Buchwald-Hartwig Amination of (Hetero)Aryl Tosylates Using a Well-Defined N-Heterocyclic Carbene / Palladium(II) Pre-Catalyst

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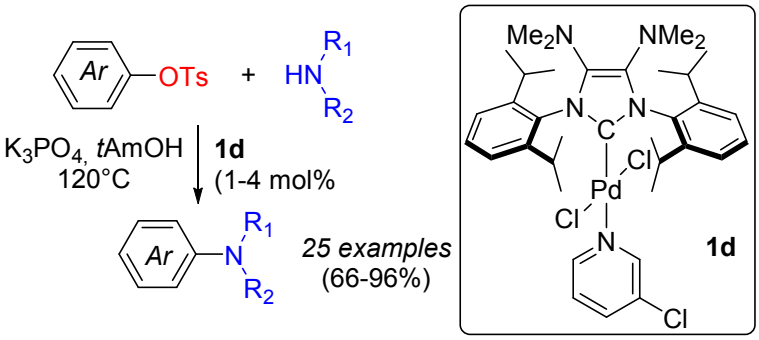
ABSTRACT

The cross-coupling of aryl tosylates with amines and anilines was achieved by using for the first time a Pd-NHC system based on the popular Pd-PEPPSI pre-catalyst platform in which the anchoring imidazol-2-ylidene ligand $IPr^{(NMe_2)_2}$, incorporates two dimethylamino groups as backbone substituents enhancing both the electronic and steric properties of the carbene. The system optimization and its application scope are disclosed.



INTRODUCTION

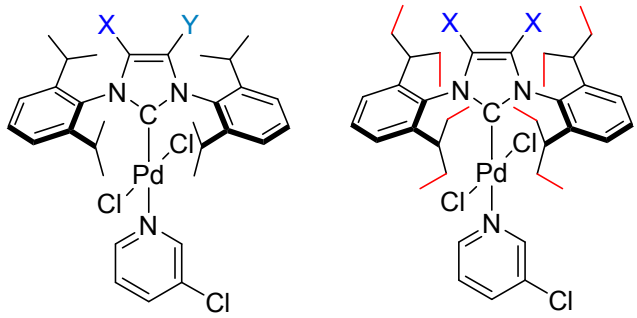
The palladium-catalyzed Buchwald-Hartwig amination has been successfully established as a highly valuable method for the formation of C(sp^2)-N bonds, having important applications in both academia and industry.[1,2] Whereas the amination of aryl halides and triflates is efficiently performed by numerous catalytic systems under very mild reaction conditions, only a handful of catalytic systems were reported for the Pd-catalyzed amination of aryl sulfonates such as aryl tosylates and mesylates.[3,4] These alternative electrophiles are attractive as commodity chemicals being readily available from phenols, easy to purify and stable against hydrolysis, but the activation/cleavage of the C_{aryl}-O bond remains a challenging problem.

N-Heterocyclic Carbenes (NHCs)[5] have been well established as ubiquitous and highly efficient supporting ligands in Pd-catalyzed cross-coupling reactions,[6] thanks to their strong electron donation and steric protection of the palladium center. Yet, – to our knowledge – the amination of aryl sulfonates using a Pd-NHC catalyst has never been documented previously.[7,8] Starting from the well-known and popular Pd-PEPPSI-IPr pre-catalyst, originally disclosed by Organ,[9] we report herein that tuning of the stereoelectronic structure of the NHC ligand is the clue to success in their implementation in this challenging catalytic reaction.

RESULTS AND DISCUSSION

The Pd-PEPPSI-NHC complexes **1a-d** and **2a-b** were selected as pre-catalysts for the study (Figure 1). Based on the assumption that the rate-limiting step of the process resides in the oxidative addition of the C(sp^2)-O bond of aryl tosylates and that it would be facilitated by electronic enhancement of the Pd(0) species, we selected complexes **1c** and **1d**, previously disclosed as pre-catalysts in our earlier work.[10] The adjunction of one or two dimethylamino groups as backbone substituents of IPr was indeed shown to sequentially increase the electron donation and steric hindrance of the resulting IPr^{NMe_2} and $IPr^{(NMe_2)_2}$ carbenes, resulting in a considerable and sequential enhancement of the catalytic performances of the corresponding **1c** and **1d** pre-catalysts in the Buchwald-Hartwig amination of aryl chlorides. On the other hand, for comparative purposes, we chose to test the pre-catalysts **2a-b** bearing the sterically

hindered, yet flexible NHCs IPent and IPent^{Cl_2}, since they still represent the most efficient Pd-NHC catalytic systems in amination reactions up to date.[11] For the sake of comparison, complex **1b**, featuring the IPr^{Cl_2} ligand, was also included in the study.



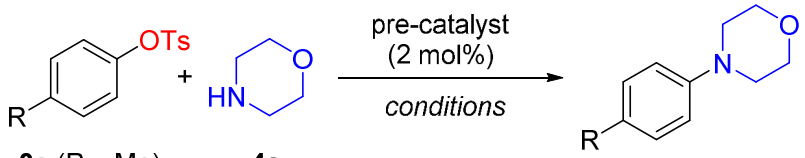
[Pd]	NHC	X	Y
1a	IPr	H	H
1b	IPr^{Cl_2}	Cl	Cl
1c	IPr^{NMe_2}	NMe_2	H
1d	IPr$^{(NMe_2)_2}$	NMe_2	NMe_2

[Pd]	NHC	X
2a	IPent	H
2b	IPent^{Cl_2}	Cl

Figure 1. Palladium PEPPSI-type complexes considered in this study (PEPPSI = Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation). IPr = 1,3-bis(2,6-diisopropylphenyl)-2*H*-imidazol-2-ylidene; IPent = 1,3-bis(2,6-bis(3-pentyl)phenyl)-2*H*-imidazol-2-ylidene.

Their respective catalytic efficiencies were evaluated in the coupling between aryl tosylates **3a-b** and morpholine **4a** as model reaction to yield the corresponding arylated amines **5aa** and **5ba** (Table 1).

Table 1. Screening of pre-catalysts 1a-d and 2a-b and reaction conditions for the Buchwald-Hartwig amination of ArOTs.[a]



3a (R = Me)
3b (R = OMe)

4a (1.5 eq.)

5aa-ba

Entry	Pre-catalyst	Substrate	base	solvent	T (°C)	GC yield (%)[b]
1	**1a**	**3a**	K_3PO_4	*t*AmOH	120	5
2	**1a**	**3b**	K_3PO_4	*t*AmOH	120	1

3	**1b**	**3a**	K_3PO_4	*t*AmOH	120	4
4	**1b**	**3b**	K_3PO_4	*t*AmOH	120	0
5	**1c**	**3a**	K_3PO_4	*t*AmOH	120	15
6	**1c**	**3b**	K_3PO_4	*t*AmOH	120	3
7	**1d**	**3a**	K_3PO_4	*t*AmOH	120	99
8	**1d**	**3b**	K_3PO_4	*t*AmOH	120	43
9	**2a**	**3a**	K_3PO_4	*t*AmOH	120	99
10	**2a**	**3b**	K_3PO_4	*t*AmOH	120	36
11	**2b**	**3a**	K_3PO_4	*t*AmOH	120	91
12	**2b**	**3b**	K_3PO_4	*t*AmOH	120	31
13	**1d**	**3a**	K_3PO_4	*t*AmOH	110	96
14	**1d**	**3a**	K_3PO_4	*t*AmOH	100	44
15	**1d**	**3a**	K_3PO_4	*t*BuOH	110	94
16	**1d**	**3a**	K_3PO_4	DMF	110	5
17	**1d**	**3a**	K_3PO_4	dioxane	110	26
18	**1d**	**3a**	K_3PO_4,$2H_2O$	*t*AmOH	110	95
19	**1d**	**3a**	K_2CO_3	*t*AmOH	110	4
20	**1d**	**3a**	Cs_2CO_3	*t*AmOH	110	73

[a] Reaction conditions: ArOTs (0.5 mmol), morpholine (0.75 mmol), pre-catalyst (0.01 mmol, 2 mol%), base (1.5 mmol), solvent (1.5 mL), 18h. [b] Calibrated GC yields were reported using dodecane as the internal standard and were averaged over two runs.

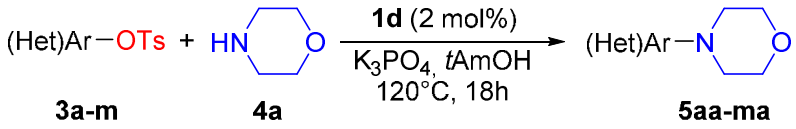
Under the standard conditions (2 mol% of pre-catalyst, K_3PO_4 as base, *tert*-amyl alcohol as solvent and 120°C as reaction temperature), the reference Pd-PEPPSI-IPr (**1a**) showed almost no ability to give products **5aa** and **5ba** (Entries 1-2). Whereas the more-electron deficient Pd-PEPPSI-IPr^{Cl_2} (**1b**) gave even worse results, the incorporation of one dimethylamino group onto the backbone of IPr induced a clear, yet still limited improvement of the activity of Pd-PEPPSI-IPr$^{(NMe_2)}$ (**1c**) (Entries 3-6). To our delight, a dramatic catalytic enhancement was observed when a second dimethylamino group was incorporated into the IPr-skeleton, with a 99% yield in **5aa** and 43% yield in **5ba** using Pd-PEPPSI-

IPr$^{(NMe_2)_2}$ (**1d**) as pre-catalyst (Entries 7-8). Such performances were approached upon using the Pd-PEPPSI-IPent (**2a**) but with a smaller 36% yield in **5ba** starting from the more difficult 4-methoxyphenyl tosylate **3b** (Entry 10), compared to the 43% yield obtained using **1d**. As in the IPr series, diminishing the electron donation of the IPent ligand by incorporating two chlorides in **2b** led to a small decrease in product yields compared to **2a**. Taken together, these results suggest that the amination of aryl tosylates is facilitated by a synergy between an electronic enrichment of the metallic center and an increase in the steric crowding of the NHC ligand, with an optimal catalytic performance reached with the Pd-PEPPSI-IPr$^{(NMe_2)_2}$ (**1d**).[10a,12] A further rapid optimization of the previous standard reaction conditions using the latter pre-catalyst (**1d**) revealed a strong influence of the temperature on the outcome of the reaction with diminished yields of 96% and 44% when reducing the temperature to 110°C and 100°C respectively (Entries 13-14). As observed earlier in most reported cases of amination of aryl tosylates, the reaction proceeds well only in alcoholic solvents such as *t*BuOH or, even better *t*AmOH, probably due to the good solubility of the substrates in these solvents. The use of K_3PO_4 (indifferently anhydrous or hydrated) as a base was found to be crucial for the success of the coupling, since the use of carbonate bases gave lower yields (Entries 19-20), and that stronger bases such as KOH or KO*t*Bu only led to the hydrolysis of the sulfonate ester.

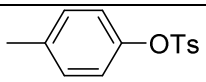
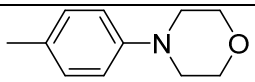
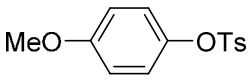
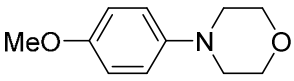
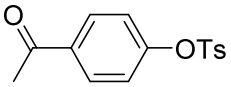
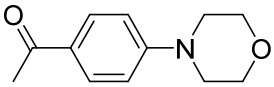
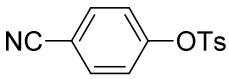
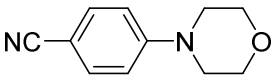
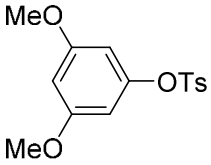
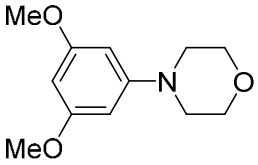
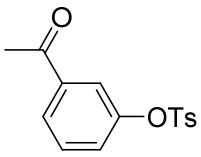
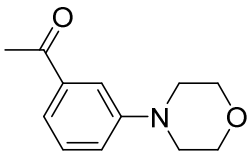
With the fully optimized catalytic conditions in hand, the substrate scope was then investigated, starting with the variation of the (hetero)aryl tosylate partner using morpholine **4a** as the common amine and 2 mol% of pre-catalyst **1d** (Table 2). Aryl tosylates **3a-d** bearing electronically-diverse *para* substituents (methyl, methoxy, acetyl, cyano respectively) were efficiently coupled in good yields (Entries 1-4). Nevertheless, for the most difficult **3b**, it appeared necessary to increase the catalyst loading up to 4 mol% to reach an acceptable 73% isolated yield. The *meta* substitution of the aryl group was found not problematic (substrates **3e-f**, entries 5-6), and the electron-rich 3,5-dimethoxyphenyl tosylate **3e** could be successfully employed to give **5ea** in an excellent 91% yield. Gratifyingly, the mildly basic conditions of the reaction tolerate the presence of base-sensitive functional groups as aryl group substituents. Whereas the sterically highly crowded mesityl tosylate **3i** remained untouched under

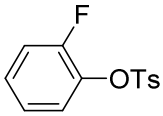
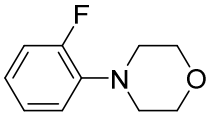
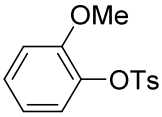
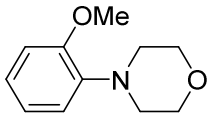
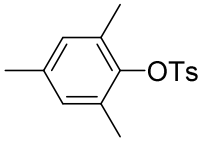
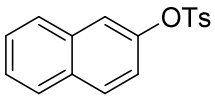
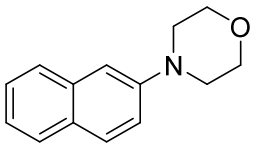
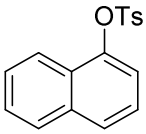
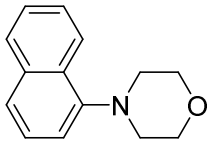
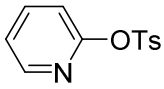
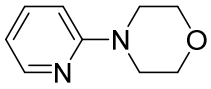
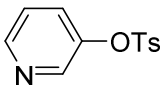
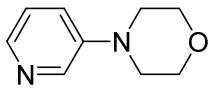
these conditions (Entry 9), the coupling of *ortho*-substituted substrates **3g-h** bearing a fluoro or methoxy substituent smoothly proceeded to give **5ga** and **5ha** in 66% and 88% (with 4 mol% of **1d** in the latter case) respectively, indicating that the catalytic species can adapt to some steric constraint in the aryl tosylate partner. Furthermore, whereas the naphthyl-based amines **5ia-ja** were obtained in very good yields, 2-and 3-pyridinyl tosylates **3k-l** were shown to be suitable substrates and yielded the corresponding amines in good yields (Entries 10-11 and 12-13).

Table 2. Buchwald-Hartwig amination of (hetero)aryl tosylates 3a-l with morpholine (4a) using pre-catalyst 1d.[a]



3a-m **4a** **5aa-ma**

Entry	substrate	product	Yield (%)[b]
1	 **3a**	 **5aa**	95
2	 **3b**	 **5ba**	73[c]
3	 **3c**	 **5ca**	87
4	 **3d**	 **5da**	80[d]
5	 **3e**	 **5ea**	91
6	 **3f**	 **5fa**	77

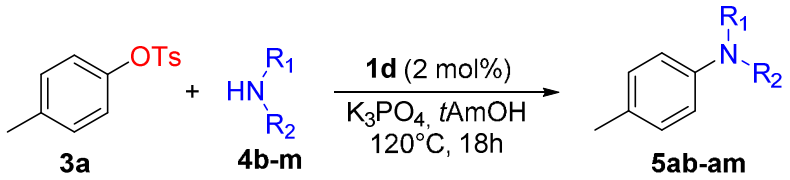
7	 **3g**	 **5ga**	66
8	 **3h**	 **5ha**	88[c]
9	 **3i**	-	0
10	 **3j**	 **5ja**	84
11	 **3k**	 **5ka**	95
12	 **3l**	 **5la**	70
13	 **3m**	 **5ma**	87

*[a] Reaction conditions: ArOTs (0.5 mmol), morpholine (0.75 mmol), **1d** (2 mol%), K_3PO_4 (1.5 mmol), tAmOH (1.5 mL), 120°C. [b] Isolated yield, average of two runs. [c] 4 mol% of **1d**. [d] 1 mol% of **1d**.*

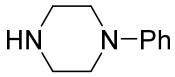
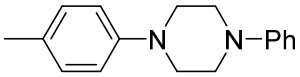
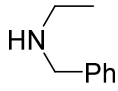
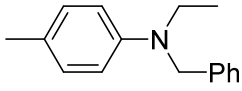
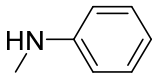
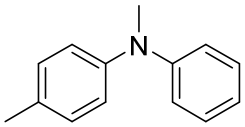
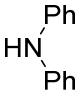
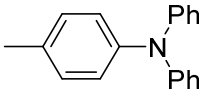
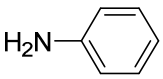
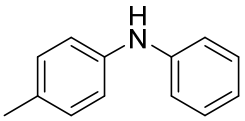
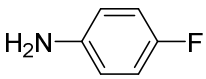
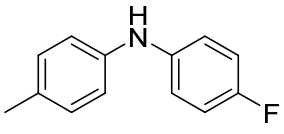
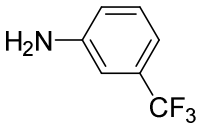
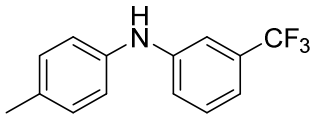
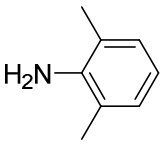
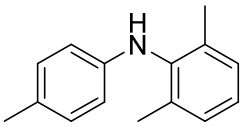
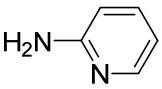
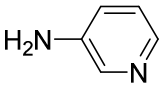
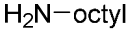
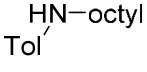
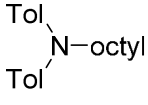
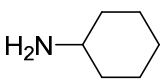
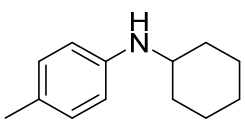
We next turned our attention to the scope of the reaction with respect to the nature of the amine using 4-toluenyl tosylate **3a** as the electrophile partner (Table 3). Irrespective to their electronic and steric nature, secondary cyclic (**4a-d**), acyclic (**4e**) amines, as well as N-methyl aniline **4f** and even the crowded and weakly nucleophilic diphenylamine **4g** underwent the transformation in good to excellent yields (Entries 1-6). Starting with the unsubstituted aniline **4h** yielded the coupling product **5ah** in 91% isolated yield and no trace of the corresponding di-arylated aniline could be detected (Entry 7). More challenging anilines **4i-j** bearing electron-withdrawing groups such as 4-fluoro and 3-trifluoromethyl

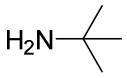
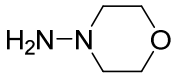
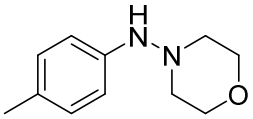
respectively and the crowded 2,6-dimethylaniline **4k** were smoothly engaged in this reaction in excellent yields, albeit requiring a small increase of the catalyst loading up to 4 mol% for the first two anilines. However, no conversion was detected when employing the low nucleophilic 2-and 3-aminopyridines **4l-m** (Entries 11-12), leaving the substrate **3a** untouched. The primary aliphatic amines were found to be suitable coupling partners, but exhibiting different outcomes according to their steric hindrance. The reaction between **3a** and octylamine **4n** proceeded well but appeared not very selective, affording the mono-and bis-arylation products **5an** and **5an'** in a 27/73 ratio (Entry 13). Under the same conditions, the use of the slightly more crowded cyclohexylamine **4o** allowed the efficient isolation of the mono-arylated product **5ao** in 93% yield (Entry 14), but the catalytic system appeared inefficient in coupling **3a** with the highly congested *tert*-butylamine **4p** (Entry 15). Finally, the procedure could be extended to the hydrazine derivative 4-aminomorpholine **4q**. The general applicability of the catalytic system throughout the above screening led us to conclude that the amine partner might not be involved in the rate determining step of the catalytic cycle, our observations being more consistent with the cleavage of the C_{Ar}-O bond of the aryl tosylate as being the rate limiting step of the catalytic cycle.

Table 3. Buchwald-Hartwig amination of 4-toluenyl tosylate 3a with amines and anilines using pre-catalyst 1d.[a]



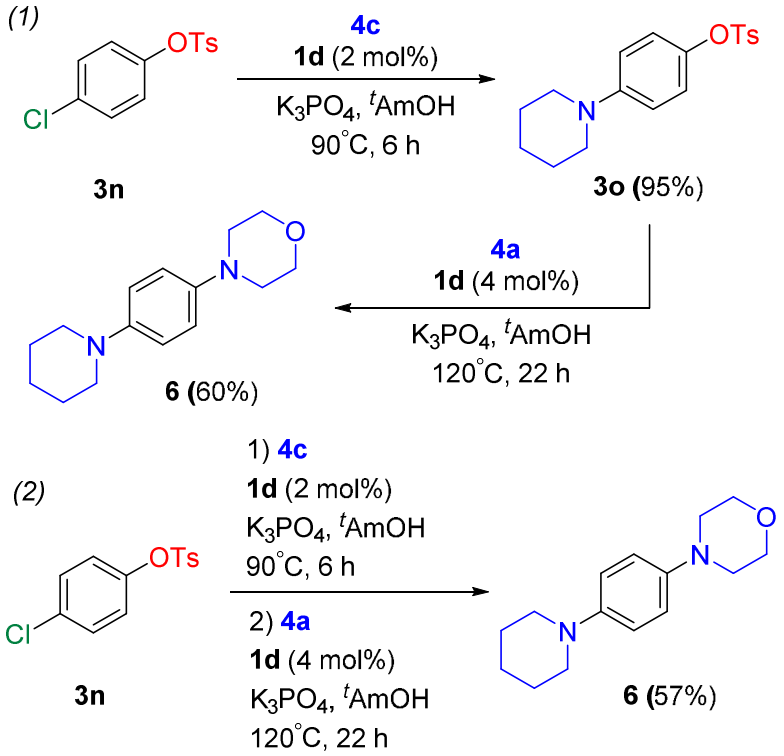
Entry	substrate	product	Yield (%)[b]
1	HN **4b**	N **5ab**	91
2	HN **4c**	N **5ac**	82

3	 **4d**	 **5ad**	96
4	 **4e**	 **5ae**	91
5	 **4f**	 **5af**	91
6	 **4g**	 **5ag**	94[c]
7	 **4h**	 **5ah**	91
8	 **4i**	 **5ai**	96[c]
9	 **4j**	 **5aj**	92[c]
10	 **4k**	 **5ak**	85
11	 **4l**	-	0
12	 **4m**	-	0
13[d]	 **4n**	 **5an**  **5an'**	82[e] (27/73[f])
14	 **4o**	 **5ao**	93

15	 **4p**	-	0
16	 **4q**	 **5aq**	83

*[a] Reaction conditions: **3a** (0.5 mmol), amine (0.75 mmol), **1d** (2 mol%), K_3PO_4 (1.5 mmol), tAmOH (1.5 mL), 120°C. [b] Isolated yield, average of two runs. [c] 4 mol% of **1d**. [d] octyl = n-C_8H_{17}, Tol = p-tolyl. [e] Global yield based on **3a**. [f] Ratio between mono and bis arylation products **5an** and **5an'**.*

To further extend the application potential of this methodology, we were thus prompted to take advantage of the different reactivity profiles between aryl chlorides and tosylates in Buchwald-Hartwig amination to selectively install different amines on the same bis-electrophilic substrate and under the same catalytic conditions. As representative example, N-(4-(piperidinyl)phenyl)morpholine **6** could be synthesized from 4-chlorophenyl tosylate **3n**, readily available from 4-chlorophenol (Scheme 1). Gratefully, when piperidine **4c** was employed as the amine partner under the standard conditions, but at 90°C instead of 120°C, 4-(piperidinyl)phenyl tosylate **3o** was obtained as the sole product in 95% yield (pathway 1). After purification and isolation, the latter was engaged in the second amination reaction with morpholine **4a** using the standard conditions. More remarkably, thanks to the high chemoselectivity of the transformation, it was possible to carry out the bis-amination in a one-pot protocol without the need to isolate the intermediate **3o** (pathway 2). The overall 57% yield in **7** was fully acceptable considering the strong electron-donating character of the piperidinyl-substituent in **3o**.



Scheme 1. Sequential (eq. 1) and one-pot (eq. 2) chemoselective bis-amination leading to bis-amine **6**.

CONCLUSION

In summary, we have disclosed the first efficient and general catalytic Pd-NHC system for the amination of aryl tosylates. The optimization strategy of the Pd-PEPPSI pre-catalyst relied on stereoelectronic modifications of the supporting imidazol-2-ylidene ligand and proved very powerful in finding out the best candidate, namely the Pd-PEPPSI-IPr$^{(NMe_2)_2}$. The optimized catalytic system was shown to achieve the amination with a wide range of amines and anilines, and to be slightly more sensitive to the nature of the aryl tosylate, indicating that the limiting step of the catalytic cycle is the oxidative addition of the C_{Ar}-O bond onto the Pd(0) species. Further studies aiming at utilizing this strategy to unveil better catalysts and new reactivities as well at understanding the beneficial features of the decorated NHC ligand are currently underway in our laboratory.

EXPERIMENTAL SECTION

General information. All manipulations were performed under an inert atmosphere of dry nitrogen by using standard vacuum line and Schlenk tube techniques. Glassware was dried at 120°C in an oven for at least three hours. 1,4-dioxane was distilled from sodium/benzophenone, *t*BuOH, *t*AmOH and

toluene from sodium, and dichloromethane was dried over CaH_2 and subsequently distilled. DMF was degassed by bubbling N_2 for 15 min and was stored over activated 4 Å MS. Pd-PEPSSI pre-catalysts **1a**,[9] **1b**,[13] **1c**,[10a] **1d**,[10a] **2a**,[14] and **2b**,[13] were synthesized according to literature procedures. Aryl tosylate substrates were synthesized upon reaction of the corresponding phenol derivative with para-toluenesulfonyl chloride according to literature procedure.[15] All other reagents were commercially available and used as received, except the liquid amines which were distilled prior to use. Anhydrous K_3PO_4 was purchased from Acros and Cs_2CO_3 was purchased from Alfa Aesar. NMR spectra were recorded on 300 MHz or 400 MHz spectrometers. Chemical shifts are reported in ppm (δ) compared to TMS (^1H and ^{13}C) using the residual peak of deuterated solvent as internal standard.[16] GC analyses were performed on a chromatograph equipped with a 30-m capillary column (fused silica capillary column, 30 m × 0.32 mm × 0.25 μm film thickness, stationary phase: poly(5% diphenyl/95% methyl siloxane)), using Helium as the vector gas. GC yields were measured according to an authentic sample/dodecane calibration curve. HRMS measurements were recorded using a TOF mass analyzer.

General procedure for the optimization of the reaction conditions (Table 1)

4-toluenyl tosylate **3a** (131 mg, 0.5 mmol, 1.0 eq) or 4-methoxyphenyl tosylate **3b** (139 mg, 0.5 mmol, 1.0 eq.), base (1.5 mmol, 3.0 eq) and Pd pre-catalyst (0.01 mmol, 2 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. Morpholine (66 μL, 0.75 mmol, 1.5 eq) and solvent (1.5 mL) were subsequently added via syringe at room temperature. The mixture was stirred for about one minute at room temperature and was then placed into a pre-heated oil bath at the desired temperature. The reaction was allowed to stir for 18 h. The reaction mixture was cooled, diluted with 10 mL ethyl acetate and dodecane was added (112 μL, 0.5 mmol) as internal standard. Yields were measured by passing an aliquot of the solution through a plug of silica gel using ethyl acetate as eluant and monitoring the relative areas of the peaks compared to that of dodecane in the GC chromatogram.

General procedure for screening of aryl tosylates (Table 2)

Aryl tosylate (0.5 mmol, 1.0 eq), K_3PO_4 (318 mg, 1.5 mmol, 3.0 eq) and complex **1d** (7.7 mg, 0.01 mmol, 2 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. Morpholine **4a** (66 μL, 0.75 mmol, 1.5 eq) and *t*AmOH (1.5 mL) were subsequently added via syringe at room temperature. The mixture was stirred for about one minute at room temperature and then transferred to a preheated oil bath at 120 °C and the reaction was stirred for 18 h. At that point, the reaction mixture was cooled down to room temperature and diluted with EtOAc (10 mL), filtered through a small plug of Silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via silica gel flash chromatography.

4-(4-methylphenyl)morpholine (5aa):[10a] Hexane/EtOAc = 20/1, white solid, 85.2 mg (96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.90-3.83 (m, 4H), 3.15-3.08 (m, 4H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 149.3, 129.9, 129.7, 116.2, 67.1, 50.1, 20.6.

4-(4-methoxylphenyl)morpholine (5ba):[10a] Hexane/EtOAc = 4/1, white solid, 70.0 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94-6.80 (m, 4H), 3.91-3.83 (m, 4H), 3.77 (s, 3H), 3.09-3.02 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 154.1, 145.8, 118.0, 114.7, 67.2, 55.7, 51.0.

4-(4-acetylphenyl)morpholine (5ca):[10b] Hexane/EtOAc = 2/1), yellow solid, 89.0 mg (87%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.93-3.76 (m, 4H), 3.36-3.23 (m, 4H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 196.6, 154.3, 130.5, 128.3, 113.4, 66.7, 47.7, 26.3.

4-morpholinophenylnitrile (5da):[10b] Pentane/Et_2O = 3/2), white solid, 75.0 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56-7.43 (m, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.92-3.74 (m, 4H), 3.38-3.15 (m, 4H). ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$): δ = 153.6, 133.6, 120.0, 114.2, 101.0, 66.5, 47.4.

4-(3,5-dimethoxyphenyl)morpholine (5ea):[17] Hexane/EtOAc = 8/1, white solid, 102 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (d, *J* = 2.0 Hz, 2H), 6.05 (t, *J* = 2.1 Hz, 1H), 3.84 (t, *J* = 5.2 Hz, 4H), 3.78 (s, 6H), 3.14 (t, *J* = 4.9 Hz, 4H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$): δ = 161.7, 153.2, 95.0, 92.2, 66.9, 55.4, 49.6.

4-(3-acetylphenyl)morpholine (5fa):[18] Hexane/EtOAc = 2/1, yellow oil, 78.8 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.10 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.85 (t, *J* = 4.5 Hz, 4H), 3.19 (t, *J* = 4.7 Hz, 4H), 2.57 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 198.5, 151.5, 138.1, 129.4, 120.3, 114.5, 66.8, 49.1, 26.8.

4-(2-methoxyphenyl)morpholine (5ga):[19] Hexane/EtOAc = 10/1), colorless oil, 85 mg (88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05-6.98 (m, 1H), 6.95-6.91 (m, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 3.92-3.87 (m, 4H), 3.86 (s, 3H), 3.20-2.97 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.3, 141.2, 123.2, 121.1, 118.1, 111.4, 67.3, 55.4, 51.2.

4-(2-fluorophenyl)morpholine (5ha):[19] Hexane/EtOAc = 10/1, colorless oil, 60 mg (66%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12-6.89 (m, 4H), 3.93-3.84 (m, 4H), 3.13-3.04 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 155.8 (d, *J* = 244 Hz), 140.1 (d, *J* = 9 Hz), 124.6 (d, *J* = 4 Hz), 122.8 (d, *J* = 8 Hz), 118.8 (d, *J* = 3 Hz), 116.3 (d, *J* = 19 Hz), 67.1, 51.0 (d, *J* = 4 Hz).

4-(napht-2-yl)morpholine (5ja):[18] Hexane/EtOAc = 8/1), white solid, 89.6 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.60 (m, 3H), 7.46-7.39 (m, 1H), 7.35-7.29 (m, 1H), 7.26 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 3.93 (t, *J* = 4.7 Hz, 4H), 3.27 (t, *J* = 4.9 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 149.1, 134.6, 129.0, 128.9, 127.6, 126.9, 126.5, 123.7, 119.0, 110.3, 67.0, 50.0.

4-(napht-1-yl)morpholine (5ka):[18] Hexane/EtOAc = 10/1, yellowish solid, 104.5 mg (98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30-8.21 (m, 1H), 7.91-7.82 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.56-7.48 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.01 (t, *J* = 4.5 Hz, 4H), 3.19 (t, *J* = 4.5 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 149.5, 134.9, 128.9, 128.6, 126.0, 125.5, 123.9, 123.5, 114.8, 67.5, 53.6.

4-(pyridin-2-yl)morpholine (5la):[10a] Pentane/Et_2O = 5/1, colorless oil; 56 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22-8.15 (m, 1H), 7.53-7.43 (m, 1H), 6.68-6.58 (m, 2H), 3.84-3.77 (m, 4H), 3.51-3.44 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 159.7, 148.0, 137.6, 113.9, 107.0, 66.9, 45.7.

4-(pyridin-3-yl)morpholine (5ma):[10a] Hexane/EtOAc = 1/1, yellow oil, 71 mg (87%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32-8.27 (m, 1H), 8.15-8.08 (m, 1H), 7.19-7.12 (m, 2H), 3.95-3.76 (m, 4H), 3.28-3.08 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 147.0, 141.3, 138.5, 123.6, 122.2, 66.8, 48.7.

General procedure for the screening of the amine partner (Table 3)

4-toluenyl tosylate **3a** (131 mg, 0.5 mmol, 1.0 eq), K_3PO_4 (318 mg, 1.5 mmol, 3.0 eq) and complex **1d** (7.7 mg, 0.01 mmol, 2 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. The amine (0.75 mmol, 1.5 eq) and *t*AmOH (1.5 mL) were subsequently added via syringe at room temperature. In case of diphenylamine, which is solid at room temperature, it was introduced into the tube prior to purging with nitrogen. The mixture was stirred for about one minute at room temperature and then transferred to a preheated oil bath at 120 °C and the reaction was stirred for 18 h. At this point, the reaction mixture was cooled down to room temperature and diluted with EtOAc (10 mL), filtered through a small plug of Silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via silica gel flash chromatography.

1-(4-methylphenyl)pyrolidine (5ab):[20] Pentane/Et_2O = 10/1, white solid, 73.7 mg (91%); ^1H NMR (400 MHz, $CDCl_3$): δ =7.06 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 2H), 3.28 (t, *J* = 6.5 Hz, 4H), 2.28 (s, 3H), 2.15-1.88 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.2, 129.8, 124.7, 112.0, 48.0, 25.5, 20.4.

1-(4-methylphenyl)piperidine (5ac):[21] Hexane/EtOAc = 50/1, colorless oil, 70.2 mg (80%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.06 (m, 2H), 6.95-6.85 (m, 2H), 3.12 (t, *J* = 5.4 Hz, 4H), 2.30 (s, 3H), 1.75 (p, *J* = 5.6 Hz, 4H), 1.64-1.55 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 150.3, 129.6, 128.9, 117.1, 51.5, 26.1, 24.4, 20.5.

1-(4-methylphenyl)-4-phenylpiperazine (5ad):[22] Hexane/EtOAc = 10/1, white shining crystals, 121 mg (96%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.97-6.86 (m, 3H), 3.40-3.25 (m, 8H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.4, 149.2, 129.8, 129.3, 120.2, 116.9, 116.5, 50.2, 49.6, 20.6.

4-methyl-*N*-ethyl-*N*-benzyl-aniline (5ae):[10a] Hexane/EtOAc = 95/5, colorless oil, 102.9 mg (91%); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.26 (m, 5H), 7.12-7.02 (m, 2H), 6.82-6.58 (m, 2H), 4.55 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.5, 139.7, 129.8, 128.6, 126.8, 126.7, 125.3, 112.6, 54.3, 45.4, 20.3, 12.2.

4-methyl-*N*-methyl-*N*-phenylaniline (5af):[10a] Hexane/EtOAc = 20/1, yellowish oil, 89.5 mg (91%); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48-7.38 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.24-7.17 (m, 2H), 7.18-7.11 (m, 2H), 7.11-7.03 (m, 1H), 3.47 (s, 3H), 2.52 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 149.4, 146.7, 132.0, 130.0, 129.1, 122.6, 119.9, 118.3, 40.3, 20.8.

***N*,*N*-diphenyl-4-methylaniline (5ag):**[23] Hexane/DCM = 10/1, white solid, 122.4 mg (94%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36-7.22 (m, 4H), 7.20-6.96 (m, 10H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 148.2, 145.4, 132.8, 130.0, 129.2, 125.1, 123.7, 122.3, 21.0.

4-methyl-*N*-phenylaniline (5ah):[10a] Hexane/EtOAc = 95/5, white solid, 80.0 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.25 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.11-7.02 (m, 4H), 6.95 (t, *J* = 7.3 Hz, 1H), 5.64 (br, s, 1H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.1, 140.4, 131.0, 130.0, 129.4, 120.4, 119.0, 117.0, 20.8.

4-fluoro-*N*-(4-methylphenyl)aniline (5ai):[24] Hexane/EtOAc = 20/1, white solid, 96.5 mg (96%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16-7.07 (m, 2H), 7.06-6.88 (m, 6H), 5.49 (br, s, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 157.7 (d, *J* = 238 Hz), 141.2, 139.9 (d, *J* = 2 Hz), 130.6, 130.0, 119.5 (d, *J* = 7 Hz), 118.0, 116.0 (d, *J* = 22 Hz), 20.7.

3-trifluoromethyl-*N*-(4-methylphenyl)aniline (5aj):[22] Hexane/EtOAc = 20/1, white solid, 115 mg (92%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.9 Hz, 1H), 7.23-6.98 (m, 7H), 5.73 (br, s, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 145.0, 139.1, 132.6, 131.8 (q, *J* = 32 Hz), 130.2, 129.9, 124.3 (q, *J* = 271 Hz), 120.3, 119.0, 116.4 (q, *J* = 4 Hz), 112.5 (q, *J* = 4 Hz), 20.9.

2,6-dimethyl-*N*-(4-methylphenyl)aniline (5ak):[25] Pentane/Et_2O = 9/1, white solid, 90.0 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.12 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.60-6.47 (m, 2H), 5.14 (br, s, 1H), 2.34 (s, 3H), 2.30 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.9, 138.8, 135.6, 129.8, 128.6, 127.5, 125.5, 113.9, 20.6, 18.5.

4-methyl-*N*-(oct-1-yl)-aniline (5an) and *N*,*N*-bis(4-methylphenyl)octyl-1-amine (5an'): Hexane/EtOAc = 98/2; a first crop of pure **5an'** was collected as the first fraction (29.4 mg) but, due to

co-elution of the two products, the second fraction consisted of a mixture of **5an** and **5an'** in a 2/1 ratio determined by integration of the ^{1}H NMR spectrum (41.1 mg). **5an:**[26] 0.11 mmol (22%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.1 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 3.46 (br s, 1H), 3.11 (t, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.73-1.53 (m, 2H), 1.48-1.20 (m, 10H), 1.01-0.82 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.4, 129.8, 126.4, 113.1, 44.6, 32.0, 29.8, 29.6, 29.4, 27.3, 22.8, 20.5, 14.2. **5an':**[27] colorless oil, 0.15 mmol (60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 8.2 Hz, 4H), 6.87 (d, *J* = 8.0 Hz, 4H), 3.62 (t, *J* = 7.0 Hz, 2H), 2.30 (s, 6H), 1.64 (p, *J* = 7.6 Hz, 2H), 1.39-1.19 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.0, 130.2, 129.7, 120.8, 52.5, 31.8, 29.4, 29.3, 27.5, 27.1, 22.7, 20.6, 14.1.

4-methyl-*N*-cyclohexylaniline (5ao):[28] Hexane/EtOAc = 95/5, white solid, 88 mg (93%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8.1 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.58 (br, s, 1H), 3.22 (tt, *J* = 10.1, 3.7 Hz, 1H), 2.23 (s, 3H), 2.11-2.00 (m, 2H), 1.75 (dt, *J* = 12.9, 3.6 Hz, 2H), 1.65 (dt, *J* = 12.6, 3.7 Hz, 1H), 1.42-1.29 (m, 2H), 1.27-1.08 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.9, 129.9, 126.5, 113.9, 52.4, 33.6, 26.1, 25.2, 20.5.

4-methyl-*N*-(morpholin-4-yl)aniline (5aq):[29] Hexane/EtOAc = 4/1, yellowish oil, 80 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$): 7.03 (d, *J* = 9.1 Hz, 2H), 6.88-6.81 (m, 2H), 4.32 (br, s, 1H), 3.81 (t, *J* = 4.6 Hz, 4H), 2.75 (s, 4H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.8, 129.8, 129.1, 114.1, 67.2, 56.5, 20.6.

4-piperidinylphenyl tosylate (3o): 4-chlorophenyl tosylate **3n** (141.4 mg, 0.5 mmol, 1.0 eq), K_3PO_4 (265 mg, 1.25 mmol, 2.5 eq) and pre-catalyst **1d** (7.7 mg, 0.01 mmol, 2 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. Piperidine (59 μL, 0.6 mmol, 1.2 eq) and *t*AmOH (1.5 mL) were subsequently added via syringe at room temperature. The mixture was stirred for about one minute at

room temperature and then transferred to a preheated oil bath (90 °C). The reaction was stirred for another 18 h. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a small plug of Silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via silica gel flash chromatography (SiO_2, Hexane/EtOAc: 2/1) to afford compound **3o** as a white solid (158.3 mg, 96% yield); mp = 123-124°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75-7.64 (m, 2H), 7.33-7.24 (m, 2H), 6.90-6.67 (m, 4H), 3.14-3.05 (m, 4H), 2.44 (s, 3H), 1.73-1.62 (m, 4H), 1.60-1.52 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 151.0, 145.1, 142.0, 132.7, 129.8, 128.7, 122.9, 116.8, 50.7, 25.9, 24.2, 21.8; IR (ATR): ν = 2936, 2854, 2815, 1595, 1508, 1450, 1372, 1246, 1188, 1176, 1157, 1124, 1092, 1019, 1007, 915, 859, 809, 754, 693, 656 cm^{-1}; MS (ESI): m/z (%): 332 (100) $[M + H]^+$; HRMS (ESI): m/z calcd. for $C_{18}H_{22}NO_3S$: 332.1320; found: 332.1321, ε_r = 0.3 ppm; elemental analysis *calcd* (%) for $C_{18}H_{21}NO_3S$ (MW = 331.43): C 65.23, H 6.39, N 4.23, *found*: C 64.98, H 6.42, N 4.19.

4-(4-piperidinylphenyl)morpholine (6):[30] 4-piperidinylphenyl tosylate **3o** (165.7 mg, 0.5mmol, 1.0 eq), K_3PO_4 (318 mg, 1.5 mmol, 2.5 eq) and complex **1d** (15.4 mg, 0.02 mmol, 4 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. Morpholine (66 µL, 0.75 mmol, 1.5 eq) and *t*AmOH (1.5 mL) were subsequently added via syringe at room temperature. The mixture was stirred for about one minute at room temperature and then transferred to a preheated oil bath (120 °C). The reaction was stirred for another 18 h. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a small plug of Silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via silica gel flash chromatography (SiO_2, Hexane/EtOAc: 2/1) to afford the title compound as a white solid (74.2 mg, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00-6.78 (m, 4H), 3.97-3.74 (m, 4H), 3.13-2.98 (m, 8H), 1.82-1.60 (m, 4H), 1.63-1.45 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 146.9, 145.1, 118.4, 117.4, 67.2, 52.0, 50.7, 26.2, 24.3.

One-pot procedure: 4-chlorophenyl tosylate **3n** (141.4 mg, 0.5 mmol, 1.0 eq), K_3PO_4 (265 mg, 1.25 mmol, 2.5 eq) and pre-catalyst **1d** (7.7 mg, 0.01 mmol, 2 mol%) were charged under air into a Schlenk tube (15 mL volume) that was sealed with a septum, and the tube was evacuated and flushed with nitrogen for three times. Piperidine (59 μL, 0.6 mmol, 1.2 eq) and *t*AmOH (1.5 mL) were subsequently added via syringe at room temperature. The mixture was stirred for about one minute at room temperature and then transferred to a preheated oil bath at 90°C for 6 h to observe the full conversion (checked by TLC). After cooling down to the room temperature, K_3PO_4 (318 mg, 1.5 mmol, 3.0 eq), pre-catalyst **1d** (15.4 mg, 0.02 mmol, 4.0 mol%) and morpholine (66 μL, 0.75 mmol, 1.5 eq) were subsequently added to the solution upon a flow of N_2. The mixture was heated at 120°C for another 18 h. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a small plug of Silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via silica gel flash chromatography (SiO_2, Hexane/EtOAc: 2/1) to afford compound **6** as a white solid (70.0 mg, 57% yield).

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SUPPORTING INFORMATION

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the internet at http://pubs.acs.org.

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