Suzuki–Miyaura Cross-Coupling of Amides by N–C Cleavage Mediated by Air-Stable, Well-Defined [Pd(NHC)(sulfide)Cl_2] Catalysts: Reaction Development, Scope and Mechanism

Shiyi Yang,[†] Xiang Yu,[†] Albert Poater,*[,‡] Luigi Cavallo,[¶] Catherine S. J. Cazin,[§] Steven P. Nolan*[,§] and Michal Szostak*[,†]

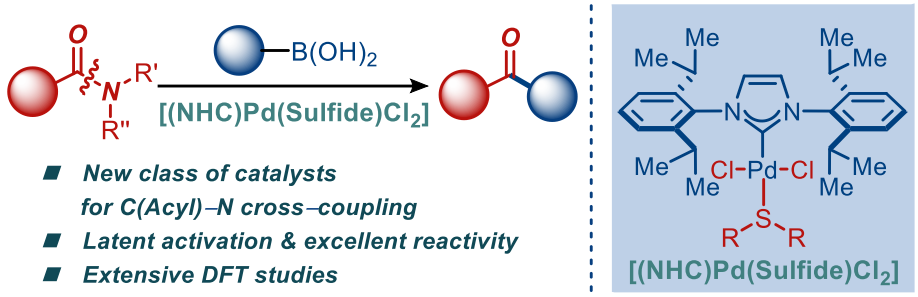
[†]*Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States*

[‡]*Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, c/ Maria Aurèlia Capmany 69, Campus Montilivi, 17003 Girona, Catalonia, Spain*

[¶]*King Abdullah University of Science & Technology, KAUST Catalysis Center (KCC), 23955-6900 Thuwal, Saudi Arabia*

[§]*Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281, S-3, B-9000 Ghent, Belgium*

Supporting Information



ABSTRACT: The Suzuki-Miyaura cross-coupling of amides by selective N–C acyl bond cleavage represents a powerful tool for constructing biaryl ketones from historically inert amide bonds. These amide bond activation reactions hinge upon efficient oxidative addition of the N–C acyl bond to Pd(0), however, in contrast to the well-researched activation of aryl halides by C(sp^2)–X oxidative addition, very few studies on the mechanism of C(acyl)–N bond oxidative addition and catalyst effect have been reported. Herein, we report a study on [Pd(NHC](sulfide)Cl_2] complexes in amide N–C bond activation. These readily prepared, well-defined, air- and moisture-stable Pd(II)–NHCs feature Me_2S (DMS = dimethylsulfide) or (CH_2CH_2)S (THT = tetrahydrothiophene) as ancillary ligands. The reaction development, kinetic studies and reaction scope are presented. DFT studies were conducted to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst effect. We expect that [Pd(NHC](sulfide)Cl_2] precatalysts featuring sulfides as well-defined, readily accessible ancillary ligands will find application in C(acyl)–X bond activation in organic synthesis and catalysis.

Introduction

In the past five years, tremendous progress has been achieved in activation of amide bonds by transition metals.[1-3] Once regarded as chemically inert due to amide resonance ($n_N \rightarrow \pi^*_{C=O}$ barrier to rotation, 15-20 mol/kcal),[4] activation of amide N–C acyl bonds has experienced a paradigm shift through ground-state-destabilization mechanism[5] that enables amides to participate in a broad range of generic cross-coupling reactions under mild conditions (Figure 1A).[1,2] This amide bond reactivity platform has captured significant attention of chemists due to the prevalence of amides in drug discovery research, agrochemistry, natural products, organic materials and biochemistry, where amides constitute the most common functional groups across various facets of academic and industrial research.[6,7]

The activation of amide C(acyl)–N bonds hinges upon efficient oxidative addition of the N–C acyl bond to Pd(0) (Figure 1A, box),[1] however, in contrast to the well-researched activation of aryl halides by C(sp^2)–X oxidative addition, very few studies on the mechanism of C(acyl)–N bond oxidative addition and catalyst effect have been reported. While early studies used Pd–phosphine and Ni–NHC catalysts for amide bond activation,[8-10] later research demonstrated that Pd–NHC complexes represent a privileged class of catalysts for amide N–C bond activation.[1a,11]

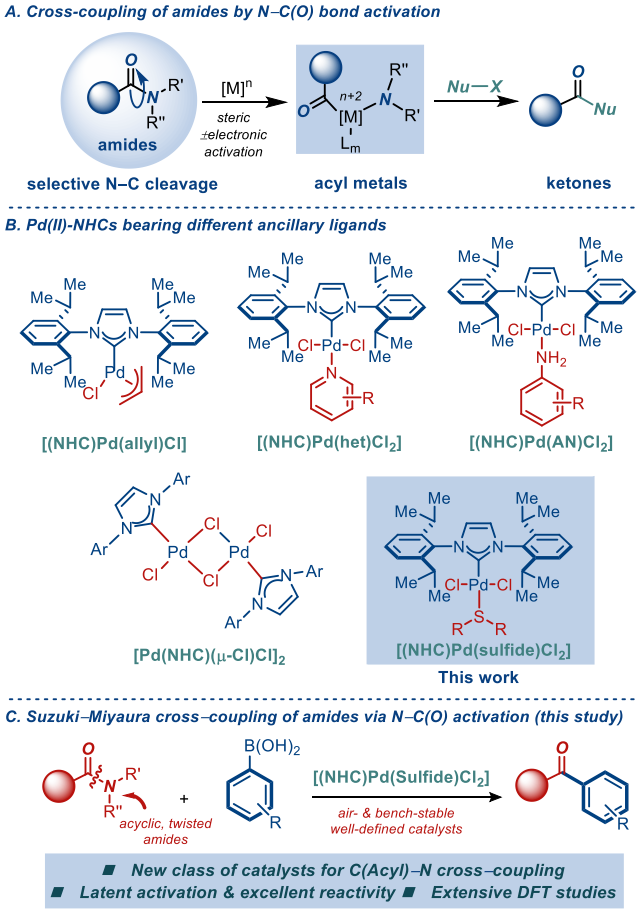


Figure 1. (a) Cross-coupling of amides by N–C(O) bond activation; (b) Pd(II)–NHCs bearing different ancillary ligands; (c) this study: Suzuki-Miyaura cross-coupling of amides via N–C(O) activation using [Pd(NHC](sulfide)Cl_2] complexes.

This class of catalysts heavily benefits from the availability of well-defined, air- and moisture-stable Pd(II)–NHC precursors, which render amide bond cross-coupling operationally-simple and applicable for a broad range of chemists.[11,12] The strong σ-donation and availability of various NHC ligands with differentiated steric properties facilitate oxidative addition of the C(acyl)–N amide bonds. The well-established functional group tolerance and broad applicability of Pd catalysis in cross-coupling enables to expand the scope of the reactions to more sensitive amide bonds using Pd(II)–NHCs.[11,12] To date, several classes of Pd(II)–NHCs bearing different ancillary throw-away ligands[13] enabling activation to catalytically-active monoligated NHC–Pd(0) have been established in amide bond cross-coupling, including allyl-based ligands,[14] heterocycle-based ligands,[15] aniline-based ligands[16] and halide-bridged dimers,[17] such as [(NHC)Pd(R-allyl)Cl], [(NHC)Pd(het)Cl_2], [(NHC)Pd(AN)Cl_2], [(NHC)Pd(μ-Cl)Cl]$_2$. To ensure broad applicability of amide bond cross-coupling, it is imperative that new classes of catalysts are identified and the mechanism of oxidative addition of C(acyl)–N amide bonds is investigated (Figure 1B).

Herein, we report a study on [Pd(NHC](sulfide)Cl_2] complexes in amide N–C bond activation (Figure 1C). These readily prepared, well-defined, air- and moisture-stable Pd(II)–NHC complexes feature Me_2S (DMS = dimethylsulfide) and (CH_2CH_2)S (THT = tetrahydrothiophene) as ancillary ligands.[18] The reaction development, kinetic studies and reaction scope are presented. DFT studies were conducted to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst effect in the cross-coupling. We expect that [Pd(NHC](sulfide)Cl_2] precatalysts featuring sulfides as well-defined, readily accessible ancillary ligands will find application in C(acyl)–X bond activation in organic synthesis and catalysis.

Results and Discussion

Considering the key effect of stabilizing ancillary ligands in Pd(II)–NHC precatalysts observed in previous studies by our groups,[11–14,18] we were attracted to Pd(II)–NHC complexes bearing *S*-stabilizing ligands. To ensure broad applicability of Pd(II)–NHC complexes for cross-coupling, catalysts must be easy to prepare, low cost, modular and air-stable. In the domain of Pd(II)–NHCs, the stabilization is afforded by the ancillary throw-away ligand, which should be readily removed during the activation step to Pd(0)–NHC, yet provide high bench- and air-stability of Pd(II)–NHC complexes.[11,12] [Pd(NHC](sulfide)Cl_2] complexes bearing DMS (DMS = Me_2S) and THF (THT = (CH_2CH_2)S) ligands are readily prepared from NHC salts and Pd(sulfide)Cl_2 using K_2CO_3 as a mild base on gram scale (Scheme 1).[18] DMS and THT are broadly available from the industrial synthesis on scale as scenting materials.

Our initial optimization is summarized in Table 1. *N*-Boc/Ph amide was selected as a model substrate because this class of ground-state-destabilized amides enables direct activation of common 1° and 2° amides through site selective *N-tert*-butoxycarboxylation of benzamides.[1a,b] This class of amides features decreased amidic resonance (RE = 7.2 kcal/mol, RE = resonance energy) in presence of moderate twisting of amide bond (τ = 29.1°; χ_N = 8.4°, Winkler-Dunitz distortion, τ = twist angle, χ_N = N pyramidalization angle). [Pd(NHC](sulfide)Cl_2] complexes bearing IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as NHC ligand and DMS and THT as sulfide ancillary ligands were selected for initial screening (Chart 1). In addition, we screened a more sterically-demanding NHC analogue, IPr*, bearing 2,6-bis(benzhydryl) substitution (IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) to test the effect of the increased steric bulk on the oxidative addition of the C(acyl)–N amide bond.[11,12]

Scheme 1. Facile Synthesis of [Pd(NHC](sulfide)Cl_2] Complexes

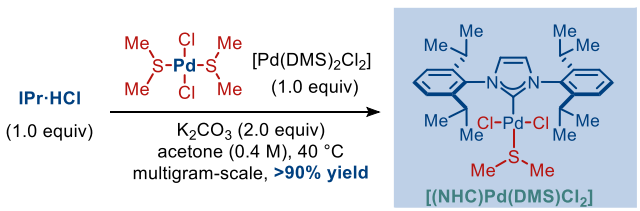
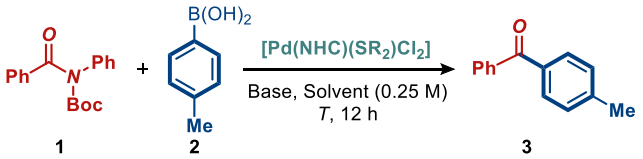


Table 1. Optimization of the Reaction Conditions[a]



Entry	[Pd] catalyst	[Pd] loading (mol%)	Base	Solvent	*T* (°C)	Yield (%)
1[b]	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	60	82
2	[Pd(IPr)(THT)Cl$_2$]	0.5	K_2CO_3	THF	60	80
3	[Pd(IPr*)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	60	0
4	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	40	0
5	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	80	87
6	[Pd(IPr)(DMS)Cl$_2$]	0.25	K_2CO_3	THF	60	15
7	[Pd(IPr)(DMS)Cl$_2$]	1.0	K_2CO_3	THF	60	85
8	[Pd(IPr)(THT)Cl$_2$]	1.0	K_2CO_3	THF	60	84
9	[Pd(IPr*)(THT)Cl$_2$]	1.0	K_2CO_3	THF	60	0
10[b]	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	40	24
11[b]	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	THF	60	97
12	[Pd(IPr)(DMS)Cl$_2$]	0.5	Cs_2CO_3	THF	60	17
13	[Pd(IPr)(DMS)Cl$_2$]	0.5	Na_2CO_3	THF	60	8
14	[Pd(IPr)(DMS)Cl$_2$]	0.5	Rb_2CO_3	THF	60	38
15	[Pd(IPr)(DMS)Cl$_2$]	0.5	KF	THF	60	62
16	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_3PO_4	THF	60	35
17	[Pd(IPr)(DMS)Cl$_2$]	0.5	KOAc	THF	60	<2
18	[Pd(IPr)(DMS)Cl$_2$]	0.5	$KHCO_3$	THF	60	<2
19	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	DME	60	10
20	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	Dioxane	60	25
21	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	Toluene	60	39
22	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	MeCN	60	<2
23	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	EtOH	60	<2
24	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	EtOAc	60	79
25	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	2-MeTHF	60	95
26[b]	[Pd(IPr)(DMS)Cl$_2$]	0.5	K_2CO_3	2-MeTHF	60	>98
27[b]	[Pd(IPr)(DMS)Cl$_2$]	0.25	K_2CO_3	2-MeTHF	60	>98
28[b]	[Pd(IPr)(DMS)Cl$_2$]	0.1	K_2CO_3	2-MeTHF	60	98
29[b]	[Pd(IPr)(DMS)Cl$_2$]	0.25	K_2CO_3	2-MeTHF	40	88
30[b]	[Pd(IPr)(DMS)Cl$_2$]	0.25	K_2CO_3	2-MeTHF	23	<2
31	[Pd(IPr)(DMS)Cl$_2$]	0.25	K_2CO_3	2-MeTHF	60	68
32[b]	[Pd(IPr)(THT)Cl$_2$]	0.1	K_2CO_3	2-MeTHF	60	95
33[b]	[Pd(IPr*)(DMS)Cl$_2$]	0.1	K_2CO_3	2-MeTHF	60	0

[a]Conditions: amide **1a** (1.0 equiv), 4-Tol-B(OH)$_2$ (2.0 equiv), base (3.0 equiv), [Pd] (0.10-0.5 mol%), solvent (0.25 M), *T*, 12 h. [b]water (5.0 equiv) as additive. SR$_2$ = DMS, THT (SMe$_2$, S(CH$_2$CH$_2$)$_2$); NHC = IPr, IPr*.

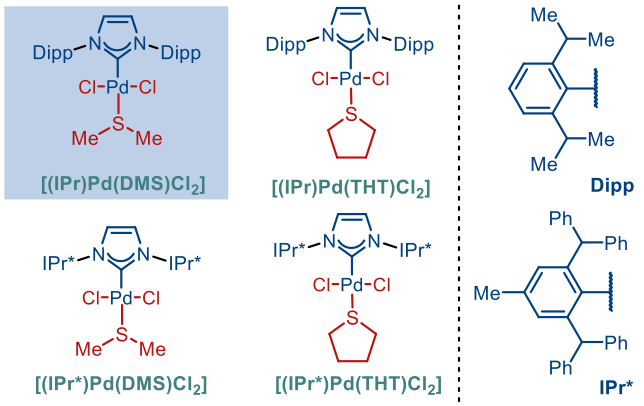
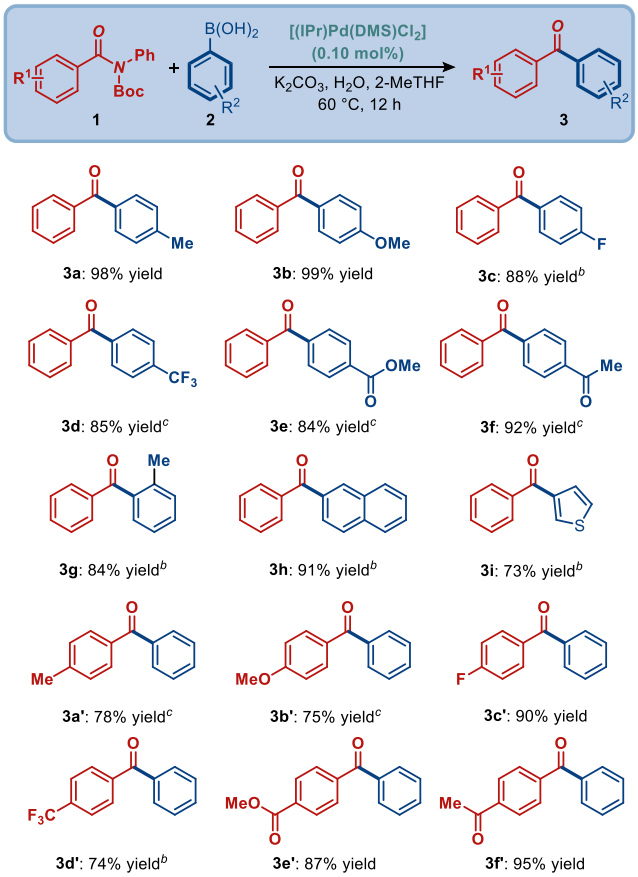


Chart 1. Structures of [Pd(NHC)(sulfide)Cl$_2$] catalysts.

We identified conditions using K_2CO_3 as a mild carbonate base in THF as a solvent at 60 °C that promoted the cross-coupling in 82% yield using 0.5 mol% [Pd(IPr)(Me$_2$S)Cl$_2$] as a catalyst (Table 1, entry 1). Interestingly, the THT congener, [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$], showed comparable albeit slightly lower reactivity under these conditions (Table 1, entry 2), while the bulky [Pd(IPr*)(Me$_2$S)Cl$_2$] was completely unreactive (Table 1, entry 3). We further established that temperature is a critical factor, with no reaction taking place at 40 °C (Table 1, entry 4), while a modest improvement in yield was observed at 80 °C (Table 1, entry 5). This finding suggests that 60 °C is required for catalyst activation, which is an important aspect of Pd(II)–NHC precatalyst stability. Furthermore, initial screening of the effect of catalyst loading indicated that a modest increase of the reaction efficiency is observed at 1 mol% with [Pd(IPr)(Me$_2$S)Cl$_2$] and [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$] catalysts, while [Pd(IPr*)(Me$_2$S)Cl$_2$] was unreactive (Table 1, entries 6-9).

Importantly, we next established that the addition of water significantly improves the reaction efficiency (Table 1, entries 10-11). Under these modified conditions, the reaction yield is close to quantitative using [Pd(IPr)(Me$_2$S)Cl$_2$] at 60 °C (Table 1, entry 10), while the reactivity initiates at 40 °C (Table 1, entry 11 cf. entry 4). This suggests that water aids in [Pd(IPr)(Me$_2$S)Cl$_2$] activation to monoligated Pd(0)–NHC. Extensive screening of different bases revealed that KF, Rb_2CO_3 and K_3PO_4 promote the cross-coupling, albeit in lower yields than using K_2CO_3, while other bases, such as Cs_2CO_3, Na_2CO_3, KOAc and $KHCO_3$ are less effective (Table 1, entries 12-18). We next evaluated different solvents and established that DME, dioxane, toluene, MeCN and EtOH were less effective (Table 1, entries 19-22), while EtOAc, and in particular, 2-MeTHF gave optimal results (Table 1, entries 23-24). It is noteworthy that both of these solvents are considered environmentally-friendly and sustainable by green chemistry principles, which is an important finding considering [Pd(NHC](sulfide)Cl$_2$] precatalysts for amide N(acyl)–C activation.[1,6,7] Furthermore, the addition of water had a beneficial effect on the cross-coupling using 2-MeTHF, resulting in a major improvement in the reaction efficiency (Table 1, entries 26-28). Under these conditions the cross-coupling proceeded in a close to quantitative yield at 0.1 mol% catalyst loading (Table 1, entry 28). Moreover, the reaction is initiated at 40 °C in high yield (Table 1, entry 29), suggesting that catalyst activation and/or transmetallation are more facile under these conditions. Note, however, that no reaction takes place at 23 °C (Table 1, entry 30). It is also instructive to compare the reaction efficiency at 0.25 mol% Pd loading under anhydrous conditions in 2-MeTHF (Table 1, entry 31) vs. THF (Table 1, entry 6), indicating the beneficial effect of 2-MeTHF on the amide C(acyl)–N cross-coupling using [Pd(NHC](sulfide)Cl$_2$], which could be useful for amide electrophiles that require strictly anhydrous conditions.

Scheme 2. Scope of the Suzuki-Miyaura Cross-Coupling of Amides by [(IPr)Pd(DMS)Cl$_2$] Catalysis[a]



[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), K_2CO_3 (3.0 equiv), [Pd] (0.10 mol%), H_2O (5 equiv), 2-MeTHF (0.25 M), 60 °C, 12 h. [b][Pd] (0.25 mol%). [c][Pd] (0.50 mol%). See SI for details.

Finally, we established that [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$] also gives high conversion in 2-MeTHF, while [Pd(IPr*)(Me$_2$S)Cl$_2$] was unreactive (Table 1, entries 32-33). This permits to establish the order of reactivity as [Pd(IPr)(Me$_2$S)Cl$_2$] > [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$] >> [Pd(IPr*)(Me$_2$S)Cl$_2$].

With the optimized conditions in hand, the scope of the Suzuki-Miyaura cross-coupling was briefly investigated (Scheme 2). We used [Pd(IPr)(Me$_2$S)Cl$_2$] at 0.1 mol% loading, while in select cases the loading was increased to 0.25 or 0.5 mol% to ensure full conversion. We found that the scope of the amide cross-coupling using [Pd(IPr)(Me$_2$S)Cl$_2$] is broad and encompasses various arylboronic acids and benzamides. As such, electronic variation on the boronic acid component is readily compatible, including electron-neutral (**3a**), electron-rich (**3b**) and electron-deficient boronic acids (**3c**–**3f**). Furthermore, steric hindrance (**3g**) is well-tolerated by this class of catalysts. Moreover, polyconjugated aromatic (**3h**) and heterocyclic boronic acids (**3i**) could be employed as well. Importantly, these conditions are well-compatible with electrophilic functional groups, such as esters (**3e**) and ketones (**3f**) that would be problematic using traditional hard organometallics. In terms of benzamide scope, the

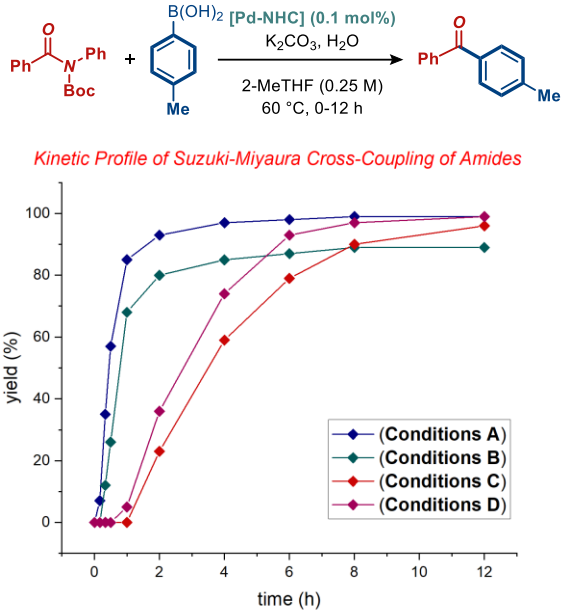


Figure 2. Kinetic studies of the Suzuki-Miyaura cross-coupling of amides using [Pd(NHC)(SR$_2$)Cl$_2$] precatalysts[a] [a]Conditions: amide (1.0 equiv), 4-Tol-B(OH)$_2$ (2.0 equiv), K_2CO_3 (3.0 equiv), [Pd] (0.10 mol%), H_2O (5 equiv), 2-MeTHF (0.25 M), 60 °C, 0-12 h. [Pd–NHC] = [Pd(IPr)(cin)Cl] (Conditions A), [Pd(IPr)(3-Cl-py)Cl$_2$] (Conditions B), [Pd(IPr)(THT)Cl$_2$] (Conditions C), [Pd(IPr)(DMS)Cl$_2$] (Conditions D). THT = S(CH$_2$CH$_2$)$_2$; DMS = SMe$_2$. See SI for details.

cross-coupling is also compatible with electron-neutral (**3a'**), electron-rich (**3b'**) and electron-deficient amide electrophiles (**3c'**–**3f'**). Again, electrophilic functional groups are well-accommodated on the amide component, providing useful handles for functionalization (**3e'**–**3f'**). Overall, the scope of the cross-coupling mediated by [Pd(IPr)(Me$_2$S)Cl$_2$] compares well with other Pd(II)–NHC precatalysts,[11,12] while having the benefit of environmentally-friendly and sustainable 2-MeTHF as a reaction medium.[19,20]

We next conducted kinetic studies to investigate the effect of air- and bench-stable [Pd(IPr)(R$_2$S)Cl$_2$] complexes on amide C(acyl)–N coupling (Figure 2). Allyl-based and heterocycle-based complexes bearing the same IPr ligand, [(IPr)Pd(cin)Cl] and [(IPr)Pd(3-Cl-py)Cl$_2$] were selected for comparison. Interestingly, we found that both [Pd(IPr)(R$_2$S)Cl$_2$] catalysts, namely [Pd(IPr)(Me$_2$S)Cl$_2$] and [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$] behave as latent precatalysts in the cross-coupling. Allyl- and heterocycle based catalysts, [(IPr)Pd(cin)Cl] and [(IPr)Pd(3-Cl-py)Cl$_2$] showed more facile activation to the active Pd(0)–NHC under the developed conditions (1 h: [(IPr)Pd(cin)Cl], 85% yield; [(IPr)Pd(3-Cl-py)Cl$_2$], 68% yield), while [Pd(IPr)(Me$_2$S)Cl$_2$] and [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$] gave no initiation (1 h: [Pd(IPr)(Me$_2$S)Cl$_2$], <5% yield; [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$], <5% yield). However, after the initiation (1-2 h), both catalysts superseded the heterocycle-based [(IPr)Pd(3-Cl-py)Cl$_2$] (12 h: [Pd(IPr)(Me$_2$S)Cl$_2$], [Pd(IPr)((CH$_2$CH$_2$)S)Cl$_2$], >95%), while the more reactive of the two [Pd(IPr)(Me$_2$S)Cl$_2$] matched the reactivity of the allyl-based [(IPr)Pd(cin)Cl] (12 h: [Pd(IPr)(Me$_2$S)Cl$_2$], >98%). Overall, the kinetic studies demonstrate latency

and high stability of [Pd(IPr)(R_2S)Cl_2] catalysts, which may open the door for the development of valuable latent protocols for amide bond cross-coupling.

Intrigued by the unusual profile of [Pd(IPr)(R_2S)Cl_2] catalysts, we conducted extensive DFT studies to gain insight into the mechanism of C(acyl)–N bond oxidative addition and catalyst effect of this class of catalysts...

Conclusions

In summary, we have reported Suzuki-Miyaura cross-coupling of amides by N–C bond activation mediated by [Pd(NHC](sulfide)Cl_2] complexes. These complexes represent a new class of readily prepared, air- and bench-stable catalysts for C(acyl)–N amide bond activation, where the stability is provided by sulfide ancillary ligands. The complexes show high reactivity in amide bond cross-coupling, enabling efficient Suzuki-Miyaura coupling at low catalyst loading. These complexes operate in environmentally-friendly and sustainable 2-MeTHF as a reaction solvent. An important feature is the unique latency exhibited by [Pd(NHC](sulfide)Cl_2] complexes, which could be exploited in synthetic protocols for amide bond activation. Extensive DFT studies provided insight into the mechanism of C(acyl)–N oxidative addition and catalyst activation pathway. We anticipate that sulfide-based Pd(II)–NHC catalysts will find application in C(acyl)–X bond activation in organic synthesis and catalysis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

albert.poater@udg.edu

steven.nolan@ugent.be

michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interest.

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