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Buchwald-Hartwig Cross-Coupling of Amides (Transamidation) by Selective N–C(O) Cleavage Mediated by Air- and Moisture-Stable [Pd(NHC)(allyl)Cl] Precatalysts: Catalyst Evaluation and Mechanism

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The Pd–NHC-catalyzed acyl-type Buchwald-Hartwig cross-coupling of amides by N–C(O) cleavage (transamidation) provides a valuable alternative to the classical methods for amide synthesis. Herein, we report a combined experimental and computational study of the Buchwald-Hartwig cross-coupling of amides using well-defined, air- and moisture-stable [(Pd(NHC)allyl] precatalysts. Most crucially, we present a comprehensive evaluation of a series of distinct Pd(II)–NHC precatalysts featuring different NHC scaffolds and throw-away ligands for the synthesis of functionalized amides that are not compatible with stoichiometric transition-metal-free transamidation methods. Furthermore, we present evaluation of the catalytic cycle by DFT methods for a series of different Pd(II)–NHC precatalysts. The viability of accessing NHC-supported acyl-palladium(II) amido complexes will have implications for the design and development of cross-coupling methods involving stable amide electrophiles.

Introduction

Amide bonds are among the most common functional groups in pharmaceuticals, agrochemicals and functional materials.[1–3] Recent estimates suggest that amide bonds are present in more than 75% of drug candidates, while amide bond forming reactions are *the* most frequently executed type of transformations performed by medicinal chemists.[4,5] Because of the importance of amide bonds, new methods for their synthesis and straightforward manipulation have found numerous applications in chemical synthesis.[6]

Generally, transition-metal-catalyzed activation of amide bonds is challenging due to amidic resonance ($n_N \rightarrow \pi^*_{C=O}$, ca. 15-20 mol/kcal in planar amides).[7] Controlled access to acyl-metal intermediates can now be achieved by direct insertion of a transition-metal into the N–C(O) bond using ground-state-destabilization concept of common acyclic amides (Fig. 1A).[8] This new activation pathway[9] of the classically inert amide bonds enables common amides to be used as electrophiles in cross-coupling reactions by acyl[10] and decarbonylative[11] mechanisms. In this context, transamidation reactions of secondary amides after site-selective N-activation of the amide bond (Z = Boc) represent a powerful method in organic synthesis (Fig. 1B).[12–17]

These new amidation methods are of particular interest for the synthesis of new amide bonds, but more importantly enable amide bond exchange reactions under mild conditions that successfully overcome kinetic and thermodynamic barriers for N–C(O) transamidation.[18] Recently, we showed that well-defined Pd(II)–NHC precatalysts (NHC = N-heterocyclic carbene) enable transamidation of secondary amides in excellent yields.[13a] Furthermore, examples of Ni-catalyzed and transition-metal-free transamidation reactions have been documented.[14–17] The use of well-defined, air- and moisture-stable and commercially-available Pd(II)–NHC precatalysts render the transamidation process practical and accessible to a wide range of interested chemists.[19–22] To further advance this catalytic transamidation platform, it has become imperative to comprehensively investigate the effect of different precatalysts and elucidate the catalytic cycle.

Herein, we report a combined experimental and computational study of the Buchwald-Hartwig cross-coupling of amides using well-defined, air- and moisture-stable [(Pd(NHC)allyl] precatalysts.[22d–f] Most crucially, we present a comprehensive evaluation of a series of distinct Pd(II)–NHC precatalysts featuring different NHC scaffolds and throw-away ligands for the synthesis of functionalized amides that are not compatible with stoichiometric transition-metal-free transamidation methods. Furthermore, we present evaluation of the catalytic cycle by density functional theory (DFT) methods[23,24] for a

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series of different Pd(II)–NHC precatalysts. We believe that the viability of accessing NHC-supported acyl-palladium(II) amido complexes will have implications for the design and development of cross-coupling methods involving stable amide electrophiles.

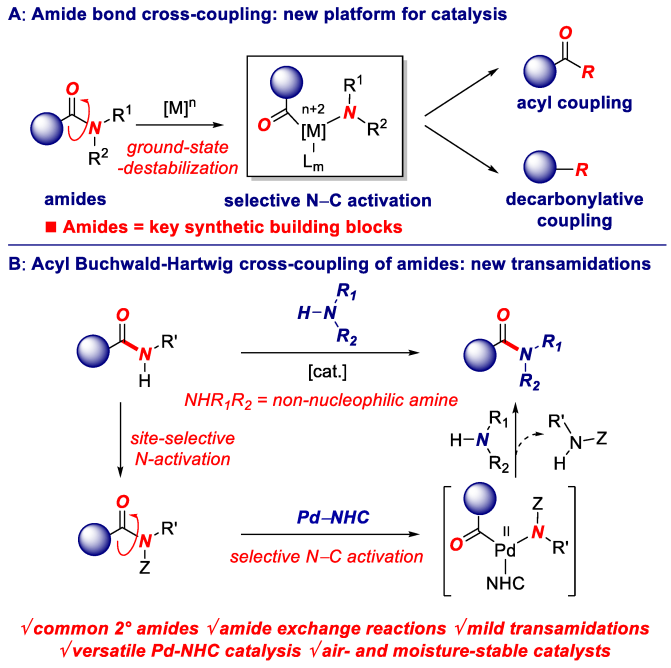


Fig. 1 (a) Cross-coupling of amides by N–C(O) activation; (b) Acyl Buchwald-Hartwig cross-coupling of amides.

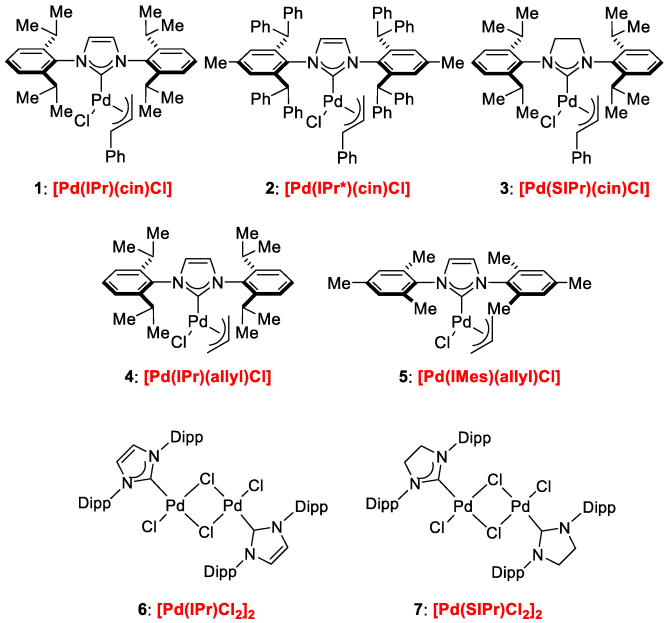


Fig. 2 Structures of Pd(II)–NHC catalysts **1–7** used in this study (Dipp = 2,6-*i*Pr$_2$-C$_6$H$_3$).

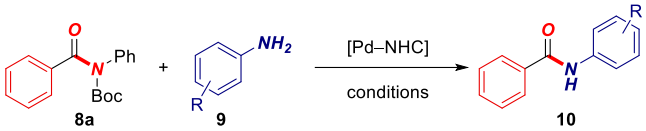
Results and Discussion

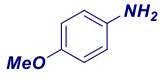
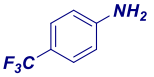
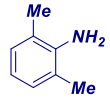
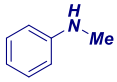
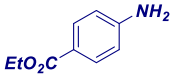
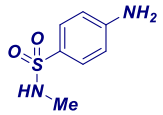
Catalyst Evaluation. Well-defined Pd(II)–NHC precatalysts selected for the study are presented in Fig. 2. These catalysts include [Pd(NHC)(allyl)Cl] type catalysts **1**–**5** featuring imidazolylidene and imidazolinylidene NHCs, including sterically-hindered IPr*, as well as different allyl-type throw-away ligands, such as [Pd(IPr)(cin)Cl] (**1**), [Pd(IPr*)(cin)Cl] (**2**), [Pd(SIPr)(cin)Cl] (**3**), [Pd(IPr)(allyl)Cl] (**4**), [Pd(IMes)(allyl)Cl] (**5**), as well as chloro-dimers **6–7**, namely [Pd(IPr)Cl$_2$]$_2$ (**6**) and [Pd(SIPr)Cl$_2$]$_2$ (**7**). *Importantly, all catalysts **1–7** are commercially-available, which should facilitate their use in amide bond transamidation reactions.*

Experiments showing compatibility of catalysts **1–7** in transamidation reactions of the model N-Ph/Boc amide **8a** (RE = 7.2 kcal/mol, RE = resonance energy)[9a,b] with different non-nucleophilic anilines are presented in Table 1. Anilines selected for the study include electronically-differentiated anilines (Table 1, entries 1-2), sterically-hindered ortho-di-substituted aniline (entry 3), secondary aniline (entry 4), electron-deficient anilines containing sensitive ester and unprotected sulphonamide functional groups that would not be compatible with stoichiometric methods for transamidation or with Ni–NHC catalysis[14,15] (entries 5-6). We were delighted to find that the reactions with electron-rich anisidine (entry 1) and electron-deficient 4-trifluoromethylaniline proceeded in excellent yields using all catalysts **1–7**, affording the desired transamidation products in 83-97% yields. Interestingly, chloro-dimers **6–7** appear to be less efficient in the reactions with anisidine than allyl-based precatalysts **1–5** (Table 1, entry 1). The reaction with more challenging sterically-hindered 2,6-dimethylaniline and N-methylaniline revealed that the sterically-demanding IPr* precatalyst **2** is less effective, as expected from the large steric demand of the bulky wingtip N-substitution (*vide infra*),[25] but also that the imidazolinylidene precatalyst [Pd(SIPr)(cin)Cl] (**3**) and chloro-dimer [Pd(SIPr)Cl$_2$]$_2$ (**7**) are less effective in promoting transamidation of these bulky substrates (Table 1, entries 3-4). Finally, we were interested to examine transamidation reactions using strongly-deactivated anilines bearing sensitive ester and sulphonamide functional handles (Table 1, entries 5-6). We were pleased to find that all catalysts **1–7** performed efficiently in these reactions, delivering the amide products in 80-98% yields.

Next, we sought to test these transamidation reactions using challenging non-nucleophilic anilines containing sensitive functional groups that are not compatible with stoichiometric transamidation methods (Table 2).[14,15] For clarity, the discussion of results is followed by mechanistic DFT studies. We found that transamidation with ethyl 4-aminobenzoate occurred in good to excellent yields with both deactivated, electron-rich amide **8b** (entry 1) and electron-deficient amide bearing sensitive methyl ester group **8c** (entry 2) using all catalysts **1–7**. In general, transamidation with amide **8b** (entry 1) is slightly more efficient than with **8c** (entry 2); however, the reaction is fully chemoselective for acyl N–C(O) cleavage (cf. O–C(O) scission).[16] Furthermore, transamidation was successful with *unprotected* 4-aminobenzamide (entry 3). These reactions delivered the bis-amide product containing differentiated amide functions in 88-94% yields using catalysts **1** and **3–5**, while catalysts **2** and **6–7** were less effective in this reaction. Finally, transamidation with 4-nitrobenzamide that also cannot be readily performed using transition-metal-free or Ni–NHC protocols[14,15] occurred in high

Table 1 Comparison of Reactivity of Pd(II)–NHC Precatalysts **1–7** in Acyl Buchwald-Hartwig Transamidation with Non-Nucleophilic Amines[a]



Entry	Aniline	10	1 yield (%)	2 yield (%)	3 yield (%)	4 yield (%)	5 yield (%)	6 yield (%)	7 yield (%)
1		**10a**	96	93	90	92	89	84	83
2		**10b**	95	90	93	94	95	96	97
3		**10c**	>98	<15	93	94	92	91	70
4		**10d**	83	38	44	82	90	83	36
5		**10e**	96	92	96	97	90	98	95
6		**10f**	80	80	88	82	84	88	88

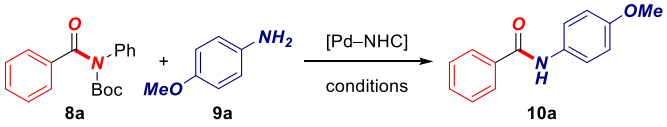
[a]Conditions: amide (1.0 equiv), aniline (2.0 equiv), [Pd] (3.0 mol%), K_2CO_3 (3.0 equiv), DME (0.25 M), 110 °C, 15 h. See ESI for details.

yields using Pd(II)–NHC precatalysts (entry 4). In this case, precatalysts **1–4** and **6** were more effective than **5** and **7**; however, all precatalysts could promote the reaction in 60-96% yields. It is further worth noting that with the exception of outliers, all catalysts gave the cross-coupling products in high yields (Tables 1-2). In our hands, we typically observe more efficient reactions using precatalysts (**1**) and (**3**) ([Pd(IPr)(cin)Cl] and [Pd(SIPr)(cin)Cl]). Clearly, the use of a mild carbonate base allows for high functional group compatibility in the Pd(II)–NHC catalysts manifold. These reactions furnish valuable functionalized N-aryl anilides that would be challenging or impossible to prepare by other transamidation methods.

Overall, the investigation of catalytic efficiency in the series of catalysts **1–7** across 10 substrate combinations (Tables 1-2) identified the following order of reaction efficiency: **1** ≈ **4** ≈ **5** > **3** ≈ **6** > **7** > **2**. Furthermore, precatalysts **1**, **3–4** are the most efficient in transamidations of non-nucleophilic, non-hindered substrates. *Thus, we recommend that catalysts **1** and **4** ([Pd(IPr)(cin)Cl] and [Pd(IPr)(allyl)Cl]) are routinely screened in developing new transamidation reactions using Pd(II)–NHC precatalysts.*[20–22]

To gain additional insight into the performance of catalysts **1–7**, we compared the model reaction using 4-anisidine (3.0 mol%, 110 °C) with conditions at low catalyst loading (0.25 mol%) and at lower reaction temperature (80 °C) (Table 3). Interestingly, we found that the reactivity at low catalyst loading is in the following order: **1** > **2** > **4** ≈ **5** > **3** ≈ **6** > **7**.

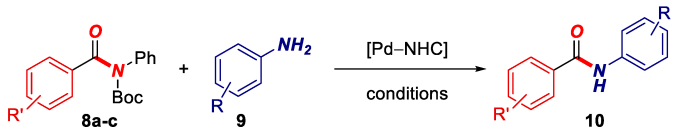
Table 3 Comparison of Reactivity of Pd(II)–NHC Precatalysts **1–7**: Low Catalyst Loading and Temperature[a]



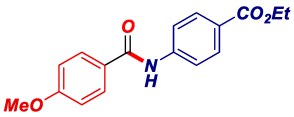
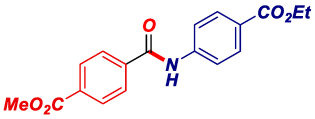
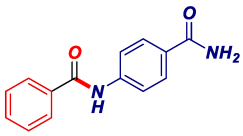
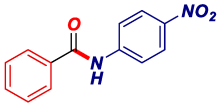
Entry	[Pd]	conditions A yield (%)	conditions B yield (%)	conditions C yield (%)
1	[Pd(IPr)(cin)Cl]	96	83	16
2	[Pd(IPr*)(cin)Cl]	93	71	26
3	[Pd(SIPr)(cin)Cl]	90	23	42
4	[Pd(IPr)(allyl)Cl]	92	44	<10
5	[Pd(IMes)(allyl)Cl]	89	45	14
6	$[Pd(IPr)Cl_2]_2$	84	16	24
7	$[Pd(SIPr)Cl_2]_2$	83	<5	18

[a]Conditions A: amide (1.0 equiv), aniline (2.0 equiv), [Pd] (3.0 mol%), K_2CO_3 (3.0 equiv), DME (0.25 M), 110 °C, 15 h. Conditions B: [Pd] (0.25 mol%). Conditions C: [Pd] (3.0 mol%), 80 °C. See ESI for details.

Table 2 Comparison of Reactivity of Pd(II)–NHC Precatalysts **1–7** in Acyl Buchwald-Hartwig Transamidation with Non-Nucleophilic Amines[a]



8a: R = H
8b: R = 4-MeO
8c: R = 4-CO_2Me

Entry	Product	10	1 yield (%)	2 yield (%)	3 yield (%)	4 yield (%)	5 yield (%)	6 yield (%)	7 yield (%)
1		**10g**	97	97	94	96	98	98	95
2		**10h**	80	78	77	85	84	85	86
3		**10i**	88	70	90	88	94	37	70
4		**10j**	96	83	95	90	64	97	60

[a]Conditions: amide (1.0 equiv), aniline (2.0 equiv), [Pd] (3.0 mol%), K_2CO_3 (3.0 equiv), DME (0.25 M), 110 °C, 15 h. See ESI for details.

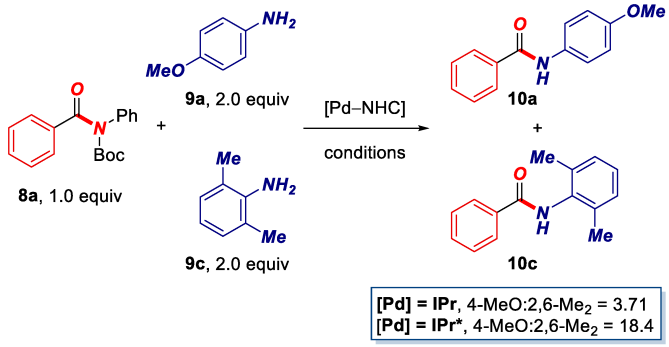
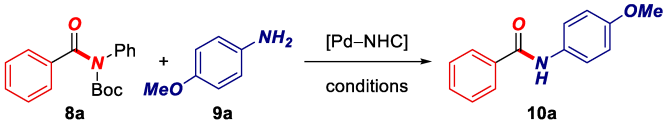


Fig. 3 Steric effect of Pd((II)–NHC precatalysts on cross-coupling. Conditions: amide (1.0 equiv), aniline (2.0 equiv each), [Pd] (3.0 mol%), K_2CO_3 (3.0 equiv), DME (0.25 M), 110 °C, 15 h. [Pd] = IPr, [Pd(IPr)(cin)Cl] (**1**); IPr*, [Pd(IPr*)(cin)Cl] (**2**).

Imidazolylidene-based precatalysts **1** and **2** ([Pd(IPr)(cin)Cl] and [Pd(IPr*)(cin)Cl]) result in TON of 280-330 under these reaction conditions. In contrast, imidazolinylidene-based precatalyst **3** [Pd(SIPr)(cin)Cl] was found to be the most easily activated under conditions C (Table 3).

Furthermore, the use of sterically-hindered [Pd(IPr*)(cin)Cl] leads to an interesting selectivity in transamidation in that deactivated anilines could be selectivity cross-coupled in the presence of sterically-hindered anilines (Fig. 3). This selectivity might find applications in the design of new selective transamidation reactions.

Kinetic studies were conducted to evaluate the relative reactivity of the model precatalyst **1** and the sterically-bulky and readily accessible precatalyst **2** (Fig. 4). Interestingly, the reaction of the model amide with 4-anisidine using [Pd(IPr*)(cin)Cl] gave >95% conversion after 3 h.



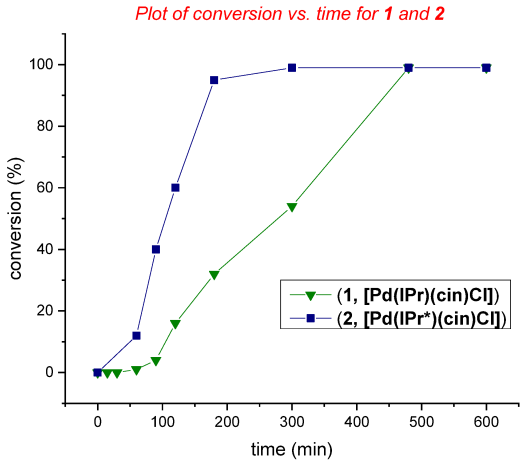


Fig. 4 Kinetic profile for **1** and **2** in the acyl Buchwald-Hartwig cross-coupling with 4-anisidine. Conditions: amide (1.0 equiv), aniline (2.0 equiv), [Pd] (3.0 mol%), K_2CO_3 (3.0 equiv), DME (0.25 M), 110 °C, 0-10 h. [Pd] = [Pd(IPr)(cin)Cl] (**1**); [Pd(IPr*)(cin)Cl] (**2**).

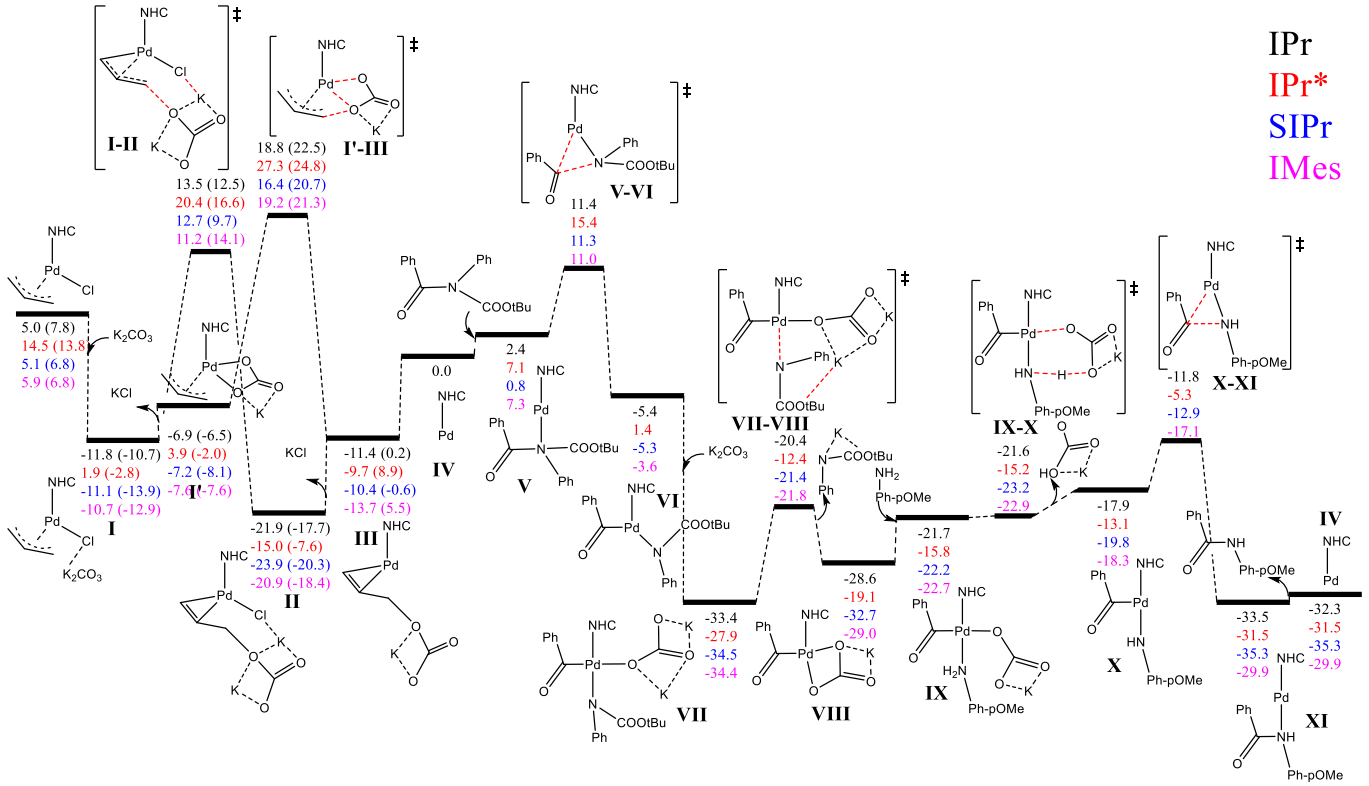


Fig. 5 Reaction Profile (in kcal/mol, at the M06/Def2-TZVP~sdd(PCM-DME)//BP86-D3/SVP~sdd level of theory) of the Buchwald-Hartwig Cross-Coupling of Amides Catalyzed by Pd(II)(allyl)–NHC precatalysts (cinnamyl values between parentheses, and the red dotted lines suggest the bonds that break/form in the transition states).

In contrast, [Pd(IPr)(cin)Cl] resulted in a slower conversion (ca. 50% after 5 h). We believe that the faster reaction rate using [Pd(IPr*)(cin)Cl] results from more facile catalyst activation to give catalytically-active Pd(0)–NHC. Thus, we recommend using precatalyst **2** for transamidation reactions that require faster reaction time.

DFT Studies. To shed light on the mechanism to locate the key step/s that tune the activity of this Buchwald-Hartwig cross-coupling of amides catalytic reaction, DFT calculations were performed (M06/Def2-TZVP~sdd(PCM-DME)//BP86-D3/SVP~sdd energies, see supporting information for details). Fig. 5 collects the energy profile bearing 4 types of palladium catalysts, including either IPr, IPr*, SIPr or IMes ligands. Further, the cinnamyl ligand was compared to the non substituted allyl, as well. From the initial Pd(II)–NHC precatalysts, the interaction of the base K_2CO_3 forms a C-O bond with the allylic moiety, but this process proceeds via two possible paths,[26] either in a step-wise way, replacing first the Cl anion by the KCO_3^- one, and second the C-O bond formation, or the external attack of the base on the allylic moiety before releasing KCl. For all catalysts this latter strategy is more expensive kinetically, specially for the catalysts bearing the cinnamyl ligand. Finally, there is a last step that consists of the decoordination of the resulting olefin bonded to the palladium from **III**. This last step of the preactivation is thermodynamically unfavoured by roughly 10 kcal/mol for the allylic catalysts, whereas isoenergetic or even favoured for the cinnamyl ones. Kinetically the upper energy barrier that leads to the catalytic species **IV** is based on the transition state **I-II**, confirming energy barriers of 25.3, 19.5, 23.8, and 21.9 kcal/mol for the catalysts with the allyl ligand, bearing IPr, IPr*, SIPr and IMes ligands, respectively. Those energy barriers are modified slightly with cinnamyl, to 23.2, 19.4, 23.6 and 27.0 kcal/mol, respectively. Thus, the destabilization is worse for the SIPr ligand, by 5.1 kcal/mol, whereas the corresponding barrier is 2.0 kcal/mol lower for IPr in agreement with results included in Table 3.

From the catalytic species **IV** there is a first coordination of the amide substrate, followed by the C-N bond cleavage of the former amide via transition state **V-VI**. Even though this step is apparently not kinetically facile, it counts with energy barriers that range from 26.8 for IPr* to 31.6 kcal/mol for SIPr, thus becoming the rate determining step (rds). Those values with cinnamyl decrease by 7.4 and 3.5 kcal/mol, respectively, because of the lower relative stability of the reference intermediate **II** for the catalysts including cinnamyl. Next, from **VI** the second incorporation of a K_2CO_3 molecule is strongly favoured to stabilize the metal sphere, before the release of KNPhCOO*t*Bu, with a maximum kinetic cost of 15.5 kcal/mol.

The second substrate, *i.e.* the amine, then bonds to palladium and with a barrierless process a molecule of $KHCO_3$ is lost to facilitate the final C-N bond formation that leads to the product. This last energy barrier has a reasonable kinetic cost that ranges from 17.3 kcal/mol for the IMes system to 22.3 kcal/mol for IPr*. To point out that all combinations were tested, involving the three potential actors, *i.e.* the two substrates (amide and amine), and the base. It was demonstrated that the lower the sterical hindrance on the metal sphere the lower the kinetic cost. This was checked comparing the transition state **VII-VIII** that favours the release of KNPhCOO*t*Bu with the potential insertion of the amine previously. Even though the latter option is thermodynamically favoured by 8.9 kcal/mol, kinetically is disfavoured by more than 60 kcal/mol.

Conclusions

In summary, we have conducted a combined experimental and computational study of the Buchwald-Hartwig cross-coupling of amides (transamidation) using well-defined, air- and moisture-stable [(Pd(NHC)allyl precatalysts. The two key insights drawn from this study are (1) the comprehensive evaluation of a series of distinct Pd(II)–NHC precatalysts featuring different NHC scaffolds, and (2) elucidation the catalytic cycle by DFT methods for a series of different Pd(II)–NHC precatalysts. These transamidation reactions enable amide exchange under mild conditions using carbonate base and non-nucleophilic anilines, showing tolerance to sensitive functional groups that would be difficult to accomplish using other transamidation methods. A key practical feature is the use of bench-stable, commercially available Pd(II)–NHC precatalysts that enable broad scope and operational-simplicity. In a broader context, these reactions enable access to medicinally relevant amides by selectivity activating N–C(O) amide bonds by transition-metals. The combination of experiments with calculations allowed the full description of the reaction mechanism, locating the key barriers that describe the feasibility of any palladium-allyl based catalyst studied here. The larger the sterical hindrance of the allyl moiety the better the catalytic performance, amazingly not for the transition state but the reference intermediate to measure the energy barrier.

We expect that the facile access to NHC-supported acyl-palladium(II) amido intermediates, the catalyst evaluation and mechanistic details presented will enable the development of improved catalyst systems and transamidation reactions of bench-stable amide electrophiles by selective formation of acyl-metals.

Conflicts of interest

"There are no conflicts to declare"

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