Active, selective, and stable single-component precatalysts for asymmetric allylic alkylation

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ABSTRACT: The stereoselective construction of new carbon-element bonds is a crucial aspect of organic synthesis. Among the many strategies developed to date, palladium-catalysed asymmetric allylic alkylation is commonly used to access chiral molecules in natural product and active pharmaceutical ingredient synthesis. The use of modular Trost-type ligands and phosphinooxazoline (PHOX) ligands results in generally high stereoselectivity for a wide range of transformations. However, these reactions nearly always require relatively high catalyst loadings (5-10 mol%), reaction-specific catalyst preactivation protocols, and excess chiral ligand to ensure high yield and selectivity. Here we report the isolation and catalytic evaluation of a series of chiral palladium(0) single-component precatalysts that are active for a variety of asymmetric allylic alkylation reactions. The four Trost-type precatalysts in this work are the first characterized examples of stable, isolable Pd complexes with the diphosphines coordinated in the desired κ^2-P,P fashion. All of the palladium(0) complexes are stable for >12 months when stored under nitrogen, and can be handled as solids and even in solution under air for hours without decomposition. A catalytic evaluation of these single-component precatalysts across 9 distinct asymmetric allylic alkylation reactions reveals excellent performance in terms of reactivity, selectivity, practicality, and minimizing palladium and chiral ligand loading. This enables both small-scale multivariate screening studies and preparative scale synthesis of key chiral building blocks, exemplified with the unprecedented enantioselective allylation of hydantoins. The optimized reaction achieves high yield and enantioselectivity with only 0.2 mol% of catalyst (turnover number of 465). These precatalysts will enable development of more efficient and robust asymmetric allylic alkylation reactions toward complex target molecules.

Homogeneous catalysis by transition metal complexes is one of the most powerful technologies in synthetic chemistry. Many of the most efficient and selective methods for the construction of organic molecules and materials are based on metal-catalysed reactions, with applications including bulk chemicals production, natural product synthesis, pharmaceutical manufacturing, and materials preparation. In synthetic organic chemistry, carbon-element bond forming reactions through organopalladium catalysis is without contest the most widely used strategy.[1–6] Key examples include the well-established Stille,[7] Suzuki-Miyaura,[8,9] Sonagashira,[10] Negishi,[11] Mizoroki-Heck,[12,13], and Buchwald-Hartwig reactions,[14] as well as the Pd(0)-catalysed allylation (the Tsuji-Trost reaction).[2,15–19] This latter example is well represented in natural product synthesis,[20–24] where it enables stereoselective Csp^3–Csp^3 and Csp^3–Nsp^3 couplings through asymmetric allylation of carbon and nitrogen nucleophiles.

A key aspect of all catalytic reactions is the generation of an active catalyst from stable precursor compounds. In many synthetic applications involving homogeneous organometallic catalysis, this is achieved through *in situ* combinations of supporting ligands and a metal source that are expected to assemble into an active form. While operationally convenient, this approach often leads to inefficient

catalyst generation, negatively impacting activity, reproducibility, and/or selectivity. An alternative strategy is to employ single-component precatalysts. These compounds already contain the required supporting ligands, along with carefully chosen reactive sites that lead to rapid and complete activation. Key examples include group 4 metallocene and post-metallocene systems for alkene polymerization;[25–28] Mo- and Ru-based complexes for olefin metathesis;[29–32] Ru-, Rh-, and Ir-based hydrogenation catalysts;[33–35] and Pd-carbene or phosphine complexes for cross-coupling reactions[36–41] (Figure 1A).

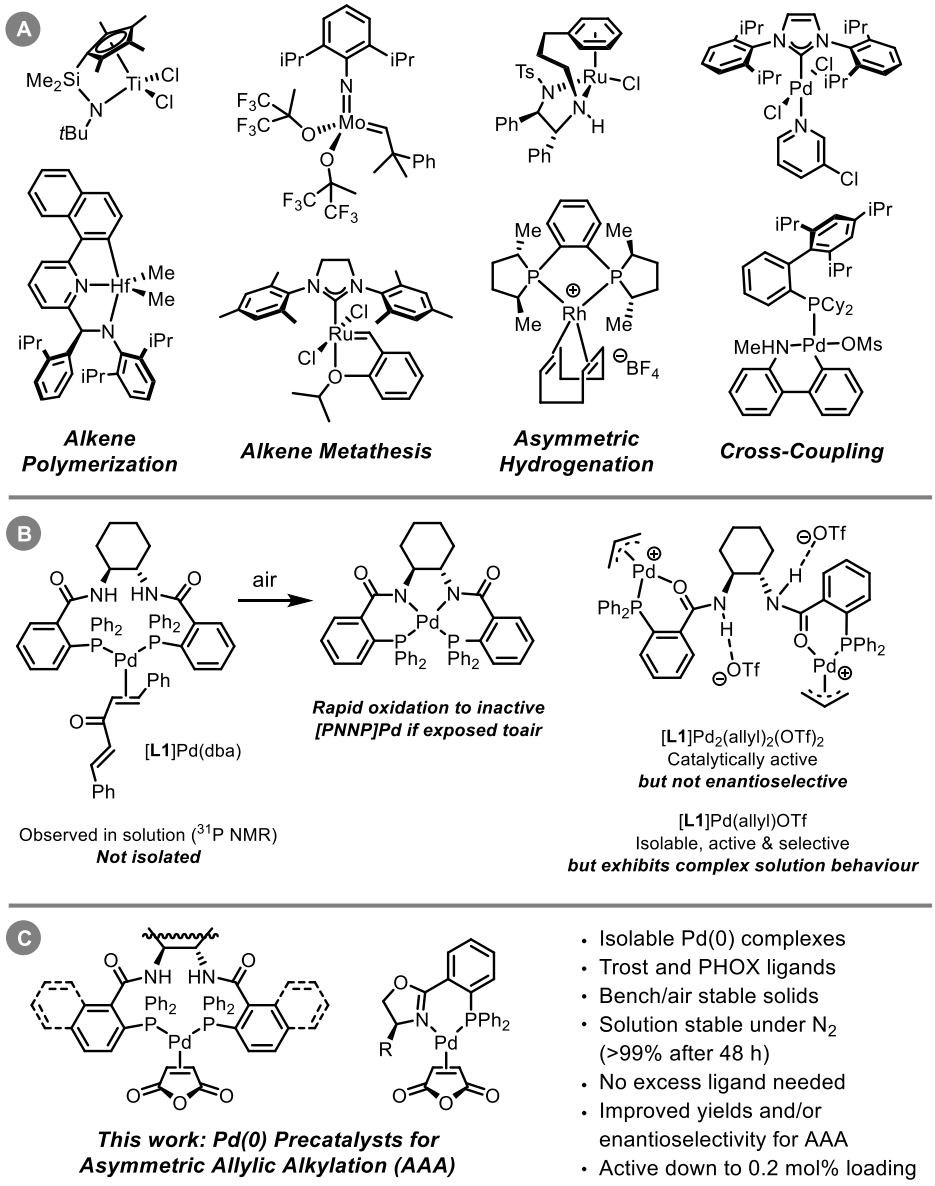

Figure 1. (**A**) Exemplar homogeneous organometallic precatalysts for specific transformations. (**B**) Challenges with accessing precatalysts containing Trost-type ligands, including rapid oxidation of Pd(0) species derived from $Pd_2(dba)_3$, and complex solution behaviour of Pd(II) allyl species. (**C**) This work: new single-component Pd(0) precatalysts for asymmetric allylic alkylation.

Despite the success and widespread application of Pd-catalysed asymmetric allylic alkylation, single-component precatalysts are only rarely used for this chemistry.[2,17–19,42–46] Instead, these reactions mainly rely on *in situ* catalyst generation, often using prolonged pre-treatment of an achiral Pd source (*e.g.* $Pd_2(dba)_3$ or $[Pd(allyl)Cl]_2$) with excess chiral ligand to ensure complete metalation. In some cases, this also requires heating for extended periods of time, rendering the process significantly more prone to

reproducibily issues. Furthermore, the use of $Pd_2(dba)_3$ is itself a reproducibily concern, given the known issues of quality and stability for this compound.[47,48] Finally, the stabilizing ligands (*e.g*. dba) must be removed from the desired product during purification, which can be non-trivial.

While a few isolable complexes of phosphinooxazoline (PHOX) type ligands to Pd(0) have been reported in the literature,[45,49–55] accessing any isolable Pd complexes of the chiral diamide bisphosphine ligand platform – the eponymous Trost ligands – has proven particularly challenging (Figure 1B). Early work from Trost, Breit, and Organ established that mixing (*S*,*S*)-1,2-diaminocyclohexane-*N*,*N'*-bis(2-diphenylphosphinobenzoyl) [(*S,S*)-^{Ph}DACH, **L1**] with $Pd_2(dba)_3$ generates a species consistent with [**L1**]Pd(dba), exhibiting a κ^2-(P,P) coordination mode; however, this species was not isolated.[56] Furthermore, this compound rapidly oxidizes when exposed to air, generating the catalytically inactive bis(amidate) complex [PNNP]Pd^{II}, making it unsuitable as an isolated precatalyst.[57,58]

Lloyd-Jones and co-workers reported a dipalladium(II) complex with **L1** where each Pd centre is coordinated by one phosphine and one carbonyl oxygen ([**L1**]$Pd_2(allyl)_2(OTf)_2$, Figure 1B).[42] While this compound is catalytically active, it gives essentially racemic product during an attempted kinetic resolution of (±)-cyclopent-2-en-1-yl pivalate with $NaCH(CO_2Me)_2$, likely due to the κ^2-(P,O) rather than κ^2-(P,P) coordination mode. A compound of the empirical formula [**L1**]Pd(allyl)(OTf) can be isolated when using a 1:1 stoichiometry of **L1** to [Pd(allyl)$(MeCN)_2$][OTf]. While this compound is active and enantioselective, it is not well-defined and exhibits complex concentration-dependent solution behaviour, generating multiple Pd-containing species including [**L1**]$Pd_2(allyl)_2(OTf)_2$ and higher oligomers.[42,44] To the best of our knowledge, [**L1**]Pd(allyl)(OTf) is the only example of an isolable single-component precatalyst based on the Trost ligand platform, though the complexities of its synthesis and characterization seem to have precluded its wider use.

Here we report a new class of stable and isolable chiral Pd precatalysts for asymmetric allylic alkylations (Figure 1C). These Pd(0) complexes, which are based on either Trost-type or PHOX-type ligands, are easily prepared, well defined, monomeric, readily handled without the need for an inert atmosphere or glovebox. In addition, they are highly effective as single-component precatalysts for a multitude of asymmetric allylic alkylation reactions, operating with improved yield, selectivity, catalyst loading, and/or operational simplicity relative to established systems. The advantages of this precatalyst class is exemplified by an ability to catalyse the unprecedented enantioselective allylation of a hydantoin-derived nucleophile, exhibiting high yield and stereoselectivity with only 0.2 mol% catalyst on gram scale.

RESULTS AND DISCUSSION

Precatalyst synthesis and characterization. Given the aforementioned challenges with accessing discrete, stable Pd precatalysts with Trost-type ligands, we targeted Pd(0) species with an appropriate stabilizing ligand. We first examined reactivity of ^{DMP}DAB-Pd-MAH – a new Pd(0) source we recently reported[59] – toward a set of six chiral ligands (**L1**-**L6**, Figure 2). In each case, reaction monitoring by ^{1}H and ^{31}P NMR spectroscopy revealed complete consumption of ^{DMP}DAB-Pd-MAH and concomitant formation of L*-Pd-MAH (**1**-**6**) in <20 min at room temperature in THF; this rapid metalation is also evident by a near-immediate colour change from red/purple to yellow. On preparative-scale, **1**-**6** can be easily isolated and purified by simple precipitation to remove the soluble ^{DMP}DAB, giving the chiral Pd(0) complexes in 63-90% isolated yield. These complexes are derived from the most common chiral ligands used in asymmetric allylation: four Trost ligands (**L1**-**L4**), and two PHOX ligands (**L5** and **L6**). In addition to full characterization by multinuclear NMR spectroscopy (*vide infra* and SI) and high-resolution mass spectrometry, we have obtained solid-state molecular structures by X-ray crystallography for three complexes (**2**, **4**, and **6**). Surprisingly, complexes **1**-**4** represent the first characterized examples of isolable Pd complexes containing Trost-type ligands bearing the desired κ^2-P,P binding mode. This is especially noteworthy given the long and extensive history of these ligands in Pd catalysis.

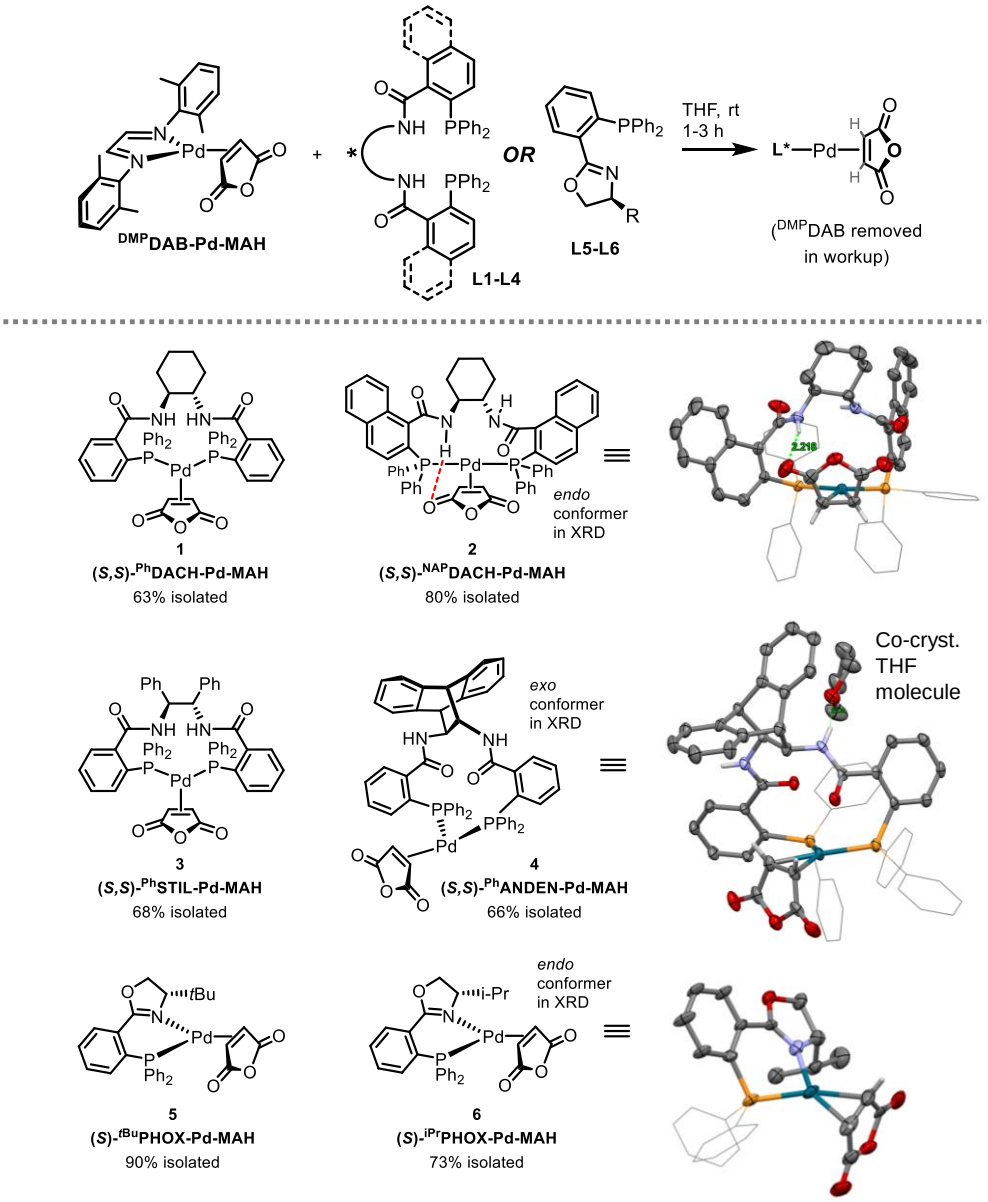

Figure 2. Synthesis of chiral Pd(0) precatalysts **1**-**6** *via* ligand substitution of ^{DMP}DAB-Pd-MAH. Solid-state molecular structures (X-ray diffraction, 50% probability ellipsoids, Ph groups on phosphorus shown in wireframe for clarity) shown for compounds **2**, **4**, and **6**; crystal/diffraction data and metrical parameters are in Supporting Information. Intramolecular H-bond in **2** indicated with green dashed line, NH---O distance = 2.22 Å. Intermolecular H-bond in **4** between amide N–H and THF molecule indicated with green dashed line, NH---O_{THF} distance = 2.23 Å.

The solid-state molecular structures of **2** and **4** reveal two distinct conformations. In complex **2**, the MAH binds with the carbonyl groups pointing toward the chiral tether of the ^{NAP}DACH ligand (*endo* conformation). This enables an intramolecular hydrogen bond between an amide N–H and a carbonyl oxygen from MAH. Importantly, this type of hydrogen bonding interaction between ligand and substrate is proposed as a mechanism for stereoinduction in many asymmetric allylic alkylation reactions.[60] Here, we are able to directly observe this interaction in both the solid state and in solution (*vide infra*). In contrast, the ^{Ph}ANDEN complex **4** has the MAH oxygens pointing away from the chiral tether (*exo* conformation). Notably, there is an intermolecular hydrogen bond observed between an amide N–H and a co-crystallized THF molecule. These alternative geometries are likely due to the flexibility of the large macrocyclic chelate in these Trost-type complexes. The solid-state molecular structure of the ^{iPr}PHOX complex **6** reveals an *endo* conformation with respect to the isopropyl group.

Solution-phase characterization of complexes **1**-**6** by multinuclear and multidimensional NMR spectroscopy reveals the presence of two distinct species in each case. For both PHOX-based complexes **5** and **6**, these two species are present in an approximately 1:1 ratio, as indicated by ^{1}H and ^{31}P NMR spectroscopy in either d_2-DCM or d_8-THF. We attribute this solution behaviour to the presence of both *endo* and *exo* conformers, with no clear energetic preference for either.[45,53] This conformer assignment is supported by 2D NMR spectroscopy characterization data, including 2D NOESY (see SI for details).

For complex **1**, ^{31}P NMR spectra obtained in either d_2-DCM or d_8-THF also contain two sets of signals, each of which is a matching pair of doublets that is characteristic of bidentate κ^2-P,P coordination to Pd (Figure 3A). In DCM, the two sets of signals have a 55:45 peak area ratio; in contrast, in THF there is a 14:1 peak area ratio between the major and minor signals. As for **5** and **6**, we attribute this to the presence of two distinct conformers, the ratio of which has a clear solvent dependence. We have ruled out a monomer/dimer equilibrium as the source of these two components by observing no change to the peak area ratio of major to minor species at different initial concentrations of **1**. We have also established the interconversion of these two species by analysing their molar ratio as a function of solvent composition in a DCM/THF mixture (Figure 3B). As the volume fraction of THF increases, the amount of the minor conformer decreases exponentially, converging to the 14:1 ratio observed in 100% THF.

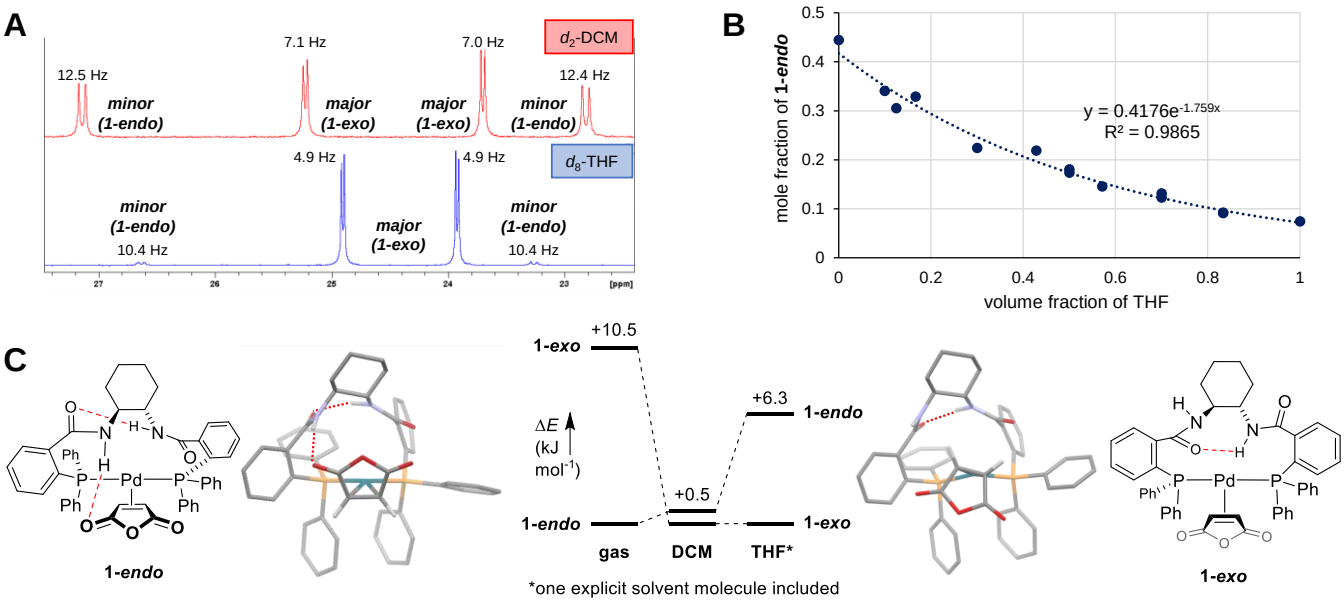

Figure 3. (**A**) ^{31}P NMR spectra of complex **1** in d_2-DCM and d_8-THF, revealing two conformers (**1-*exo*** and **1-*endo***). (**B**) Mole fraction of minor conformer (**1-*endo***) versus volume fraction of THF in DCM, which follows an exponential correlation (equation and R^2 value given). (**C**) Calculated structures of **1-*endo*** and **1-*exo*** (gas phase geometry shown), with relative free energies in the gas phase, DCM, and THF (implicit solvation models; one explicit THF molecule included in THF-solvation calculations).

Based on these data and the solid-state molecular structures of **2** and **4**, we propose that the two species in solution are conformers **1-*endo*** and **1-*exo***, with **1-*exo*** being the major (based on extensive NMR spectroscopy, Figures S1-S19). To explain these observations, we propose that in a relatively non-polar solvent (*e.g.* DCM), **1-*endo*** and **1-*exo*** are similar in energy; however, with the addition of a hydrogen-bond-accepting solvent (*e.g.* THF), hydrogen bonding between an N–H on the ligand and the solvent will stabilize the **1-*exo*** conformation. Notably, complexes **2**-**4** exhibit similar NMR spectroscopic characteristics (see SI for further details).

To test this hypothesis, we examined the conformer ratio in 10:1 mixtures of DCM and other hydrogen-bond-accepting solvents (Figure S112). While a 10:1 DCM/THF mixture gives a 65:35 ratio of **1-*exo*** to **1-**

endo, 10:1 DCM/DMF and 10:1 DCM/MeOH mixtures give an 80:20 **1-*exo*** to **1-*endo*** ratio. Addition of weakly hydrogen-bond-accepting solvents such as CPME and NEt_3 results in no change to the conformer ratio relative to that observed in DCM. Finally, to support our conformer assignments, we calculated relative electronic energies of the **1-*exo*** and the **1-*endo*** conformers (RI-B2PLYP-D3BJ/def2-TZVP//RI-BP86-D3BJ/def2-SVP, with def2-TZVP/C and def2/J auxiliary basis sets for the RI part, respectively) using CPCM implicit solvation models.[61] In gas phase calculations, both conformers exhibit an intramolecular hydrogen bond between the amides, and the ***1-endo*** conformer has an additional hydrogen bond between an amide N–H and the MAH (as observed in the solid-state structure of **2**). This leads to the **1-*endo*** conformer being 10.5 kJ mol^{-1} more stable than ***1-exo***. However, the **1-*exo*** and **1-*endo*** energies calculated in DCM solvent are very close, with **1-*exo*** only slightly more stable (0.5 kJ mol^{-1} difference). To compare energies in THF, we used both the CPCM implicit model and included one explicit THF molecule hydrogen-bonding to a ligand N–H in ***1-exo*** (as observed in the solid-state structure of **4**). This results in **1-*exo*** being 6.3 kJ mol^{-1} more stable. These calculations support not only the assignment of **1-*exo*** as the major conformer in THF, but also exhibit the same solvent effect trend as our spectroscopic observations.

To assess the suitability of complexes **1**-**6** as robust precatalysts, we examined their solution stability in THF (15-50 mg/mL) over 48 h by ^{31}P NMR spectroscopy (Figure 4). With solutions prepared under N_2, the concentrations of all six complexes remain unchanged over this period. Given the aforementioned rapid oxidation of [**L1**]Pd(dba) to the tetradentate [PNNP]Pd^{II} species, we also assessed the stability of a THF solution of complex **1** after exposure to air. After 48 h, there is still >80% of **1** intact, with the mass balance comprised of [PNNP]Pd^{II}. In stark contrast, a mixture of **L1** and $Pd_2(dba)_3{\cdot}CHCl_3$ is 50% oxidized after only 30 min, and is completely converted to [PNNP]Pd^{II} within 18 h. As a solid, complex **1** is indefinitely stable when stored under N_2 at room temperature (2 years thus far). Complex **1** is even stable for weeks as a solid under air (<6% area of new signals observed in ^{31}P NMR spectra after one month). Thus, precatalysts **1**-**6** can be handled and used without the need for a glovebox. In fact, all catalytic evaluations were carried out by weighing the precatalysts and preparing solutions under air (*vide infra*).

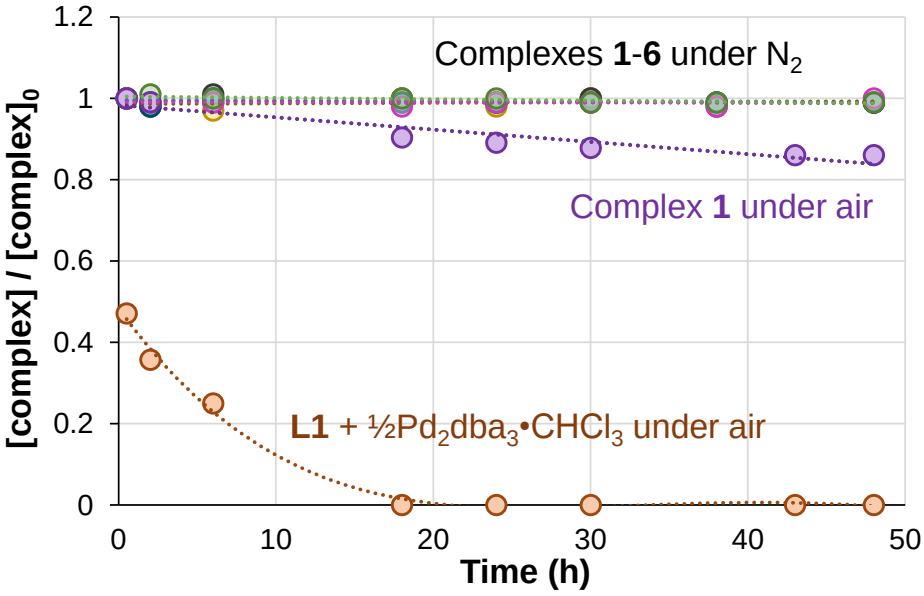

Figure 4. Concentration versus time plot for complexes **1**-**6** in THF under N_2, showing no decomposition over at least 48 h, as well as complex **1** and **L1** + $Pd_2(dba)_3{\cdot}CHCl_3$ under air. These latter experiments show slow decomposition of **1** (>80% intact after 48 h) and rapid decomposition of [**L1**]Pd(dba) (<50% remaining after 30 min).

Deploying single-component precatalysts in asymmetric allylic alkylations. To conduct an initial assessment of the performance of precatalysts **1**-**6** in diverse asymmetric allylic alkylations, we compared them against standard catalyst systems for a series of benchmark reactions. Representative comparisons at identical Pd loading are given in Figure 5; additional comparator data under alternative reaction conditions is available in Tables S5-S8. We chose five criteria to evaluate each catalyst system, visualized in a radar plot analysis, including isolated yield, enantioselectivity, reaction time, the Pd to chiral ligand ratio, and any additional steps required to generate the active catalyst ("Practicality" in Figures 5-7).

We initially evaluated the extensively studied malonate allylation with racemic cyclohex-2-en-1-yl methyl carbonate (**7**) (Figure 5A, Table S5).[60,62] Under standard reaction conditions (*i.e.* 5 mol% Pd, a Pd:L ratio of 1:1.5, and a 30 min pre-treatment of Pd precursor and ligand), the allylation proceeds efficiently and selectively using $Pd_2(dba)_3{\cdot}CHCl_3$ to give **8** (96% yield, 95% *ee*). However, simply reducing the Pd:L ratio to 1:1 results in no observable reaction. Not only is this undesirable from a cost perspective, it indicates a potential failure mode if insufficient **L1** is used. In sharp contrast, the use of ^{Ph}DACH-Pd-MAH (**1**) as a single-component precatalyst, which has a 1:1 Pd:L ratio and does not require any pre-treatment to ensure complete metalation, delivers **8** in 86% isolated yield and 96% *ee*.

A classic example in asymmetric allylation is the desymmetrisation of *meso*-2-en-1,4-diol diester **9** using the Pd/**L1** system (Figure 5B, Table S6). We employed the *bis*(acetate) substrate **9** to accentuate reactivity differences between the systems, as it is less reactive than the more commonly used *bis*(benzoate) derivative.[63,64] At a Pd loading of 2 mol% and a Pd:**L1** ratio of 1:1, $Pd_2dba_3{\cdot}CHCl_3$ performs poorly (15% yield, 92% *ee*) while $[Pd(allyl)Cl]_2$ generates **10** in high enantiopurity but only modest yield (46% yield, 99% *ee*). ^{Ph}DACH-Pd-MAH (**1**) is superior to these known systems, exhibiting excellent enantioselectivity with improved yield, all without the need for preactivation (68% yield, 98% *ee*).

Next, we examined the Pd-catalysed asymmetric allylation of phthalimide (**11**) as a nitrogen-based nucleophile using racemic epoxide **12** (Figure 5C, Table S7); this transformation has been utilised in several total syntheses.[65–67] Using $[Pd(allyl)Cl]_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ as the Pd source with ^{NAP}DACH (**L2**) as the ligand (0.8 mol% Pd, 1:1.5 ratio of Pd:**L2**), we obtained good yields of the homoallyl alcohol **13** (99% and 82% respectively); however, we were not able to achieve the reported level of enantioselectivity even after rigorous purification of every component of the reaction mixture (72% and 64% versus the reported 96%). Notably, the single-component precatalyst ^{NAP}DACH-Pd-MAH (**2**) achieves excellent yield while attaining higher enantioselectivity than the *in situ* systems, without the need for excess **L2** or preactivation (99% yield, 81% *ee*). This result highlights the robustness of our Pd(0) precatalysts, which are effective even for reactions that are clearly sensitive to the specific reaction conditions.

Decarboxylative asymmetric allylic alkylation (DAAA) reactions represent a broad class of Pd-catalysed allylation chemistry, and hence an important testing ground for our precatalysts.[68] We therefore examined Pd-catalysed DAAA of allyl (2-phenyl-cyclohexyl)carbonate (**14**, Figure 5D, Table S8) using (*S,S*)-^{Ph}ANDEN (**L4**) based catalysts. At 2 mol% Pd loading and 3 mol% of **L4**, $Pd_2(dba)_3{\cdot}CHCl_3$ is able to achieve complete conversion in 30 min, giving **15** in 77% yield with good enantioselectivity (83% *ee*). However, this system fails to reach completion even after 24 h when the Pd:**L4** ratio reduced to 1:1 (39% yield). The single-component ^{Ph}ANDEN-Pd-MAH (**4**) complex is able to achieve complete conversion and good enantioselectivity without the need for excess **L4** (87% yield, 81% *ee*).

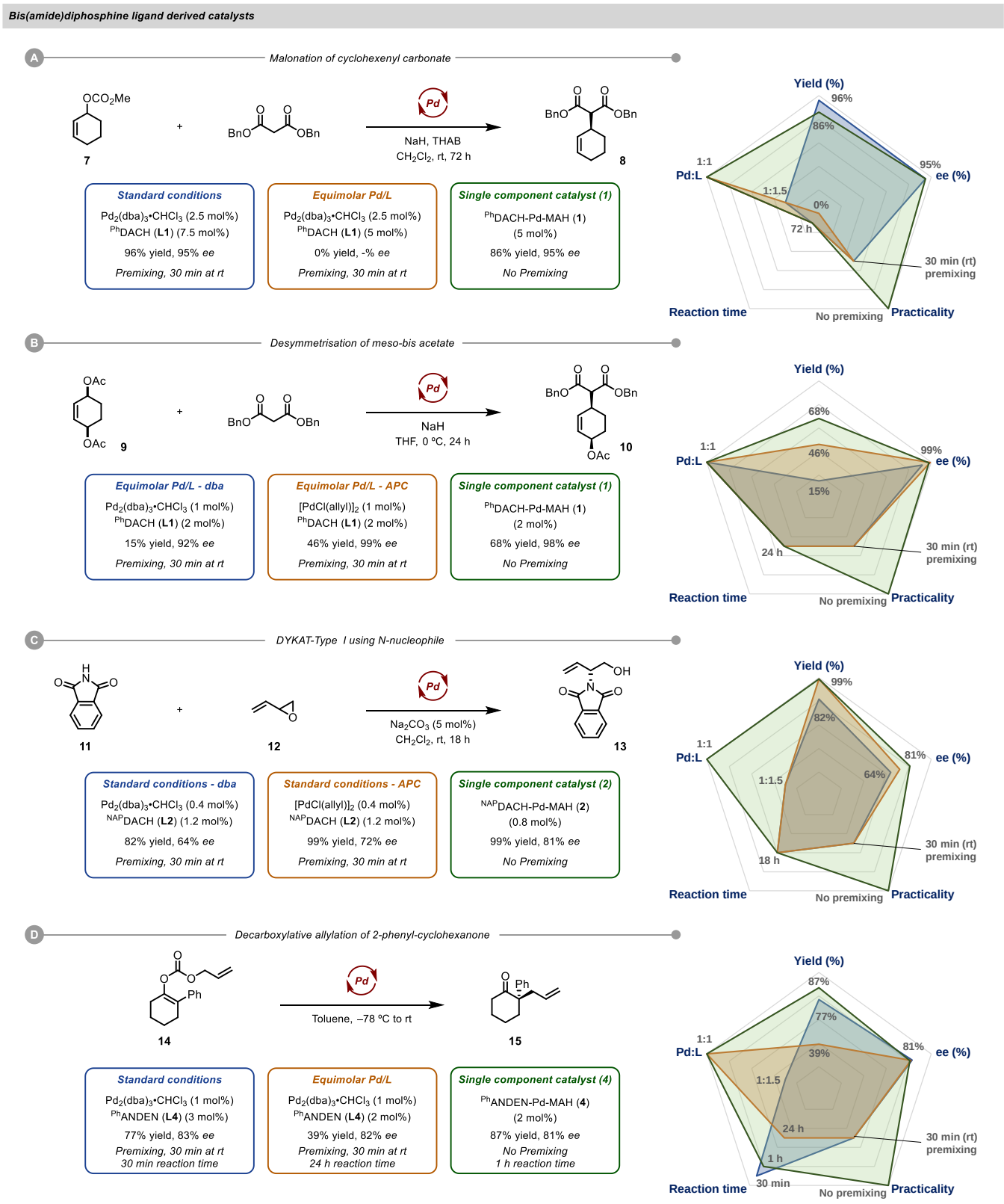

Figure 5. Comparison of established catalyst systems with new single-component precatalysts for benchmark AAA reactions. (**A**) Malonation of cyclohexenyl carbonate. (**B**) Desymmetrization of *meso* bis(acetate). (**C**) Dynamic kinetic asymmetric transformation (DYKAT) of racemic epoxide **12** with phthalimide (**11**). (**D**) Intramolecular decarboxylative asymmetric allylic alkylation (DAAA).

To assess PHOX-type precatalysts **5** and **6**, we used the reaction of racemic allyl acetate **16** with dimethyl malonate, which is often used as a model reaction when developing novel Pd catalysts for asymmetric allylation chemistry. Hence, we compared $[Pd(allyl)Cl]_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ with complexes **5** and **6** for the synthesis of **17** (Figure 6, Table S9).[51,69] Using conditions for mild enolate generation with bis(trimethylsilyl)acetamide (BSA) and catalytic KOAc, and the established method of premixing the Pd source and PHOX ligand (1.25 equiv. per Pd) at 50 °C for 1 h to ensure complete metalation, $[Pd(allyl)Cl]_2$ delivered **17** in 93% yield and 95% *ee* after 1 h (2 mol% Pd). However, if the 1 h pre-activation step is conducted at room temperature, $[Pd(allyl)Cl]_2$ suffers from diminished yield even after 24 h (67%). The single-component chiral precatalyst (*S*)-^{iPr}PHOX-Pd-MAH (**6**), which can simply be added as a solid to the reaction mixture and therefore requires no preactivation or excess chiral ligand, provides **17** in 84% isolated yield and 96% *ee* (opposite enantiomer to that obtained with (*R*)-^{iPr}PHOX), though the reaction requires 24 h to reach completion. Use of the ^{tBu}PHOX ligand resulted in similar outcomes, where $[Pd(allyl)Cl]_2$ outperforms the MAH-based catalyst **5** in terms of rate, but the *in situ* system again requires pre-activation at 50 °C. In this case, we also observe a reduction in enantioselectivity for the MAH-based system (82% *ee* versus 96% *ee*).

In contrast to the weakly basic BSA/KOAc reaction conditions, use of KH to generate a harder potassium enolate results in excellent reaction rates for all three catalyst systems (Figure 6B), with the single-component precatalysts **5** and **6** matching the reactivity of the $[Pd(allyl)Cl]_2$ based *in situ* system (1 h reaction time for complete conversion in each case). In addition, both precatalysts exhibit excellent enantioselectivity. The increase in reaction rate for the MAH-based systems under strongly basic conditions indicate that catalyst activation processes are likely dependent on reaction conditions; further in-depth mechanistic studies are ongoing to elucidate these pathways.

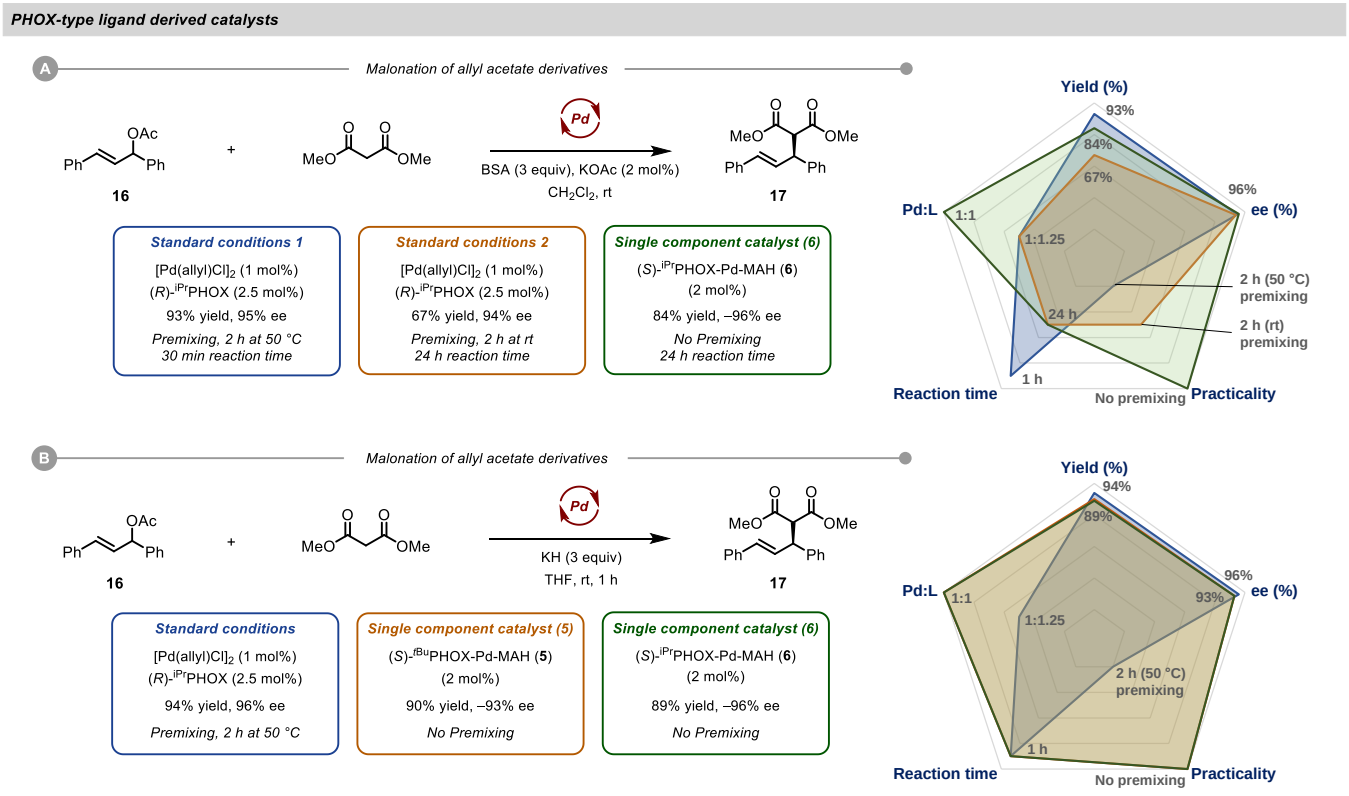

Figure 6. Comparison of established PHOX-type catalyst systems with new single-component precatalysts for benchmark AAA reactions. (**A**) Malonation of allyl acetate derivatives using weakly basic conditions for soft enolization. (**B**) Malonation of allyl acetate derivatives using strongly basic conditions to generate a potassium enolate nucleophile.

Single-component precatalysts enable asymmetric allylation of butenolide nucleophiles. To explore the suitability of our new precatalysts beyond well-known allylation chemistry, we turned toward the preparation of enantioenriched heterocycles relevant to the synthesis of natural products and commodity chemicals. Specifically, the enantioselective functionalisation of prochiral heterocycles is a vast field with scores of possible methodologies. In Pd-catalysed asymmetric allylation, there are three predominant methods: a) the direct allylation of a prochiral heterocycle (*e.g*. **18**, Figure 7A); b) the decarboxylative allylation (*e.g.* of **20**, Figure 7B); or c) the allylation of the corresponding enol silane (*e.g.* **21**, Figure 7C). We explored the formation of chiral butenolide **19** by each of these methods, comparing *in situ* catalyst formation using $Pd_2(dba)_3{\cdot}CHCl_3$ to the use of single-component chiral precatalyst **1**.[70,71]

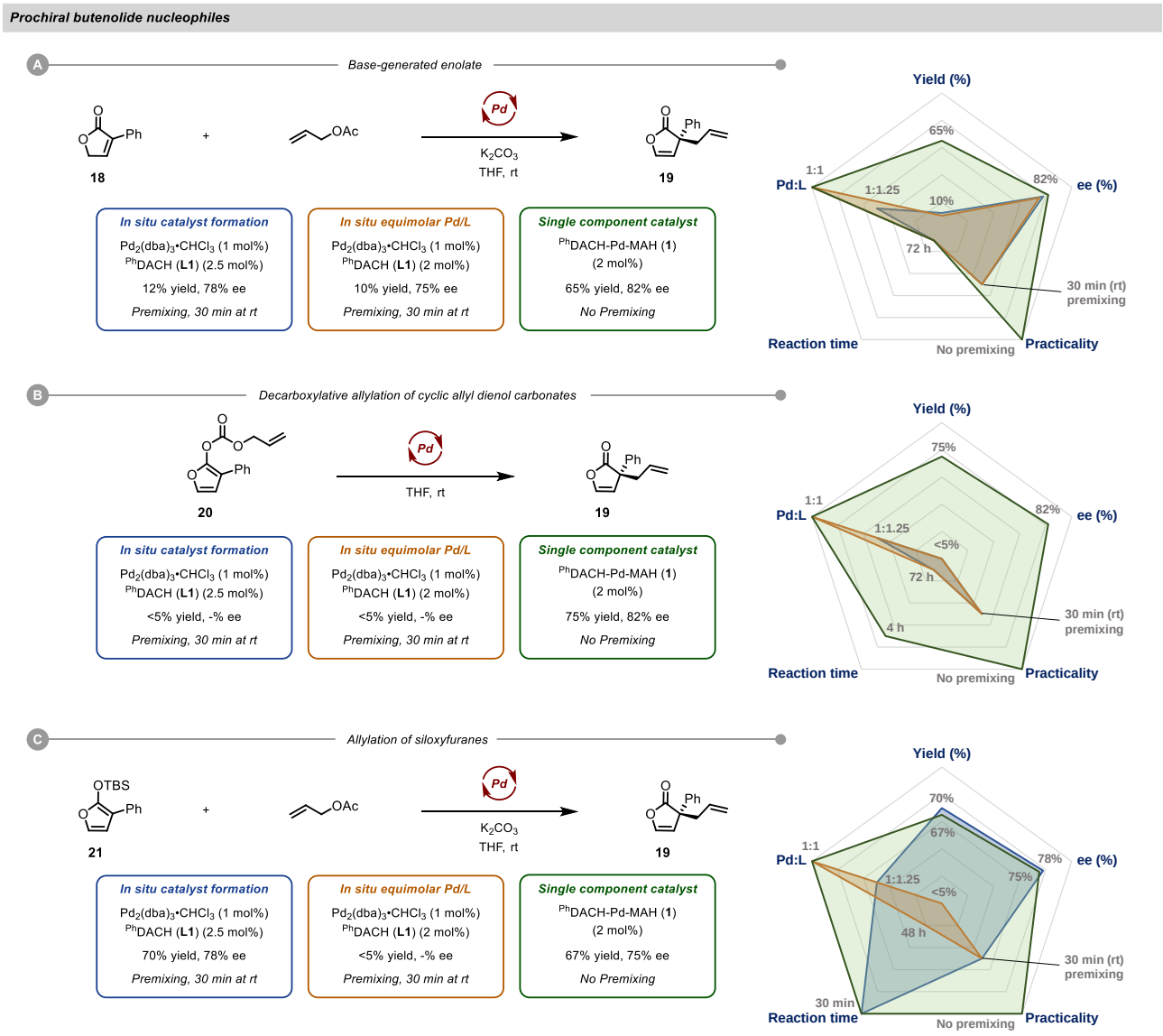

Figure 7. Comparison of precatalyst **1** to *in situ* systems for challenging asymmetric allylic alkylation reactions in the synthesis of chiral butenolide **19**. (**A**) Direct allylation of **18**. (**B**) Decarboxylative allylation of **20**. (**C**) Allylation of siloxyfuran **21**.

The direct allylation of **18** and the decarboxylative allylation of **20** did proceed using high $Pd_2(dba)_3{\cdot}CHCl_3$ loading (Tables S10 and S11); however, both approaches were ineffective when lowering the Pd loading from 10 to 2 mol%, resulting in little to no reactivity even after extended reaction times (Figure 7A and 7B). In sharp contrast, ^{Ph}DACH-Pd-MAH (**1**) operates at 2 mol% loading to give **21** in good yield (65-75%) and enantiopurity (82% *ee*) under both conditions. While the direct allylation reaction time is long (72 h), **1** is able to catalyse complete decarboxylative allylation to form **19** within 4 h.

In the third approach, involving allylation of the enol silane **21**, $Pd_2(dba)_3{\cdot}CHCl_3$ is able to operate at the lower 2 mol% Pd loading, giving full conversion and good yields after only 15 min; however, this system failed when the Pd:L ratio was reduced to 1:1 (Figure 7C). This was circumvented by using 2 mol% of ^{Ph}DACH-Pd-MAH (**1**) under otherwise identical conditions, giving comparable yield and selectivity without the need for excess chiral ligand. Overall, the ability to reliably reduce both Pd and L loading in these transformations is a significant advantage in both cost and robustness.

Precatalyst-enabled discovery and optimization of enantioselective hydantoin allylation. The rapid *in situ* metalation of Trost-type and PHOX-type ligands to the ^{DMP}DAB-Pd-MAH precursor, and the stability/ease-of-use for the single-component precatalysts **1**-**6**, render these systems particularly suited to reaction discovery and optimization *via* parallel experimentation techniques. Indeed, the remarkable air stability of the L*-Pd-MAH complexes both in the solid state and in solution makes setting up array-based experiments operationally simple without the need for a glovebox. To demonstrate this feature of our precatalysts, we employed them in the rapid optimisation of a Pd-catalysed asymmetric allylation of hydantoin **22** (Figure 8). Hydantoin heterocycles are common motifs in FDA approved drugs; however, there are a striking lack of methods for their asymmetric functionalisation.[72–75] To the best of our knowledge, there are no prior reports of enantioselective hydantoin allylation using Pd catalysis. If realized, this would be a powerful method to install a stereogenic tetrasubstituted carbon into a protected amino acid motif.

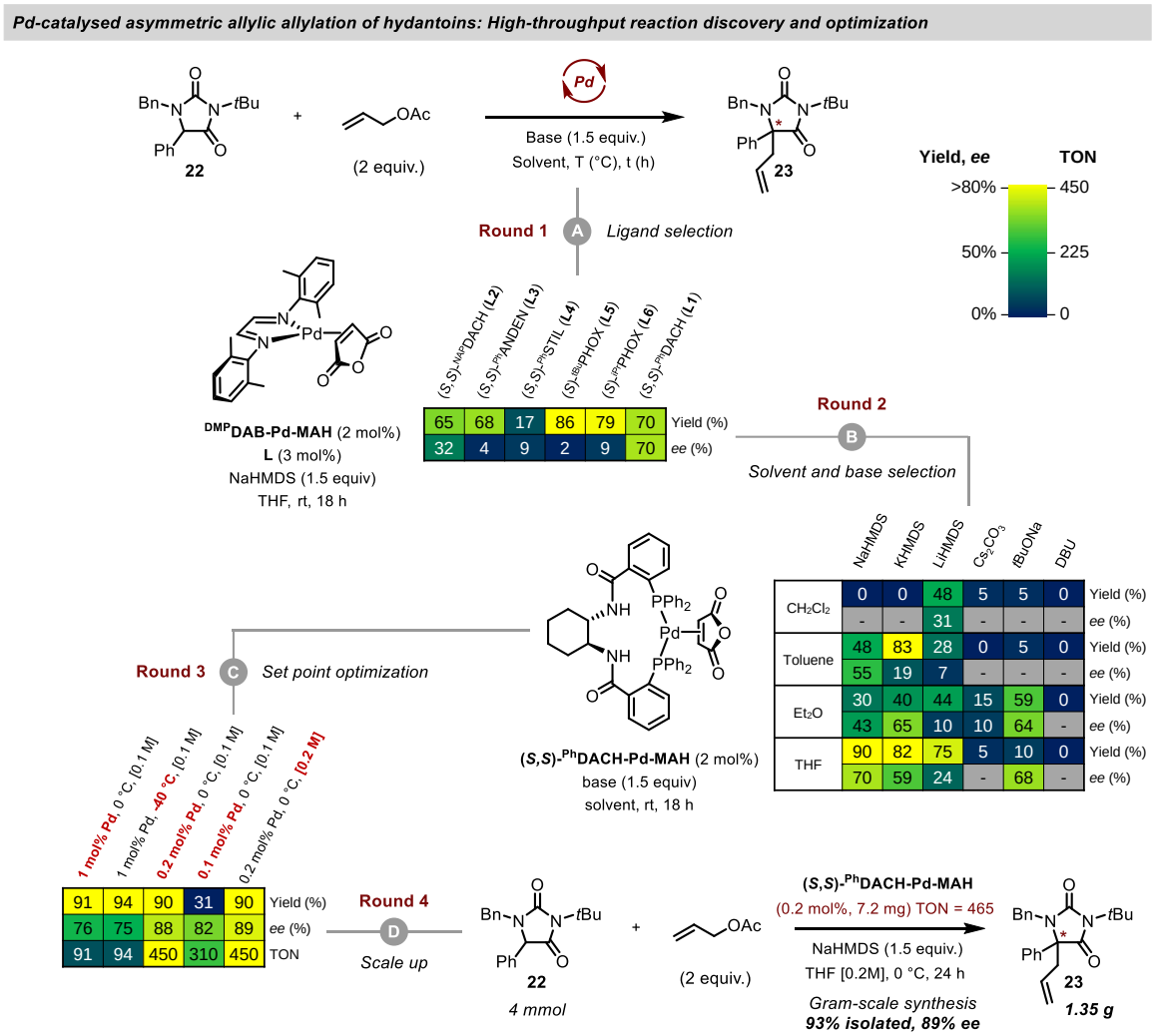

Figure 8. Application of MAH-based Pd precatalysts in reaction discovery and optimisation for the asymmetric allylation of hydantoin **22**. Demonstration of gram scale (4 mmol) enantioselective allylation at low Pd loading (0.2 mol%, TON = 465).

Our initial set of experiments (**Round 1**) used ^{DMP}DAB-Pd-MAH (2 mol%) as the source of Pd(0) to screen chiral ligands for the proposed reaction using *in situ* catalyst formation (Pd/L, 1:1.5) in the presence of NaHMDS (1.5 equiv) in THF (0.1 M) at room temperature. All stock solutions of catalysts, ligands, and starting materials for these experiments were prepared under air. Notably, only (*S,S*)-^{Ph}DACH gave good enantioselectivity (70% *ee*), with all other ligands providing poor selectivity. **Round 2** screening utilised chiral complex (*S,S*)-^{Ph}DACH-Pd-MAH (**1**, 2 mol%) in a solvent/base array to rapidly optimise the reaction conditions at room temperature. While the use of the single-component chiral precatalyst did increase the yield to 90% using NaHMDS/THF, all other solvent/base combinations either failed to give product in >40% yield (15 of 24 reactions) and/or failed to improve the enantioselectivity.

To further optimise the enantioselectivity and catalytic efficiency of this reaction, we performed **Round 3** of experiments to adjust catalyst loading, lower reaction temperature, and increase reactant concentration. All experiments were performed at either 0 °C or below. Consistent with previous reports showing that higher catalyst concentrations can decrease stereoselectivity, we observe improved % *ee* when lowering the Pd loading from 1 mol% (76% *ee*) to 0.2 mol% (86% *ee*).[42–44,76] We do not observe any improvement to enantioselectivity when carrying out the reaction at −40 °C, nor when lowering further the Pd loading to 0.1 mol% (which also reduces reactivity to an unacceptable degree). Finally, increasing the overall reaction concentration to 0.2 M and maintaining a Pd catalyst loading of 0.2 mol%, we are able to achieve 90% yield (TON = 450) and 88% *ee*. Translating these reaction conditions to a gram scale (4 mmol) preparation gave 93% isolated yield of **23** with 88% *ee* and a TON of 465. Notably, only 7.2 mg of precatalyst **1** is required to produce 1.34 g of **23**. Indeed, such low chiral catalyst loading is extremely rare for Pd-catalysed asymmetric allylation chemistry, and clearly demonstrates the power of using a single-component catalyst system for both screening and preparative-scale synthesis.

CONCLUSIONS

We have developed a set of bench stable chiral Pd(0) precatalysts based on the two key ligand classes used in Pd-catalysed asymmetric allylation chemistry. By exploiting the rapid ligand substitution chemistry exhibited by the ^{DMP}DAB-Pd-MAH precursor, Pd complexes with Trost-type and PHOX-type ligands can either be generated *in situ*, or isolated as single-component precatalysts. These complexes were fully characterized, including X-ray diffraction studies on three examples, enabling interrogation of their conformations in solution and the solid-state. Importantly for their application in catalysis, the Trost-type complexes **1**-**4** do not suffer from rapid decomposition *via* oxidation.

To demonstrate the potential of these precatalysts, we have applied them to 9 distinct Pd-catalysed asymmetric allylation reactions. In all cases, the new precatalysts compared favourably with traditional catalytic systems, maintaining enantioselectivity while enabling lower catalyst loadings. In addition, the single-component nature of **1**-**6** gives a perfectly controlled Pd/L stoichiometry, and circumvents the need to ensure ligand metalation is complete prior to substrate addition. We further demonstrate the lowest reported catalyst loading for a Trost ligand system in the unprecedented enantioselective allylation of a hydantoin derivative. The discovery and optimization of this new reaction was enabled by microscale array-based experiments, to which our precatalysts are ideally suited. Overall, the selectivity, activity, stability, and practicality of the single-component precatalysts make them powerful and attractive alternatives to established *in situ* procedures. Complexes **1**-**6** and analogues thereof should therefore be evaluated as standard systems for Pd-catalysed asymmetric allylations in academic and industrial applications alike.

METHODS

General procedure for the synthesis of the single-component chiral catalysts. These reactions were set up in a glovebox under an inert nitrogen atmosphere. A representative procedure for the synthesis of **1** is given here, with specific procedures for all precatalysts given in the Supporting Information. A 4 dram (~15 mL) vial was charged with ^{DMP}DAB-Pd-MAH (100.1 mg, 0.21 mmol), **L1** (147.2 mg, 0.21 mmol, 1.0 equiv), anhydrous inhibitor-free THF (4 mL) and a cross-shaped magnetic stirbar. The reaction mixture was stirred at room temperature for 1 h. The solvent was then removed *in vacuo* to give a yellow solid residue. This residue was mixed thoroughly with hexanes/diethyl ether (1:1), followed by decantation of the liquid phase (with or without centrifugation as required). This trituration/decantation process was repeated 5 more times to remove the ^{DMP}DAB byproduct as well as any excess phosphine ligand. The solid was then dried *in vacuo* to give the corresponding single-component chiral catalyst **1** as a pale yellow solid (121.0 mg, 63% yield).

Procedure for the gram-scale synthesis of 23. This reaction was set up without use of a glovebox using standard air-free techniques involving nitrogen streams and balloons. An oven-dried 50 mL round-bottom flask was charged with **22** (1.29 g, 4.00 mmol) and a teflon-coated stirbar. The flask was sealed with a rubber septum and placed under nitrogen atmosphere. THF (14 mL) was added, and the contents cooled to 0 °C. NaHMDS (1 M in THF, 6.00 mL, 6.00 mmol, 1.5 equiv) was added via syringe with stirring, and the mixture was stirred for 1 h at 0 °C. ^{Ph}DACH-Pd-MAH (**1**) was then added as a solid (7.2 mg, 0.0080 mmol, 0.2 mol%), followed by allyl acetate via syringe (0.860 mL, 8.00 mmol, 2 equiv). The mixture was stirred at 0 °C for 24 h, after which time TLC analysis indicated complete conversion. The reaction was quenched with the addition of H_2O (50 mL), followed by extraction with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with 10% wt/wt aqueous citric acid (2 x 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography using silica gel and hexane/EtOAc eluent (100:0 to 80:20 v/v) to yield **23** (1.35 g, 89% *ee*). Enantiopurity was measured by HPLC using a hexane/isopropanol mobile phase (isocratic 9:1 v/v, 1 mL/min) and a Daicel CHIRALPAK^{TM} IC column (250 x 4.6 mm; 5 µm; 35 °C).

Specific procedures for all catalytic reactions are given in the Supporting Information.

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AUTHOR CONTRIBUTIONS

J.H., T.K., D.C.L. and S.A. conceived and designed the study. J.H., T.K., and F.R. performed the synthetic experiments and analysed the data for all compounds. J.L. performed computational analysis. S.E.J. conducted single crystal X-ray diffraction experiments and analysis. A.J., S.A., and D.C.L. supervised the research. J.H., T.K., F.R., S.A., and D.C.L. co-wrote the paper with input from all authors.

NOTES

The authors declare the following competing financial interest(s): PCT international patent applications have been filed based partly on this work. ^{DMP}DAB-Pd-MAH is commercially available from MilliporeSigma (product number 922889). Crystallographic information files (CIFs) for crystal structures determined by X-ray diffraction are deposited with the CCDC; deposition numbers CCDC 2258957-2258960.

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