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Experimental and kinetic modelling study of NC palladacycles mechanosynthesis†

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Ball mill mechanosynthesis provides a method for direct C–H activation to prepare NC palladacycle precatalysts *via* liquid-assisted grinding (LAG). Methanol and dimethylsulfoxide were used as non-innocent LAG reagents, coordinating to the Pd center and producing more reactive intermediates to speed reactions. Kinetic modelling results are consistent with a mechanism of nucleation and autocatalytic growth in these processes.

Introduction

Molecular mechanosynthesis, production of small molecules and complexes *via* the introduction of mechanical energy, presents an exciting opportunity for more sustainable synthesis due to the eliminated use of solvent and higher yields.[1–4] However, balling milling and other mechanosynthetic methods are still not widely adopted in synthetic laboratories. A more thorough kinetic understanding of mechanosynthesis was recently highlighted as being necessary for wider adoption of the technique.[5] Our group[6–9] and others[10–17] have determined the models[18,19] developed for the preparation of extended networks and co-crystals are applicable to molecular mechanosynthesis. *In situ* monitoring techniques specifically modified for use with a mill (*e.g.* IR[20,21] or Raman[22–25] spectroscopy, X-ray diffractometry,[23,26–30]) are generally seen as ideal for these studies based on a variety of measures.[20–30] However, there are trade-offs to *in situ* methods, as has been recently reviewed.[31] Multi-purpose, *ex situ* analysis methods democratize mechanochemistry for researchers interested in inexpensive, sustainable routes to products rather than the synthesis technique. In many cases, NMR analysis is ideal due to the rapid analysis timescale in comparison to slow solid-state reaction in the absence of milling.[6–9] By combining accessible monitoring strategies with simple, intuitive reaction models, mechanosynthesis becomes a more attractive replacement for traditional solution methods.

The use of ball milling for direct C–H activation by palladium species has been previously demonstrated, and this work extends that methodology to high value precatalysts.[8,32] Palladacycle precatalysts are used for a wide variety of carbon–carbon and carbon–heteroatom bond formation reactions in the pharmaceutical and other industries[33] to produce active Pd(0) catalysts *in situ* during coupling reactions including Mizoroki–Heck, Suzuki–Miyaura, Stille, and Sonogashira coupling.[34–37] The precatalysts in Fig. 1 belong to a widely-used class of compounds that are tremendously resource wasteful in their production. Although characterized as the "most powerful precatalyst in C–C and C–heteroatom coupling",[37] the 2-aminobiphenyl palladacycle (**1**, Fig. 1) is commonly prepared in 75% yield *via* a process taking one week.[38] Here the use of liquid assisted grinding (LAG) gives quantitative yield in just over two hours, yet uses only microliters of added liquid.

LAG agents can have many roles in increasing reaction rate. Partially dissolved reagents and/or increased mixture tractability[39–41] are common results of LAG. Borrowing from the terminology of solution chemistry, the reactions herein utilize what we have termed "non-innocent" LAG.[9] Non-innocent solvents are both solvent and reagent. Here dimethyl sulfoxide (DMSO) and methanol are used as non-innocent LAG agents with $PdCl_2$ and palladium acetate, $Pd(OAc)_2$. $PdCl_2$ and $Pd(OAc)_2$ both react quickly with DMSO to produce adducts,[42–44] while methanol and $Pd(OAc)_2$ produce methoxo-species with concurrent production of acetic acid.[45] These more reactive

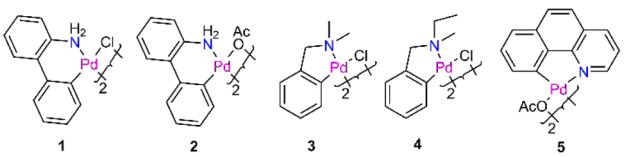

Fig. 1 Complexes mechanosynthesized for this research.

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Table 1 $Pd(OAc)_2$ (**1**, **2**, and **5**) or $PdCl_2$ (**3** and **4**) and various amines were reacted in 5 mL polytetrafluorethylene (PTFE) vials using two 6.35 mm stainless steel balls using a SPEX 8000M ball mill. Specific details on reaction conditions can be found in the ESI. Conversion fractions (α) and milling times determined as the average of three replicates by ^{1}H NMR spectroscopy and compared to solution reaction results. Mechanosynthesis were termed "ineffective" if desired product was not observable by ^{1}H NMR spectroscopy after 120 min milling

	Mechanosynthesis conversion fraction (α) and time				
	Neat[a]	$\eta = 0.3$ DMSO-d_6 LAG	$\eta > 0.3$ MeOH LAG	Other LAG	Solution % yield and time
1	Ineffective	0.3 ± 0.1, 120 min	1.00, 135 min ($\eta = 1.2$)		75%, 1 week[38]
2	Ineffective	1.00, 120 min	1.00, 20 min ($\eta = 0.6$)		85%, 24 h (ref. 38)
3[b]	1.00, 240 min	1.00, 120 min	1.00, 20 min ($\eta = 0.9$)	1.00, 30 min[c]	44%, 240 min (ref. 49)
4[b]	1.00, 360 min	1.00, 210 min	1.00, 120 min ($\eta = 0.9$)		[d]
5	0.98 ± 0.02, 330 min	0.95 ± 0.02, 90 min	0.98 ± 0.04, 110 min ($\eta = 0.5$)	0.93 ± 0.01, 150 min[e]	86%, 360 min (ref. 50)
5[b]	0.81 ± 0.03, 300 min				

[a] Where the amine was a liquid (**3** and **4**), the amine volume was included in the calculation of η, but reactions without additional solvent added are termed "neat". [b] Na_2CO_3 was also added to this reaction mixture. [c] $\eta = 0.3$ MeOH LAG. [d] New compound. [e] $\eta = 0.5$ EtOH LAG.

species formed *via* inner-sphere coordination of the LAG agent then undergo cyclization with an added amine, regenerating the LAG species while forming the palladacycle.

Kinetic analysis allows for greater understanding of how LAG affects reactions. These agents are critical to increasing the rates of reactions and can even allow for formation of products that cannot be made under neat conditions. However, very little kinetic analysis of molecular mechanochemistry has been made either by examining LAG conversion over time or through kinetic modeling.[8,9,46–48]

Synthesis

In LAG reactions, the η-parameter is calculated in μL liquid per mg solid, and $0 < \eta \leq 2$. LAG reaction mixtures are often pastes, but the same η value may give very different results depending on the added liquid. In this study, parameters were varied to achieve a paste of the desired palladium reagent, amine, and LAG agent (Table 1). Notably, DMSO LAG reaction mixtures had much lower η-parameters to avoid runny mixtures.

Conversion fraction (α) over time was determined by NMR spectroscopy, and spectra are provided in the ESI.† In *ex situ* analysis, the potential for sampling to affect results is always a concern. While solution reaction during the time required for the analysis was negligible, other difficulties do arise with *ex situ* methods.

To mediate issues that might occur from sampling heterogenous milling mixtures,[31] all kinetic models were fitted to points taken in triplicate, as shown for in Fig. 2 (top) for the preparation of **1**. Where possible, reactions mixtures were sampled multiple times in order to minimize resources use. Kinetic data were then fitted to the average results of three reactions. These are referred to as "multi-sample" analyses and are represented with solid data points in all figures. To determine if sampling affected conversion, "single-sample" analyses were performed by sampling reaction mixtures only once. Single-sample data are shown by open data points in all figures. Preparation of **1** showed good agreement between multi-and single-sample data, and no sampling effect. When sampling did affect conversion, kinetic modelling was fitted to single-sample data.

Two common causes of *ex situ* sampling effect were observed. The first was poor bulk mixing. While milling balls provide mechanical energy to induce reaction, they also homogenize the reaction mixture. The physical properties of molecular mechanosynthetic mixtures can vary drastically during the course of reaction,[7,9] and a mill may provide sufficient energy for reaction, without homogenizing the reaction mixture. Here, the methanol LAG syntheses of **2** suffered from poor bulk mixing. Ineffectively homogenized mixtures are hand-mixed to a more uniform consistency during sampling, allowing for faster conversion compared to reaction mixtures sampled only once (Fig. 3). If reactions are hand-mixed at multiple intervals while only sampling once, conversion agrees with multi-sample results (Fig. 3). The second common sampling effect is loss of volatile components as the vial is opened for milling. In the MeOH LAG mechanosyntheses of **2** and **3**, component loss was so pronounced that only single time point data could be used for modelling (Fig. 2).

Direct mechanosynthesis of **1** from $PdCl_2$ and 2-aminobiphenyl was ineffective, and neither addition of Na_2CO_3 nor DMSO LAG improves effectiveness. Palladium acetate is an effective palladium source for this reaction, and addition of NaCl allows for production of the chloride-bridged palladacycle. NMR analysis shows that **2** is produced as an intermediate in this process, and can be produced as the desired product by omitting NaCl from the reaction mixture; however, these mechanosyntheses are ineffective in the absence of LAG agents (Fig. 2). In both cases, methanol LAG is significantly more effective than DMSO LAG.

As *N*,*N*-dimethylbenzylamine (HDMBA) and *N*-ethyl-*N*-methylbenzylamine (HEMBA) are liquids, η changes during syntheses of **3** and **4**, and neat reactions have an initial $\eta = 0.2$. Neat mechanosynthesis of $PdCl_2$ and HDMBA does not produce the desired palladacycle (**3**) even after 150 min of milling. Addition of Na_2CO_3 did allow for formation of product, but this occurred with significant induction period (Figure 2, **3**). LAG significantly improved reaction times, but liquid selection was critical. Methanol was a more effective LAG solvent than DMSO, and increasing the η parameter above 0.3 produced slightly

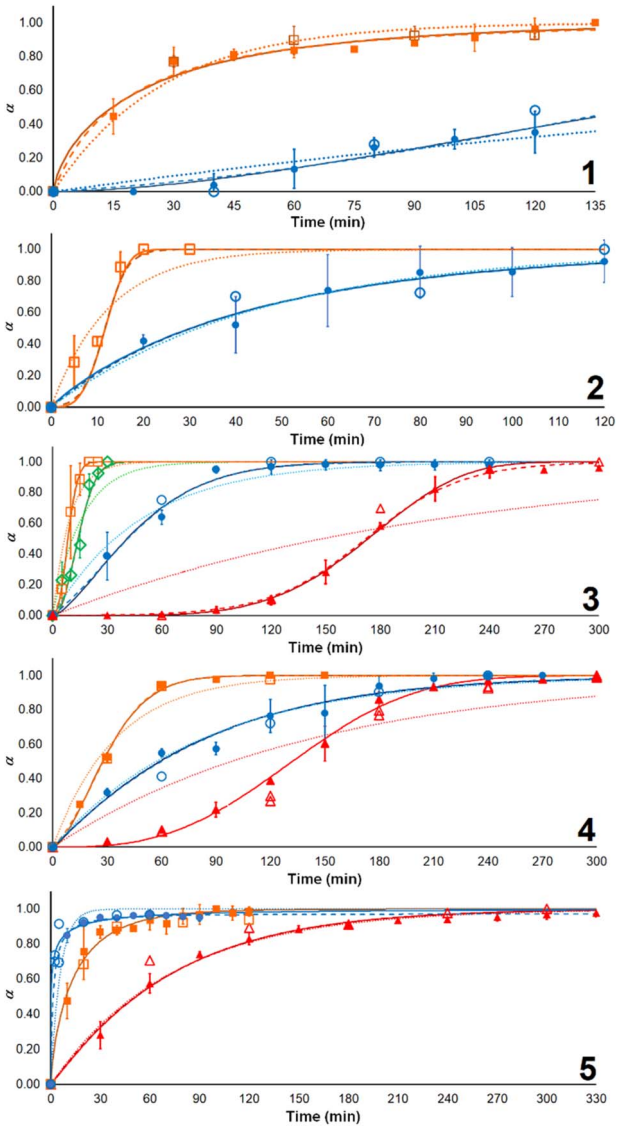

Fig. 2 Conversion over time during mechanosynthesis under neat (▲, △), $\eta = 0.3$ DMSO-d_6 LAG (●, ○), $\eta = 0.3$ MeOH LAG (◆, ◇), and $\eta >$ 0.3 MeOH LAG (■, □) conditions for reaction mixtures sampled once (△, ○, ◇, □) and multiple times (▲, ●, ◆, ■) for compounds **1**, **2**, **3**, **4**, and **5** (top to bottom). JMAYK (solid lines), FW (dashed lines), and first order modelling (dotted lines) results shown.

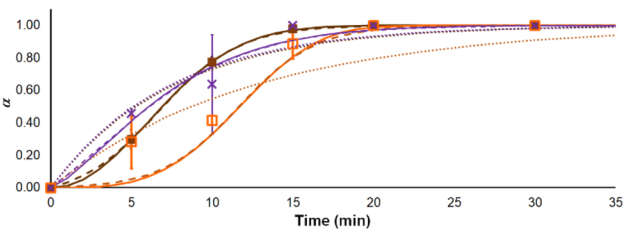

Fig. 3 Measured conversion in mechanosynthesis of **2** is affected by sampling. Hand-mixing at 5 min intervals but sampling only once (×) gives similar results to sampling reaction mixtures multiple times (■). Combining the results of 15 reactions each sampled once gives conversion obtained solely through milling (□). JMAYK (solid lines), FW (dashed lines), and first order modelling (dotted lines) shown.

improved reaction times. Reactions with *N*-ethyl-*N*-methylbenzylamine gave similar results (Figure 2, **4**).

Compound **5** (Fig. 2) can be mechanosynthesized neat, but the process is slow. Methanol LAG makes the process much more effective, as was observed for all the palladacycles here. Ethanol LAG proved similarly effective albeit with slightly lower conversion (Fig. 4). When $PdCl_2$ was used as the palladium reagent (**3**, **4**), an external base was critical to the mechanosynthesis, but in syntheses involving palladium acetate (*e.g.* **5**), addition of Na_2CO_3 decreased conversion.

Kinetic analysis

The Allenbaugh group has previously described the fitting of kinetic data to various models.[7–9] The Johnson–Mehl–Avrami–Yerofeev–Kolmogorov (JMAYK, eqn (1)) and Finke–Watzky (FW, eqn (2))[51,52] models were developed from a mechanism of nucleation followed by autocatalytic growth[53] The JMAYK model utilized herein was developed by Finney and Finke to give its rate related parameter (k) time^{-1} units, and n is Avrami exponent. The JMAYK model is empirical, while the mechanistically derived FW model has separate rate related parameters for nucleation (k_1) and autocatalytic growth (k_2). In the FW model, $k_2' = k_2[A]_0$ to remove concentration dependence.

$$\alpha = 1 - e^{-(kt)^n} \quad (1)$$

$$\alpha = 1 - \frac{k_1 + k_2'}{k_2' + k_1 e^{(k_1 + k_2')t}} \quad (2)$$

Finney and Finke previously demonstrated that the empirically derived JMAYK model can be correlated to the FW model, with both k and n being related to both nucleation and autocatalytic growth steps, effectively explaining why the FW and JMAYK models often fit data equally well,[7–9,53] as is also observed here. These models converge if the mechanism of the reaction becomes entirely nucleation based (*i.e.* $k_2' = 0$). In that case, $n = 1$ and $k = k_1$. This model (eqn (3)) has gone through various names in the literature,[18,54] but will be referred to as the first order model here due to the similarities with first order solution kinetics. The first order model differs most strikingly from the JMAYK and FW models in that the JMAYK and FW models allow for an induction period at the start of a reaction where conversion is very slow. This followed by a period of acceleratory conversion, before conversion slows leading to an overall "S-shaped" conversion *vs.* time plot. To be well-fitted by a first order model, the data must lack a significant induction period. Induction periods are most noticeable when $k_2' \gg k_1$, and k_1 values are small, resulting in a pronounced S-shape. As k_1 becomes larger, the length of the induction period decreases, and the resulting curve becomes more first order in appearance. A data set may be well-fitted by a first order kinetic model while still having a considerable autocatalytic growth parameter if k_1 is large. In those cases, the first order model provides a simple method for predicting completion time, but glosses over the complexity of the reaction mechanism.

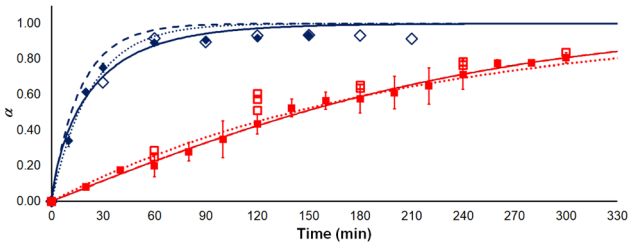

Fig. 4 Compound **5** can also be prepared by $\eta = 0.5$ EtOH LAG (◆, ◇) and with the addition of Na_2CO_3 to the neat reaction mixture (■, □). Data shown for reaction mixtures sampled once (◇, □) and those sampled multiple times (◆, ■). JMAYK (solid lines), FW (dashed lines), and first order modelling (dotted lines) shown.

$$\alpha = 1 - e^{-kt} = 1 - e^{-k_1 t} \quad (3)$$

Modelling results were evaluated using Akaike weights (w) and evidence ratios (ER) as discussed previously[8] and in the ESI.† Because the JMAYK and FW models fit the data equally well, the more interesting comparison can be made between the FW and first order models. For this comparison, the FW model is preferred over the empirical JMAYK model because there are separate parameters for the nucleation and autocatalytic growth steps. In accordance the original measures of significance developed by Finney and Finke,[53] ER $\geq 10^4$ show the FW model fits the data significantly better, while ER $\leq 10^{-4}$ show that the first order model is preferred (eqn (4)). ER between those limits result from two models that fit the data equally well within experimental error. ER data are provided in Tables 2 and 3 along with coefficient of determination (R^2) values. Although R^2 values provide a measure of how well a statistical model predicts an outcome, the R^2 value obtained from one model cannot be directly compared to the R^2 value from another. Finney and Finke[53] address the problems with comparing R^2 values extensively. Most notably for this study, the FW and JMAYK models have two parameters, while the first order model has only one. This can allow for a model to give a lower R^2 value, while still giving a statistically equivalent fitting to a model with a higher R^2 value as determined by ER (*e.g.* **1d**, Table 3).

$$\mathrm{ER} = \frac{w_{\mathrm{FW}}}{w_{\mathrm{First\ order}}} \quad (4)$$

Recently there has been work in more clearly differentiating the macroscopic and microscopic processes affecting mechanosynthesis rates.[55] The macroscopic effects of milling (*e.g.* particle size reduction and uniform distribution of reagents) are termed "secondary" processes. The primary processes are those involved in chemical bond breakage/formation. In terms of the nucleation and autocatalytic growth model proposed for these reactions, both steps could be affected by secondary processes. Previous work by our group[9] has shown that the nucleation sites are likely pre-existing on the surface of $PdCl_2$ crystals, and the facility with which reagents move to and from these sites affects reaction rate. Autocatalytic growth occurs from these higher energy "defect" sites in the crystal, and might be aided by secondary processes further deforming the defect site. Products **3** and **4** are prepared from liquid amines. Their preparation occurs with considerable induction period, and the data are

Table 2 Kinetic results for mechanosyntheses of **3** and **4** using Na_2CO_3 under neat (**n**) and LAG conditions with methanol (**m**), ethanol (**e**), and DMSO (**d**). Due to the liquid amine, neat reactions have $\eta = 0.2$. Unless noted, data from multi-sample results

	Model parameters			
Reaction η	JMAYK	FW	1st order	ER
3n $\eta = 0.2$	$k = 0.0053$	$k_1 = 5.7 \times 10^{-5}$	$k = 0.0047$	1.6×10^{11}
	$n = 4.7774$	$k_2' = 0.0377$		
	$R^2 = 0.9974$ $w = 0.2193$	$R^2 = 0.9982$ $w = 0.7807$	$R^2 = 0.7068$ $w = 5.0 \times 10^{-12}$	
3d $\eta = 0.3$	$k = 0.0190$	$k_1 = 0.0098$	$k = 0.0203$	1.7×10^{1}
	$n = 1.4553$	$k_2' = 0.0287$		
	$R^2 = 0.9901$ $w = 0.4189$	$R^2 = 0.9906$ $w = 0.5487$	$R^2 = 0.9746$ $w = 0.0324$	
3m[a] $\eta = 0.3$	$k = 0.0604$	$k_1 = 0.0113$	$k = 0.0623$	1.3×10^{1}
	$n = 2.1654$	$k_2' = 0.1997$		
	$R^2 = 0.9564$ $w = 0.3221$	$R^2 = 0.9641$ $w = 0.6318$	$R^2 = 0.8655$ $w = 0.0461$	
3m[a] $\eta = 0.9$	$k = 0.1013$	$k_1 = 0.0156$	$k = 0.1071$	2.3×10^{4}
	$n = 2.2436$	$k_2' = 0.3681$		
	$R^2 = 0.9971$ $w = 0.4975$	$R^2 = 0.9971$ $w = 0.5025$	$R^2 = 0.9106$ $w = 1.2 \times 10^{-5}$	
4n $\eta = 0.2$	$k = 0.0067$	$k_1 = 0.0005$	$k = 0.0070$	2.8×10^{12}
	$n = 2.8907$	$k_2' = 0.0311$		
	$R^2 = 0.9773$ $w = 0.0920$	$R^2 = 0.9981$ $w = 0.9080$	$R^2 = 0.8621$ $w = 3.3 \times 10^{-13}$	
4d $\eta = 0.3$	$k = 0.0120$	$k_1 = 0.0107$	$k = 0.0122$	2.8×10^{-1}
	$n = 1.0617$	$k_2' = 0.0034$		
	$R^2 = 0.9776$ $w = 0.4189$	$R^2 = 0.9781$ $w = 0.5487$	$R^2 = 0.9768$ $w = 0.0324$	
4m $\eta = 0.9$	$k = 0.0291$	$k_1 = 0.0111$	$k = 0.0290$	9.6×10^{3}
	$n = 1.6344$	$k_2' = 0.0611$		
	$R^2 = 0.9981$ $w = 0.8237$	$R^2 = 0.9987$ $w = 8.6 \times 10^{-5}$	$R^2 = 0.9696$ $w = 0.1762$	

[a] Single sampling results, three experiments averaged for each data point.

Table 3 Kinetic results for mechanosyntheses of **1**, **2**, and **5** under neat (**n**) and LAG conditions with methanol (**m**), ethanol (**e**), and DMSO (**d**). Unless noted, data from multi-sample experiments

	Model parameters			
Reaction η	JMAYK	FW	1st order	ER
1d $\eta = 0.3$	$k = 0.0053$	$k_1 = 0.0016$	$k = 0.0033$	2.3
	$n = 1.6761$	$k_2' = 0.0123$		
	$R^2 = 0.9645$ $w = 0.7182$	$R^2 = 0.9487$ $w = 0.1970$	$R^2 = 0.8843$ $w = 0.0847$	
1m $\eta = 1.2$	$k = 0.0406$	$k_1 = 0.0604$	$k = 0.0367$	1.1×10^1
	$n = 0.7059$	$k_2' = -0.0471$		
	$R^2 = 0.9785$ $w = 0.3440$	$R^2 = 0.9812$ $w = 0.6005$	$R^2 = 0.9577$ $w = 0.0555$	
2m $\eta = 0.6$	$k = 0.1216$	$k_1 = 0.0261$	$k = 0.1316$	4.9×10^5
	$n = 2.0990$	$k_2' = 0.3764$		
	$R^2 = 0.9718$ $w = 0.9587$	$R^2 = 0.9722$ $w = 0.0413$	$R^2 = 0.9587$ $w = 8.5 \times 10^{-8}$	
2m[a] $\eta = 0.6$	$k = 0.0769$	$k_1 = 0.0032$	$k = 0.0795$	4.2×10^1
	$n = 3.4791$	$k_2' = 0.4169$		
	$R^2 = 0.9718$ $w = 0.3826$	$R^2 = 0.9722$ $w = 0.6032$	$R^2 = 0.9587$ $w = 0.0142$	
2m[b] $\eta = 0.6$	$k = 0.1258$	$k_1 = 0.0749$	$k = 0.1355$	3.2×10^{-1}
	$n = 1.3724$	$k_2' = 0.1537$		
	$R^2 = 0.9718$ $w = 0.1954$	$R^2 = 0.9722$ $w = 0.6167$	$R^2 = 0.9587$ $w = 0.1879$	
2d $\eta = 0.3$	$k = 0.0221$	$k_1 = 0.0245$	$k = 0.0218$	0.1812
	$n = 0.9143$	$k_2' = -0.0063$		
	$R^2 = 0.9867$ $w = 4.7 \times 10^{-5}$	$R^2 = 0.9862$ $w = 0.8268$	$R^2 = 0.9850$ $w = 0.1732$	
5n[c] $\eta = 0$	$k = 0.0051$	$k_1 = 0.0038$	$k = 0.0049$	1.8×10^2
	$n = 1.1626$	$k_2' = 0.0035$		
	$R^2 = 0.9934$ $w = 3.0 \times 10^{-3}$	$R^2 = 0.9936$ $w = 0.5410$	$R^2 = 0.9855$ $w = 0.4560$	
5n $\eta = 0$	$k = 0.0137$	$k_1 = 0.0129$	$k = 0.0138$	3.1×10^{-1}
	$n = 1.0547$	$k_2' = 0.0022$		
	$R^2 = 0.9943$ $w = 0.2278$	$R^2 = 0.9940$ $w = 0.1810$	$R^2 = 0.9938$ $w = 0.5912$	
5d $\eta = 0.3$	$k = 1.2352$	$k_1 = 0.6684$	$k = 0.1757$	9.1×10^5
	$n = 0.2743$	$k_2' = -0.6885$		
	$R^2 = 0.9980$ $w = 0.0185$	$R^2 = 0.9991$ $w = 0.9815$	$R^2 = 0.9807$ $w = 1.1 \times 10^{-5}$	
5e $\eta = 0.5$	$k = 0.0426$	$k_1 = 0.0634$	$k = 0.0437$	1.3
	$n = 0.7837$	$k_2' = -0.0492$		
	$R^2 = 0.9822$ $w = 0.1657$	$R^2 = 0.9864$ $w = 0.4750$	$R^2 = 0.9771$ $w = 0.3593$	
5m $\eta = 0.5$	$k = 0.0406$	$k_1 = 0.0604$	$k = 0.0367$	
	$n = 0.7059$	$k_2' = -0.0471$		
	$R^2 = 0.9785$ $w = 0.3440$	$R^2 = 0.9812$ $w = 0.6005$	$R^2 = 0.9577$ $w = 0.0555$	2.4×10^1

[a] Single sampling results, three experiments averaged for each data point. [b] Experiments were carried out as in the previous footnote, but the reaction mixtures were manually stirred at intervals in addition to milling. [c] Na_2CO_3 was added to this reaction mixture.

significantly better fitted by FW modelling (Table 2). Addition of a LAG reagent gives much more first order behaviour, and the results of FW and first order modelling are statistically equivalent. This is consistent with a change from a process of slow nucleation and autocatalytic growth to one nucleation is more significant, likely due to the increased reactivity of Pd-solvent adducts compared to $PdCl_2$.

The induction periods observed during neat reactions could also be the result of localized reagent depletion caused by heterogeneous reaction mixtures. Because the amines used in the preparation of **3** and **4** are liquids, very rapid homogenisation of reaction mixtures would be expected, and the effects of secondary processing requirements should be reduced compared to reactions involving solid amines. However, preparations of **3** and **4** require Na_2CO_3 and corresponding increases in the volumes of these reaction mixtures. Since **3** and **4** are not formed in the absence of Na_2CO_3, synthesis of **5** was used to help determine if Na_2CO_3 related secondary processes caused the induction periods. Addition of Na_2CO_3 in the preparation of **5** significantly reduces reaction rate (Fig. 4), but no induction period is observed, and the data are well-fitted by the first order model. Autocatalytic growth is not significant in the neat mechanosynthesis of **5** with or without added Na_2CO_3. Additives may play a more critical kinetic role than the physical state of the amine due to an increase in the secondary mechanochemical processes necessary to bring reagents together. This results in decreased nucleation as reflected in reduced k_1 values.

Among the solid–amine reactions, FW modelling is only significantly better than first order modelling in the methanol LAG synthesis of **2** and the dimethyl sulfoxide LAG mechanosynthesis of **5** (**2m** and **5d**, Table 3). LAG mechanosynthesis of **2** demonstrated a significant initial affect depending on the homogenization of the reaction mixture. Reaction mixtures that had been homogenized either by intentional hand-mixing or by inadvertent mixing during sampling demonstrated reduced induction periods (Fig. 3). This presents an inverse to the effects

of adding Na_2CO_3 to the preparation of **5**, and further demonstrates the importance of secondary processes. In the preparation of **5**, additional material increased the secondary processes necessary for nucleation, decreasing k_1. In the case of **2**, externally promoting secondary processes by hand-mixing increased nucleation and k_1. This increase in nucleation is sufficient to largely eliminate the induction period, leading to the data being equally well fitted by the FW and first order models despite significant autocatalytic growth as demonstrated by the k_2' values.

Although the mechanism of reaction appears to be one of nucleation and autocatalytic growth, selecting conditions to promote rapid nucleation (*e.g.* non-innocent LAG, hand-mixing) eliminates induction periods and speeds overall conversion, leading to first order type behaviour. These results show how exceedingly simple first order reaction kinetics can be used in many cases to predict reaction completion times based on preliminary sampling data which can be easily obtained by NMR spectroscopy. This further demonstrates that mechanochemistry is an applicable method for researchers interested easy transitions from traditional solution preparations to more sustainable mechanosynthetic methods.

Conclusions

A variety of palladacycle precatalysts can be more rapidly and sustainably prepared by mechanosynthesis then by traditional solution methods demonstrating the utility of ball mills for direct C–H activation chemistry. The selection of LAG solvent and ancillary agents such as external bases like Na_2CO_3 can impact the effectiveness of mechanosynthesis. Critically, the failure of neat mechanosynthesis can be overcome by addition of a non-innocent LAG solvent. External monitoring *via* ^{1}H NMR spectroscopy provides a simple, widely available method to monitor these reactions, and simple first order kinetic models can be effective for many of these preparations.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Rachel J. Allenbaugh: conceptualization, data curation, formal analysis, funding acquisition, investigation (equal), project administration, resources, supervision, validation (equal), visualization, writing – original draft preparation, writing – reviewing & editing (lead). Tia M. Ariagno: investigation (equal), validation (equal), writing – reviewing & editing (supporting). Jeffrey Selby: investigation (equal), validation (equal), reviewing & editing (supporting).

Conflicts of interest

There are no conflicts to declare.

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