΔG = 14.2 kcal/mol).

There are a number of routes through which hydrometallation of Ms-3-Py may occur from **1**. The most favourable emerged as the stepwise association of Ms-3-Py (**TS1-1A**) leading to the pentacoordinated intermediate **1A** followed by loss of CO (**TS1A-2**), shown in Scheme 2. **
The highest barrier is $\Delta G^{\ddagger}$ = 22.8 kcal/mol, which is associated with **TS1A-2**. **TS1-1A** and **TS1A-2** are illustrated in Figure 1. **TS1-1A** clearly shows the association of Ms-3-Py with Pd – C distances of 2.56 and 2.63 Å observed between the transition metal centre and the coordinating olefin. As a result of the dihydropyrrole entering the first coordination sphere around palladium, the square planar geometry of **1** is perturbed and CO moves from a position within the P – Pd – P plane to the apical site. This occurs with a slight shortening of the Pd – $C_{(O)}$ bond from 2.03 Å in **1** to 2.01 Å at **TS1-1A**. In **TS1A-2** the Pd – $C_{(3\text{-}pyrr)}$ bonds have decreased to within bonding distance (2.32 Å and 2.38 Å) and the olefin double bond lengthens by 0.02 Å due to backbonding from the metal. At this saddle point the carbonyl ligand dissociates which carries a high free energy cost of 22.8 kcal/mol. The resulting product, **2**, is uphill by ΔG=12.6 kcal/mol against **1** and therefore the formation of a Ms-3-Py coordinated palladium complex is highly endergonic.

Due to this endergonicity the backwards reaction from **2** to **1** is readily accessible with a kinetic free energy cost of 10.2 kcal/mol. This ease of conducting the backwards reaction coupled with the greater degree of thermodynamic stability afforded by **1** relative to Ms-3-Py bound complex **2** results in **1** being recalcitrant to forming a complex primed for hydrometallation. Even if complex **2** undergoes the readily accessible hydrometallation step ($\Delta G^{\ddagger}$ = 15.4 kcal/mol against **1**, 2.8 kcal/mol against **2**) the resulting alkylpalladium complex **4** remains uphill in free energy at 7.6 kcal/mol against **1**. This again favours the reformation of **1**, instead of progression into the carbonylation reaction. In fact the activation energy required for entering into carbonylation is only 1.2 kcal/mol lower than that of the highest point on the backwards reaction, further disfavouring movement away from **1** ($\Delta G^{\mathbf{TS4\text{-}5}}$ = 21.6 kcal/mol, $\Delta G^{\mathbf{TS4\text{-}5}}$ = 22.8 kcal/mol).

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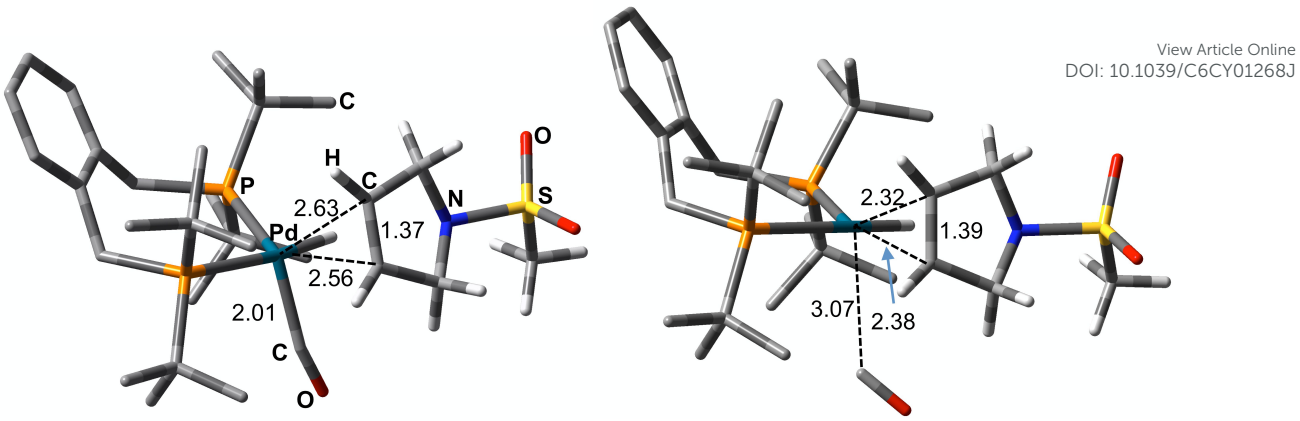
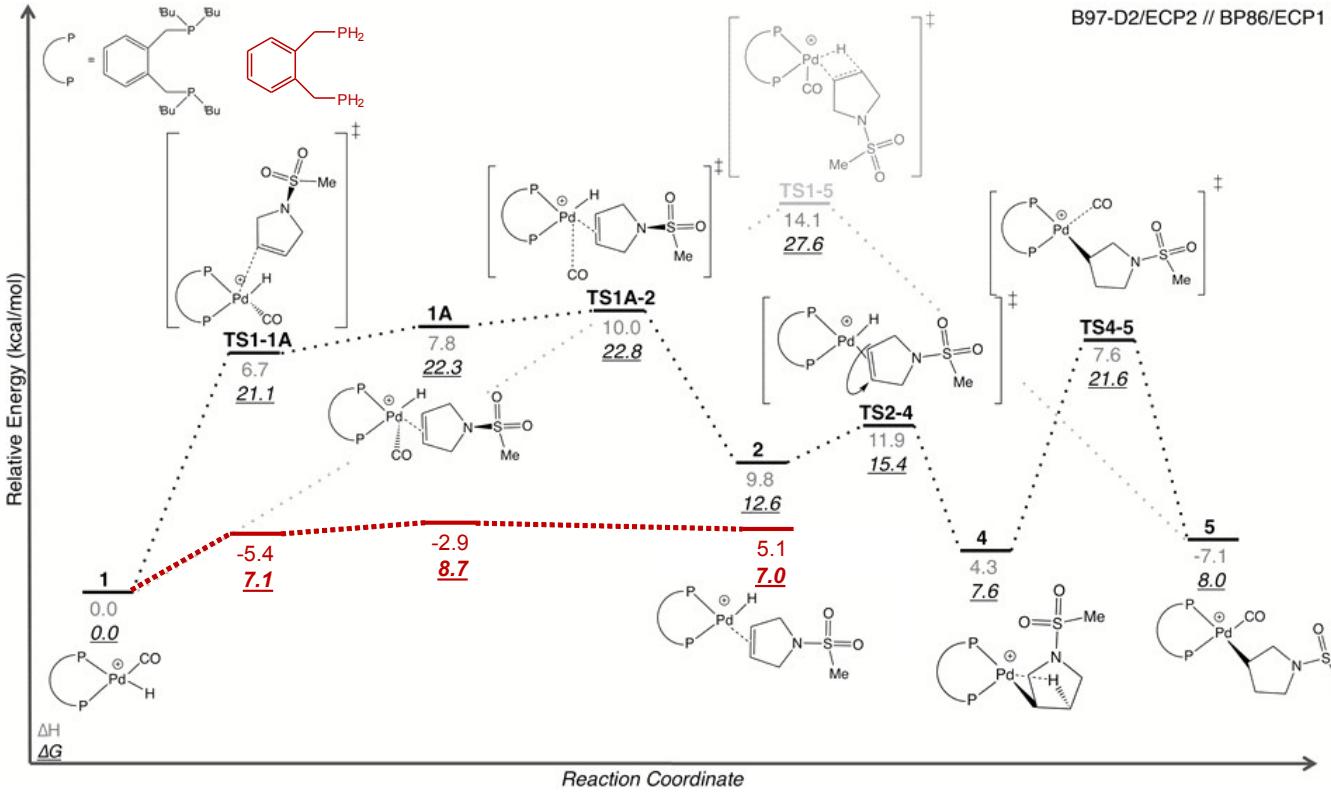


Figure 1: **TS1-1A** (left) and **TS1A-2** (right). Distances in Å. Hydrogens of the DTBPX ligand have been removed for clarity.



Scheme 2: Routes leading to alkylpalladium species **4** and **5** from CO coordinated resting state **1**. Ms-3-Py may approach the transition metal centre with the methylsulfonyl moiety orientated towards the hydride or away. Both routes were tested and only the most stable, the sulfonyl unit orientated away from the complex, is presented throughout. Energies in kcal/mol and relative to **1** (in dark red: analogs with the much less bulky parent phosphine (PH_2-substituted) model).

Alternatively the CO coordinated complex **5** could be formed directly from **1**. A corresponding transition state, **TS1-5** was located, showing the association of Ms-3-Py with concerted hydrometallation. **TS1-5** has CO coordinated in an apical position while the hydride is delivered to the unsaturated carbon and a Pd – C bond begins to form (see Figure ESI-Fig1). With an activation free energy of 27.6 kcal/mol this route is energetically prohibitive; it is not competitive

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with the stepwise process through **TS1A-2 → 2 → TS4-5**, which has an overall free energy barrier of 22.8 kcal/mol.

Through the combination of CO displacement pathways that are challenging on the free energy landscape (**TS1A-2** and **TS1-5**), the deep potential well in which the starting complex **1** rests and the reversibility of the reactions, CO pressure inhibits the alkoxycarbonylation of Ms-3-Py with the DTBPX and Pd system. To probe for the effect of the steric bulk of the DTBPX ligand, we repeated the first stages of this reaction with the parent bis-phosphine where the tBu groups have been replaced with H atoms. **TS1A-2**, the highest point with DTBPX in Scheme 2, does not exist with this ligand (the energy changes monotonously upon CO dissociation), and very little kinetic hindrance is predicted for formation of the olefin complex **2** (see pathway highlighted in dark red in Scheme 2).

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Reaction of *N*-(methanesulfonyl)-3-pyrroline with Pd/DTBPX in the absence of CO

Alkene coordination is hindered by the presence of CO, and both isomerisation pathways and especially carbonylation pathways are challenging. In the absence of CO, the carbonylation pathway cannot proceed, but the isomerisation pathway is significantly facilitated (Scheme 1). To form the methane-sulfonyl derivative of side product, **B**, the $[(DTBPX)Pd(H)]^+$ system must facilitate an interconversion of Ms-3-Py (*N*-(methanesulfonyl)-3-pyrroline) to *N*-(methanesulfonyl)-2-pyrroline, further referred to as Ms-2-Py. DFT calculations indicate a notable driving force for the conversion of Ms-3-Py to Ms-2-Py, with the latter being more stable by ΔH = 3.8 kcal/mol and ΔG = 3.3 kcal/mol.

In the absence of CO the presumed starting species is **3**, $[(DTBPX)Pd(H)MeOH)]^+$ (Scheme 3) due to the high abundance of methanol when it is used as the solvent. Unlike **1**, **3** does not rest in a deep potential energy well and the exchange of MeOH for Ms-3-Py is slightly thermodynamically favourable, allowing for a preferential formation of complex **2** due to this intermediate being 1.6 kcal/mol more stable than the solvent coordinated complex (Scheme 3).

From **2** the rotation and migratory insertion required to yield an alkylpalladium intermediate costs only ΔG = 2.8 kcal/mol and is favoured by formation of **4** that is stabilised by a β-agostic interaction. Another rotation follows at **TS4-6**, requiring only 2.8 kcal/mol in activation free energy, and this leads to a more stable complex, **6** which has a β-agostic interaction (Pd – H = 1.84 Å, H – C = 1.20 Å) that primes **6** for β-hydride elimination. Reformation of the double bond yielding Ms-2-Py coordinated to Pd (via **TS6-7**) emerges as being kinetically more accessible, at $\Delta G^{\ddagger}$ = 3.5 kcal/mol, than the backwards reaction and also thermodynamically more favourable (ΔG = -8.6 kcal/mol against **3**). In **TS6-7**, the Pd – H distance decreases to 1.62 Å while the C – H bond is lost, the distance between these centres increasing to 1.74 Å. Geometries for **2**, **4**, **TS4-6**, **6**, **TS6-7** and **7** are shown in the electronic supporting information-Figure 2. One further feature worth noting here concerns how the resulting Ms-2-Py coordinated product, **7** (Fig. 2), exhibits a less symmetric binding mode of the alkene (Pd – C lengths of 2.24 and 2.70 Å) compared to that of Ms-3-Py in **2** (Pd – C distances of 2.32 and 2.33 Å). Furthermore on going from **2** to **7** the C – N distance is shortened by 0.11 Å. The onset of conjugation with the nitrogen lone pair bestows some η^1-allyl character on the olefin complex, resulting in the preferential conversion of Ms-3-Py to Ms-2-Py. Ms-2-Py is then susceptible to acid catalysed addition under the protic conditions, leading to eventual formation of the experimentally observed *N,O*-acetal side product.

The preferential binding of Ms-3-Py to the $[(DTBPX)Pd(H)]^+$ fragment over MeOH, low barriers for all transformations shown in Scheme 3 and the continuously energetically downhill nature of the intermediates ensures that in the absence of CO, Ms-3-Py rapidly converts to Ms-2-Py.

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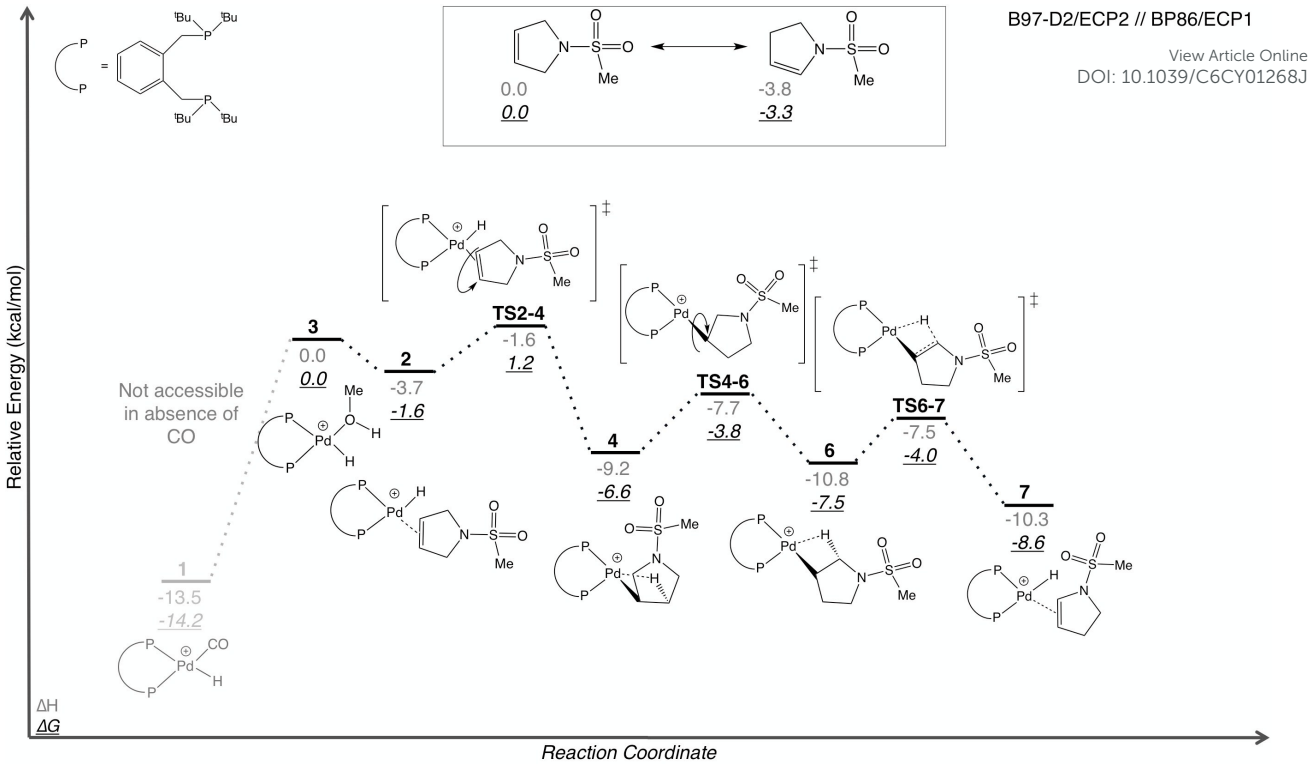

Scheme 3: Conversion of Ms-3-Py to Ms-2-Py in the absence of CO. Energies for the reaction profile are presented in kcal/mol and relative to **3**.

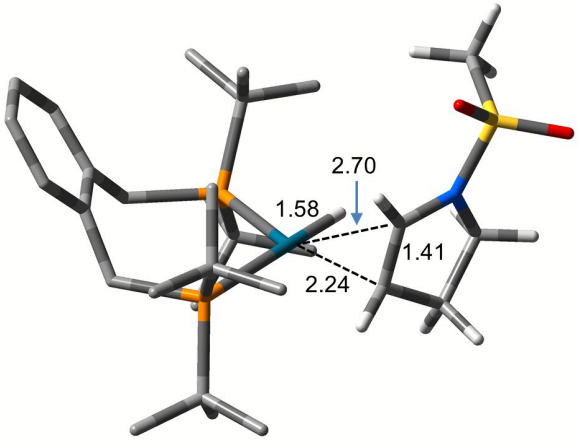

Figure 2: Complex **7**. All distances are in Å.

Conclusions from theoretical studies

Density functional calculations offer a rationale as to why the Pd catalysts derived from the bulky DTBPX diphosphine are ineffective in the alkoxycarbonylation of *N*-tosyl-3-pyrroline. Computations show that this is due to the deep potential energy well in which $[(DTBPX)Pd(H)(CO)]^+$ rests, challenging barriers associated with the forward reaction leading to an alkylpalladium intermediate and the presence of accessible reverse reactions due to endergonic intermediates.

The origins of an *N,O*-acetal side product in the absence of CO are also clearly demonstrated. While this product cannot be generated from Ms-3-Py directly, the $[(DTBPX)Pd(H)]^+$ fragment readily acts as a catalyst to convert Ms-3-Py to Ms-2-Py through a series of hydrometallation, dihedral rotation and β-hydride elimination reactions – all with barriers beneath 7 kcal/mol. Since formation of linear esters from internal isomers of octene and related substrates has also been shown to be effective,[5] this catalyst is highly active for alkene

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isomerisation.[10] In the previous work, a slight preference towards a linear Pd-alkyl species that readily undergoes carbonylation was established by DFT calculations,[5d] while here the alkene formed after isomerisation (**Ts-2-Py**) does not take part in carbonylations, most likely since it is too readily converted into the iminium ion by reaction with acid and then quenched with methanol or any other nucleophile present in the reaction mixture. For these substrates, and undoubtedly for some other synthetic targets, isomerisation-carbonylation is not desirable and needs to be avoided. The calculations also show a pronounced difference between PH_2 and $P(t\text{-}Bu)_2$ containing catalysts. The smaller PH_2 based complex has low barriers associated with forming the desired alkene complex from the resting state, $[(DTBPX)Pd(H)(CO)]^+$. We therefore considered that some less bulky catalysts should be examined in this process, *but at higher CO pressure*; If movement away from the Pd-CO resting state, **1**, is more favoured, it should be possible to divert the reaction towards the carbonylation pathway by increasing CO concentration without the extra CO present stabilising the $[(DTBPX)Pd(H)(CO)]^+$ complex too much.

Testing of less sterically hindered catalysts: (i) methoxycarbonylation.

To explore these ideas, we examined both $[PdCl_2(PPh_3)_2]$ and the less sterically hindered, and normally less effective member of the Pd/Phanephos systems for this reaction. In the hydroxycarbonylation of vinyl arenes, the Phanephos based catalysts only function well if excess Pd is introduced in the form of a Pd dimer **8d** (see Table 2 for structure). However, methoxycarbonylations generally delivered similar results regardless of the nature of the Pd species introduced. In this study, we have used the relatively unhindered catalyst, $[PdCl_2$(*S*)-Xyl-Phanephos)], **8m** in the enantioselective methoxycarbonylation of N-tosyl-3-pyrroline (Table 1, entry 4). This catalyst initially delivered the methoxycarbonylation product **A** as the minor product in the reaction (7%) but with a good enantiomeric excess of 80% (Table 1, entry 4). The *N,O*-acetal, **B**, was the major product in the reaction (87%). Product **B** was checked to be a racemate in all cases, including when the PTSA co-catalyst is swapped with (*S*)-Binaphthylphosphoric acid as promoter (not shown). $[PdCl_2(PPh_3)_2]$ was also used as a benchmark, affording the same mixture of products with a similar ratio under similar conditions (Table 1, entry 1). We examined the effect of pressure in the formation of the carbonylation product versus the isomerisation-addition product. Higher CO pressure should favor migratory insertion of CO into the Pd-alkyl bond over β-hydride elimination, and that was the case (Table 1, entries 1-3). The chemoselectivity and e.e. of the methoxycarbonylation product **A** at 70 bar using catalyst [(*S*)-**8m**] was also slightly improved (Table 1, entry 5). Acid is needed to promote the formation of both products; reducing the amount of acid in the reaction did not lead to the suppression of *N,O*-acetal **B** (Table 1, entry 6). Pleasingly, reducing the amount of MeOH and using less polar solvents (Table 1, entry 7 and 8) tuned the chemoselectivity of the reaction to favour the formation of the ester, giving **A** with 45 and 63% conversion respectively. To improve the reaction further, we evaluated the influence of the concentration of alkene (and MeOH). Doubling the amount of solvent (Table 1, entries 9 and 10) lead to a further improvement of the chemoselectivity (71%) with no detrimental effect in the enantioselectivity of the reaction (80-90%). The use of less bulky catalysts, higher CO pressure along with using a lower concentration of methanol and less polar environment are sufficient to convert a reaction that was not proceeding at all into a workable synthetic procedure, albeit one that would need significant improvements for very large scale use. This corroborates the conclusions drawn from the DFT studies and may also be a strategy that can be used for other alkenes that do not readily form the required $[Pd(L)(H)(alkene)]^+$ intermediate.

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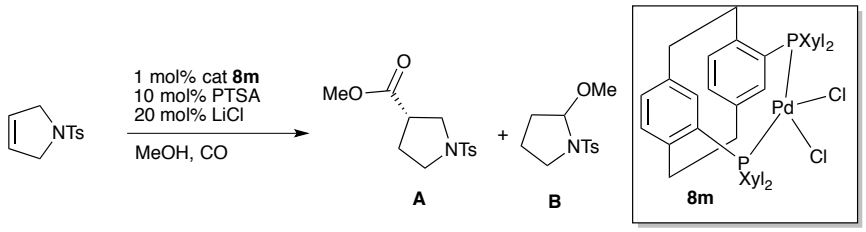
Table 1: Enantioselective methoxycarbonylation of Ts-3-Py



Entry[a]	Catalyst	T (ºC)	P (bar)	t (h)	Conv. (%)[b]	**A** (%)[b] [yield][c]	**B** (%)[b] [yield][c]	ee (**A**) (%)[d]
1	**$[PdCl_2(PPh_3)_2]$**	80	30	64	93	45 [35]	44	0
2	**$[PdCl_2(PPh_3)_2]$**	80	10	64	>99	19	69	0
3	**$[PdCl_2(PPh_3)_2]$**	80	50	64	93	53	40	0
4	**(*S*)-8m**	80	30	64	>99	7	87 [72]	80
5	**(*S*)-8m**	80	70	64	>99	17	77	84
6[e]	**(*S*)-8m**	80	50	64	>99	12 [10]	84 [71]	84
7[f]	**(*S*)-8m**	80	70	64	>99	45	55	77
8[g]	**(*S*)-8m**	80	70	64	>99	63	37	77
9[h]	**(*S*)-8m**	70	70	90	>99	n.d.	n.d.	90
10[i]	**(*S*)-8m**	**70**	**70**	**68**	**99**	**71 [64]**	**28**	**80**

[a] Unless otherwise stated, reactions were carried out using 0.5 mmol of *N*-tosyl-*3*-pyrroline, 1 mol% catalyst, 20 mol% LiCl and 10 mol% PTSA hydrate in 1.5 ml of degassed MeOH. [b] Conversion determined by ^{1}H NMR. [c] Isolated by column chromatography. [d] Enantioselectivity determined using chiral HPLC. [e] 2.5 mol% PTSA. [f] Toluene as solvent, 4 equiv. MeOH. [g] Toluene as solvent, 2 equiv. MeOH. [h] Toluene as solvent but half the usual concentration of substrate (0.17M instead of 0.33M), 2 equiv. MeOH. Several trace products observed in this reaction, making mass balance problematic, ratio **A**:**B** = 5. [i] Reaction pre-stirred 10 min till complete solution of the substrate, 1-Methylnaphthalene used as internal standard, otherwise as in entry 9.

Testing of less sterically hindered catalysts: (ii) hydroxycarbonylation.

Catalysts **8m** and **8d** were also studied as a catalyst in the hydroxy-carbonylation of **Ts-3-Py** (Table 2). In almost all reactions, it was clear that not all of the alkene was converted into the desired acid product, with some cases giving very substantial amounts of side products. The crude ^{1}H NMR spectra were in fact rather complicated, at first leading us to believe that an oligomer might be forming. In fact, the side product can be ascribed to the product of an isomerisation to *N*-tosyl-2-pyrroline and then acid catalysed addition of the butanone solvent, giving two diastereoisomers and two regio-isomers as products. Conclusive evidence of this came from NMR and MS analysis of reaction mixtures run using acetone, butanone and pentanone as solvents. The acetone product, (racemic) **G** was isolated and characterised (Scheme 4).

By comparing the almost exclusive formation of the acetone addition product at 10 bar (Scheme 4) with the results in Table 2, the requirement for high CO pressures is clear. Similar conditions of high pressure and the use of less polar solvents was beneficial in the hydroxycarbonylation reactions aswell. None-the-less when ketone solvents were replaced by Me-THF or toluene, an alternative side product, **F**, formed from addition of water to Ts-2-Py is formed in place of the ketone addition products.

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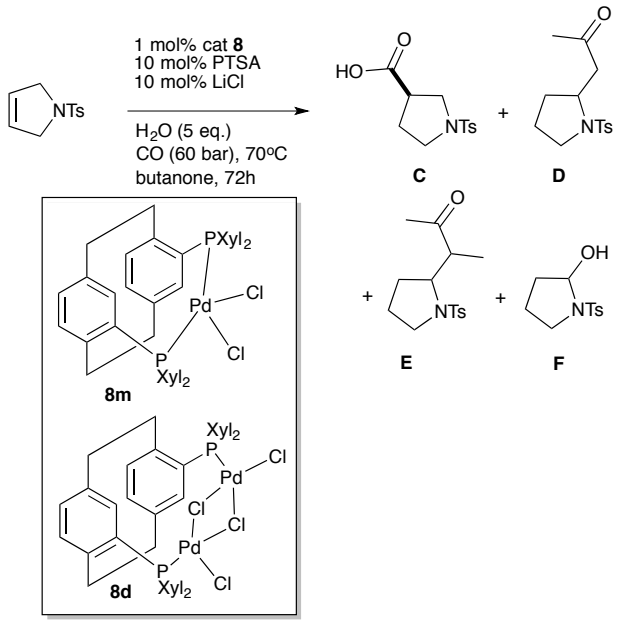
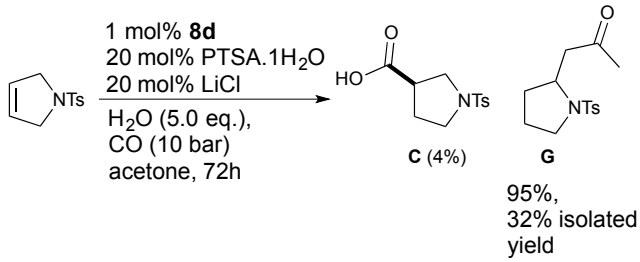
Table 2: Enantioselective hydroxycarbonylation of Ts-3-Py



Entry[a]	Catalyst	Solvent	Conversion (%)[b]	% **C**[b] [yield][c]	e.e. (%)[d]
1	**(*S*)-8d**	2-butanone	>99	47[f] [34]	80 (*S*)
2	**(*S*)-8m**	2-butanone	>99	46[g] [38]	80 (*S*)
3	**(*S*)-8d**	MeTHF	99	55[h] [50]	78 (*S*)
4	**(*R*)-8m**	MeTHF	87	48[i] [38]	79 (*R*)
5[e]	**(*S*)-8d**	toluene	>99	41[j] [40]	84 (*S*)

[a] Unless otherwise stated, reactions were carried out using 0.5 mmol of *N*-tosyl-*3*-pyrroline, 1 mol% catalyst, 5.0 equiv. water, 10 mol% LiCl and 10 mol% PTSA hydrate at 60 bar CO at 70 °C in 1.5 ml of degassed butanone. [b] Conversion determined by ^{1}H NMR using 1-methylnaphthalene as internal standard. [c] Pure acid isolated after acid/base extraction. [d] Enantioselectivity determined using chiral HPLC. (*S*)-Configured catalyst gives (*S*)-configured product and *vice versa.* [e] 2.5 equiv. water, 70 bar CO. [f] **D**+**E** 28%, **F** 22%. [g] **D**+**E** 24%, **F** 24%. [h] **F** 36%. [i] **F** 36%. [j] **F** 42%.



Scheme 4. From a hydroxycarbonylation of Ts-3-Py at lower pressure in acetone solvent, an acetone addition product can be isolated.

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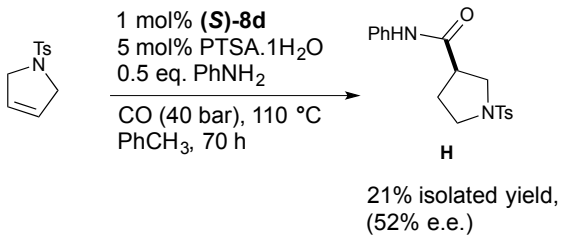
Testing of less sterically hindered catalysts: (iii) aminocarbonylation.
Water (hydroxycarbonylation) and alcohols (alkoxycarbonylation) have been widely used as nucleophiles in the palladium catalysed carbonylation reaction of alkenes with carbon monoxide. The use of other nucleophiles such as amines has received much less attention probably due to the harsh conditions and the formation of undesired by-products.[2f, 9] That was also the case in our hands when catalyst **8d** was studied in the enantioselective aminocarbonylation of N-tosyl-3-pyrroline. Nevertheless, catalyst **8d** afforded amine **H** with an e.e. of 52% under the reaction conditions shown in Scheme 5. This result, to the best of our knowledge, is the first example of an enantioselective intermolecular catalytic aminocarbonylation of an alkene, but further work is needed to improve reaction rate and enantioselectivity in the reaction; so far changes in pressure stoichiometry, solvents and temperatures did not improve on this result.



Scheme 5. Palladium catalysed enantioselective intermolecular hydroaminocarbonylation is possible, but is significantly more challenging than alkoxycarbonylations.

Conclusions:

Methoxycarbonylation of *N*-tosyl-3-pyrroline under a pretty standard set of conditions for this reaction does not proceed to any great extent, even when a very active catalyst for ethylene methoxycarbonylation is used. DFT calculations reveal that the formation of $[(DTBPX)Pd(H)(alkene)]^+$ from the stable resting state $[(DTBPX)Pd(CO)(H)]^+$ is an uphill process. These calculations show that the barrier for this type of reaction is far lower when the bulky diphosphine ligand with *tert*-butyl substituents is exchanged for a PH_2 analogue. Following on from this, three changes to the standard conditions were employed successfully, namely the use of a less bulky (normally less reactive) catalyst, the use of higher pressure, and the use of lower methanol concentrations. These lead to a workable level of chemoselectivity and enantiomerically enriched esters to be isolated in pure form. We have shown that enantioselective hydroxycarbonylation is also possible with 80% e.e. The side products that predominate under 'standard conditions', or that are present as separable minor products under optimised conditions, have been identified and characterised and in some cases isolated in a preparative manner. The side products stem from the intermediate Pd-alkyl species undergoing β-hydride elimination to give the 2-pyrroline derivative instead of migratory insertion of CO. The isomerised alkene readily stabilises carbo-cation intermediates formed by protonation, so undergoes addition reactions with nucleophiles present in the reaction media (water, methanol, ketone solvents). Given the interest in catalytic isomerisation of alkenes over the years, it is possible knowledge of this reactivity could have some value as well. The catalytic turnover is below that observed using simpler alkenes like styrene, and further development of new chiral catalysts for enantioselective alkene carbonylation is still very much desired.

Experimental.

Full details of catalytic experiments, analytical data and NMR spectra are available in the ESI.
For research data (NMR f.i.d's and computational data), see:
http://dx.doi.org/10.17630/bc6e299a-35e0-410c-9119-20559f0ffdad

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Computational Methodology

Density Functional Theory (DFT) was utilised to investigate possible side reactions leading to the *N,O*-acetal product and to explore possibilities for inhibition under CO pressure. In this computational study 1-(methylsulfonyl)-2,5-dihydropyrrole (further referred to as Ms-3-Py) was used as a model system for 1-(tosyl)-2,5-dihydropyrrole due to reduced computational cost associated with replacing the phenyl moiety with methyl. Due to the preferential binding modes of the pyrrole substrate we do not anticipate a large difference in steric impact on potential reaction paths between these groups. The side product 1-(methylsulfonyl)-2,3-dihydropyrrole is denoted as Ms-2-Py throughout this section and the full DTBPX ligand was used for all calculations except where noted (Scheme 2, red).

The BP86 [11,12] GGA functional was used for all optimisations to either minima or transition states (TS). The latter were found using scans and coordinate driving methods (with subsequent direct optimisation to the TS) or the QST3[13,14] algorithm, and were confirmed using intrinsic reaction coordinate calculations as well as checking for the correct number of imaginary frequencies. Frequencies were computed using a harmonic approximation and thermochemical corrections determined at 1 atm and 298.15 K. In this optimisation protocol a mixed 6-31G*(*) basis set, where additional polarisation functions were applied to select "reactive" hydrogens (those of the hydride moiety and substrates), was used to describe the non-metal atoms while the SSD pseudopotential[15-17] and corresponding outer electron basis set was employed to model palladium, inclusive of scalar relativistic effects. For all optimisations density fitting, as implemented in Gaussian 09,[18] was employed for expedited computation times using the automated auxiliary basis set specification. This level of theory is further denoted as BP86/ECP1.

Further refinements to the electronic energy were made by way of single point calculations on the BP86/ECP1 optimised geometries. These were undertaken using the B97-D2[19,20] functional, inclusive of dispersion, and a larger 6-311+G** basis set on the phosphorus atoms and those of the substrates. The remaining atoms of the bidentate diphosphine ligands were given the 6-31G* basis set while the SDD basis set and pseudopotential[15-17] were used for palladium. This level of theory is further referred to as B97-D2/ECP2 and to it were added corrections for bulk solvation through a polarisable continuum model (PCM)[21-22] with dielectric constant corresponding to methanol. Dispersion corrections were only included at the level of the single-point energy calculations, not at that of the optimisations, because it has been shown for bulky phosphine complexes that binding energies are not very sensitive to the level of geometry optimisation.[23a] At our chosen level some of the Pd···C bond distances in the minima may be somewhat overestimated (exceeding 2.3 Å in the η^2-complexes, cf. Figure 2, although Pd···C bond distances approaching 2.3 Å are also known experimentally[24]).

Enthalpies or free energies are determined from thermochemical corrections of the geometries obtained at the BP86/ECP1 level and are applied to electronic energies, including PCM corrections, at the level of B97-D2/ECP2 on the BP86/ECP1 structures. This or similar levels have performed well in previous studies in the context of homogeneous catalysis.[23]

Footnotes:

** A dissociative pathway, where CO dissociates first under formation of a coordinatively unsaturated $[(DTBPX)Pd(H)]^+$, is unfavorable (computed ΔH = 23.3 kcal/mol and ΔG = 12.7 kcal/mol), making the associative pathway discussed here more likely. Because **1A** is not indicated to be a true intermediate at our final level (where it is slightly higher in free energy than the preceding **TS1-1A**, see Scheme 2), the mechanism would rather be classified as associative

interchange; Note that **TS1-1A** and **1A** are true transition state and minimum, respectively, at the lower BP86/ECP1 level of optimisation.

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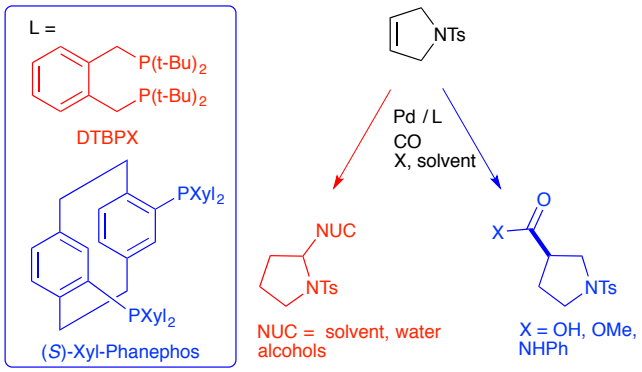
Isomerisation versus carbonylative pathways in the hydroxy-carbonylation, methoxy-carbonylation, and amino-carbonylation of *N*-tosyl 3-pyrroline.

José A. Fuentes,[a] Jamie T. Durrani,[a] Stuart M. Leckie,[a] Luke Crawford,[a] Michael Bühl*[a], and Matthew L Clarke*[a]

DFT calculations show that accessing the desired carbonylation cycle using the Pd/DTBPX catalyst is problematic due to the ready reverse reaction to the stable resting state [Pd(H)(DTBPX)(CO)], and being side-tracked into isomerisation pathways (red). Using less bulky, normally less effective, members of Pd/ Phanephos family of catalysts under higher pressures enables carbonylation products to be formed with good e.e.



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