N-Heterocyclic Carbenes (NHCs) Containing *N*-*C*-Palladacycle Complexes: Synthesis and Reactivity in Aryl Amination Reactions

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Starting from the corresponding dimer, new saturated NHC-containing *N*,*N*-dimethyl biphenylamine (DMBPA) palladacycle complexes have been synthesized and fully characterized. Catalytic activity of these well-defined, air- and moisture-stable palladium(II) complexes was evaluated in the Buchwald−Hartwig amination involving a range of unactivated aryl chlorides. From a practical perspective, the reaction conditions required when using [(NHC)Pd(palladacycle)Cl] systems are very appealing. The organic biphenyl ligand used in the synthesis of the palladacycles has been synthesized using a Suzuki−Miyaura cross-coupling employing the novel palladacycle-NHC complexes.

Introduction

N-heterocyclic carbene (NHC)-containing transition metal complexes[1] have been reported to efficiently catalyze a number of reactions such as ruthenium-mediated metathesis,[2] cycloaddition, and hydrosylilation using copper complexes,[3] gold-catalyzed transformations,[4] palladium-mediated cross-coupling reactions,[5] among others. The NHCs have gained great popularity as they are, in most cases, better σ-donors than phosphines, and possess in general higher thermal stability, and the use of NHC as supporting ligand usually leads to better complex stability.[6] Especially in the area of palladium-mediated cross-coupling reactions, NHC-containing Pd-catalysts[5] have proven to be an excellent alternative to catalytic systems involving tertiary phosphines.[7] The σ-donating character of NHC ligands allows for the synthesis of well-defined, air- and moisture-stable NHC-bearing palladium(II). Moreover, NHC ligands provide stabilization of the low-coordinated catalytically active Pd(0) species involved in the catalytic cycle, thus minimizing oxidative degradation and side reactions observed with tertiary phosphines.[8] A number of structures of NHC-Pd complexes such as dimer,[9] allyl,[10] cinnamyl,[11] pyridine (PEPPSI),[12] or acac (acetylacetonate)[13] have been investigated, and these complexes exhibit excellent catalytic activity.

Complexes juxtaposing the highly σ-donating properties and sterically demanding properties of NHCs with the stability imparted by palladacycle scaffolds[14] have also been investigated.[15] In 2003, our group published the first *N*,*N*-dimethyl biphenylamine (DMBPA) complexes combining nitrogen−carbon−palladacycle framework with unsaturated NHCs (Figure 1, **1** and **2**).[16,17] These appeared to be efficient precatalysts in the Buchwald−Hartwig reaction, α-ketone arylation, Suzuki−

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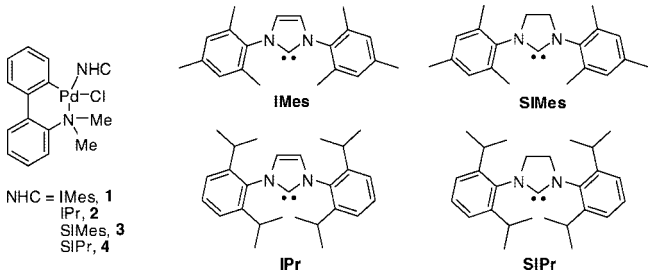


Figure 1. DMBPA *N-C*-palladacycle complexes bearing NHC ligands.

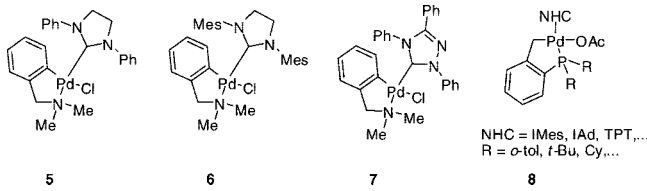
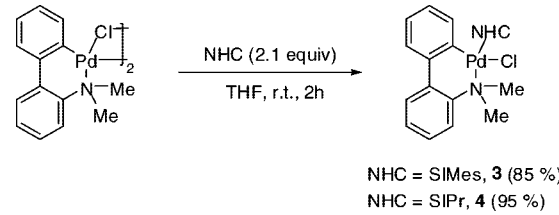


Figure 2. DMBA and phospha-palladacycle complexes bearing NHC ligands.

Miyaura coupling, and dehalogenation reaction.[17−19] Independently, Iyer reported applications in Mizoroki−Heck cross-coupling[20] of the previously described saturated NHC-containing dimethylbenzylamine (DMBA) palladacycle **5** (Figure 2).[21] These researchers obtained moderate to good yields at very low catalyst loading (0.0016 mol% Pd). However, reactions were carried out with aryl bromides or activated aryl chlorides at very high temperature (140 °C).[20,22] In 2005, Herrmann published another *N*-palladacycle coupled with a triazolin-5-ylidene (TPT) **7** and the first series of NHC-substituted phospha-palladacycles **8**, also showing high thermal stability.[23] At elevated temperature, Heck reactions were performed with phospha-palladacycles **8**, which proved efficient for the olefination of deactivated aryl bromides. The *N*-palladacycle **7** was the only one capable of quantitatively coupling an aryl chloride. In contrast to **8**, palladium black was formed in the presence of **7**.

The constant need for more efficient catalysts prompted us to develop new NHC-containing *N-C*-palladacycle complexes. Because of their convenient synthesis and the stability of the free NHC, unsaturated imidazol-2-ylidenes are widely used as ancillary ligands. In spite of similar steric and electronic properties,[24] unsaturated and saturated NHCs are often found to exhibit significantly different activity in catalysis. Olefin metathesis[25] is one such example, but palladium-catalyzed cross-coupling reactions also demonstrate the differences between

Scheme 1. Synthesis of Palladium Complexes 3 and 4



saturated and unsaturated NHC supporting ligands.[10,11] In order to examine whether such differences could be observed in the related palladacyclic scaffolds examined in 2003, we report here the synthesis and full characterization of new saturated NHC-containing Pd(cycle) complexes. The catalytic activity of these new well-defined, air- and moisture-stable palladium(II) complexes was evaluated in the Buchwald−Hartwig amination and used for the synthesis of the palladacycle biphenyl ligand through a Suzuki−Miyaura cross-coupling.

Results and Discussion

Synthesis and Structure Determination of [(SIMes)Pd(Cycle)Cl] (3) and [(SIPr)Pd(Cycle)Cl] (4). The reactions leading to the titled complexes involved the coordination of the NHC to the palladium center by simple cleavage of the dimer $[Pd(Cycle)Cl]_2$ by two equivalents of NHC ligands, such as SIMes and SIPr, giving rise to the expected 16-electron species [(NHC)Pd(Cycle)Cl] (Scheme 1) in good to excellent isolated yields. Of note, these complexes were found perfectly air- and moisture-stable and thus could be handle in air. The ^{1}H NMR spectra of **3** and **4** showed a characteristic resonance at 4 ppm for the imidazolidine protons. The ^{13}C NMR spectra displayed characteristic low-field resonances for the carbenic carbon at around 198−201 ppm, while the carbenic carbon resonance for the unsaturated complexes **1** and **2** was found at a higher field (173−175 ppm).[17] Elemental analyses and high-resolution mass spectroscopy also confirmed the compositions of **3** and **4**.

To unambiguously establish the structure of complexes **3** and **4**, suitable crystals for single-crystal diffraction studies were obtained by slow diffusion of *n*-octane in DCM saturated solutions of **3** and **4**. Ball-and-stick representations with selected bond distances and angles are presented in Figures 3 (**3**) and 4 (**4**). Complexes **3** and **4** show the expected distorted square-planar geometry around the metal center with bond angles

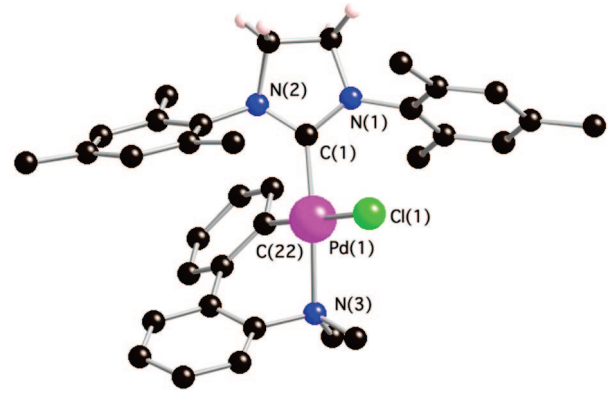


Figure 3. Ball-and-stick representation of [(SIMes)Pd(Cycle)Cl] (**3**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.9684(11), Pd(1)−C(22) 2.0053(11), Pd(1)−N(3) 2.1957(10), Pd(1)−Cl(1) 2.3911(3); C(1)−Pd(1)−N(3) 175.27(4), C(1)−Pd(1)−C(22) 88.96(4), and C(22)−Pd(1)−Cl(1) 178.82(3).

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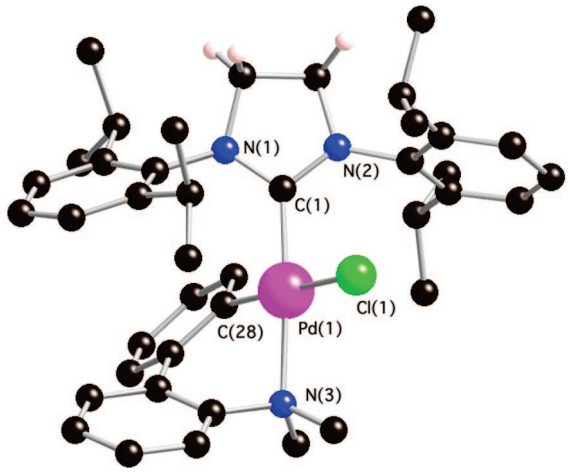


Figure 4. Ball-and-stick representation of [(SIPr)Pd(Cycle)Cl] (**4**). Most hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) 1.9788(9), Pd(1)−C(28) 2.0007(10), Pd(1)−N(3) 2.2033(9), Pd(1)−Cl(1) 2.3966(3); C(1)−Pd(1)−N(3) 175.58(4), C(1)−Pd(1)−C(28) 90.34(4), and C(28)−Pd-(1)−Cl(1) 177.22(3).

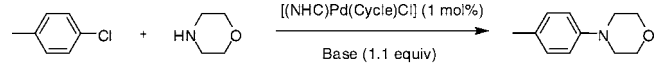
Table 1. Crystallographic Data for Compounds [(NHC)Pd(Cycle)Cl]

	[(SIMes)Pd(Cycle)Cl] (**3**)	[(SIPr)Pd(Cycle)Cl] (**4**)
chemical formula	$C_{36}H_{42}Cl_2N_3Pd$	$C_{42}H_{54}Cl_3N_3Pd$
fw	694.03	813.63
space group	*Pbca*	*P*2 (1)/*n*
cryst syst	orthorhombic	monoclinic
a, Å	13.6779(6)	10.3012(5)
b, Å	14.7453(6)	20.3145(10)
c, Å	32.7016(12)	19.4043(8)
α, deg	90	90
β, deg	90	98.103(2)
γ, deg	90	90
Z	8	4
D_{calc}, g cm^{-3}	1.398	1.344
μ (Mo), mm^{-1}	0.754	0.693
F(000)	2872	1696
θ range, deg	3.03 to 39.28	2.88 to 39.81
no. of reflns collected	57986	48649
no. of unique reflns/R_{int}	19144/0.0306	22808/00.0262
no. of params/restraints	387/0	480 /4
final *R* indices [*I* >2 *σ* (*I*)]	R_1 = 00.0326, wR_2 = 00.0768	R_1 = 0.0326, wR_2 = 0.0833
R indices (all indices)	R_1 = 00.0466, wR_2 = 00.0836	R_1 = 0.0439, wR_2 = 0.0896
goodness-of-fit on F^2	1.025	1.022
peak/hole, e Å^{-3}	0.873 and −00.995	1.717 and − 0.791

between 85° and 94°. Both **3** and **4** having the NHC ligand and amino group disposed trans to each other. In order to satisfy the square-planar geometry of the complexes, the biphenyl ligand is twisted. Of note, the *N*-aryl substituents of the saturated NHC are much more tilted to each other than the unsaturated NHC IMes and IPr (complexes **1** and **2**),[17] probably due to the skewed geometry of the NHC backbone. In general, the Pd−C(NHC) distances in **3** and **4** suggest single-bond character and are in good accord with their almost exclusive *σ*-donor character. The Pd−C(NHC) bond lengths in **3** (1.9684(11) Å) and **4** (1.9788(9) Å) are significantly smaller to analogous distances in related palladacycle carbene complexes (2.038 Å in **1**, 1.992 Å in **2**, and 1.991(1) Å in *N*,*N*′-dimethylbenzylamine **6** bearing SIMes).[17,26] Other bond distances were found comparable to those reported for similar complexes (Table 1).

Optimization of the Buchwald−Hartwig Reaction Conditions. Among cross-coupling reactions, the *N*-aryl amination has emerged as a practical and popular method for the formation

Table 2. Optimization of the Aryl Amination of 4-Chlorotoluene by Morpholine Catalyzed by [(NHC)Pd(Cycle)Cl] Complexes[a]



1 equiv 1.1 equiv

entry	catalyst	base	solvent	*T* (°C)	time	conversion GC[b]
1	**2**	NaO^{t}Bu	0.3 M dioxane	50	2 h	94%
2	**4**	NaO^{t}Bu	0.3 M dioxane	50	2 h	93%
3	**3**	NaO^{t}Bu	0.3 M dioxane	50	48 h	21%
4	**4**	NaO^{t}Bu	0.3 M dioxane	r.t.	72 h	89%
5	**4**	NaO^{t}Bu	0.3 M dioxane	70	40 min	91%
6	**4**	NaO^{t}Bu	0.3 M DME	50	1 h	92%
7	**4**	NaO^{t}Bu	0.3 M THF	50	2 h	93%
8	**4**	NaO^{t}Bu	0.3 M toluene	50	2 h	40%
9	**4**	NaO^{t}Bu	0.3M^{t}PrOH	50	30 min	0%[c]
10	**4**	KO^{t}Bu	0.3 M DME	50	5 min	96%
11	**4**	NaOH	0.3 M DME	50	2 h	0%[d]
12	**4**	NaOMe	0.3 M DME	50	2 h	0%[d]
13	**4**	KO^{t}Bu	1 M DME	50	2 min	96%
14	**2**	KO^{t}Bu	1 M DME	50	5 min	95%
15	**4**	KO^{t}Bu	1 M DME	r.t.	1 h	25%
16	**4**	KO^{t}Bu	1 M DME	50, MW[e]	5 min	90%
17	-	KO^{t}Bu	1 M DME	50	24 h	0%[d]

[a] Reaction conditions: 4-chlorotoluene (1 mmol), morpholine (1.1 mmol), [(NHC)Pd(Cycle)Cl] (1 mol%), base (1 0.1 mmol). [b] Conversions are the average of at least two runs. [c] 95% of toluene as dehalogenation product. [d] Starting material recovered. [e] MW = microwave.

of carbon−nitrogen bonds.[27] The classical copper-mediated Ullmann and the more recently developed palladium(0)-catalyzed Buchwald−Hartwig aryl coupling are commonly used methods. However, the Ullmann type reaction generally suffers from important limitations such as elevated reaction temperatures (≥140 °C), high catalyst loading, and poor substrate generality.[28] These drawbacks encourage the development of Pd-based catalyst systems for the preparation of aryl amines. Therefore, having two new saturated NHC-containing *N*-*C*-palladacycle complexes on hand, we initiated a study focusing on their catalytic activity in aryl amination using 4-chlorotoluene and morpholine as standard substrates (Table 2). First, we explored the reactivity of saturated **3** and **4** versus the unsaturated [(IPr)Pd(Cycle)Cl] (**2**), using the conditions previously described.[17] In several precedent cases, we[10c,11] and others[29] reported that SIPr-containing complexes perform better than IPr analogues in the Buchwald−Hartwig amination. Surprisingly, in this case, **2** (IPr) and **4** (SIPr) did not show any differences in terms of reactivity (entries 1 and 2). However, precatalyst **3** bearing the smaller NHC SIMes displayed a low activity at 50 °C (entry 3), confirming that as a general trend less bulky NHCs complexes bearing mesityl as imidazole substituents are less catalytically efficient.[16,17] The reactions conducted with **2** were previously performed at 70 °C, in 3 mL of dioxane and with NaO^{t}Bu as base.[17] We re-examined these conditions for **4**. As expected, the reaction proceeded faster at 70 °C (entry 5). However, under milder conditions, at 50 °C, amination still occurred in reasonable reaction times (entry 1). At room

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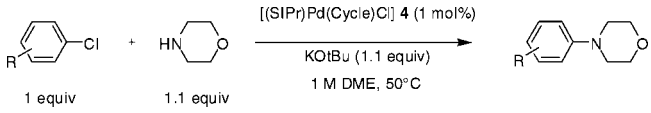
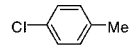
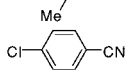
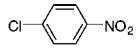
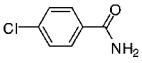
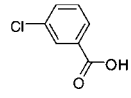
Table 3. Cross Coupling of Morpholine with Various Aryl Chlorides Mediated by 4[a]



entry	Ar-Cl	time	conversion GC[b]	yield[c]
1		2 min	96%	91%
2		3 h	83%	74%
3		1 h	96%	90 %
4		2 h	95%	95%
5		2 h	88%	68%
6		24 h	0%	-
7		24 h	0%	-
8		24 h	62%[d]	61%
9		24 h	>99%[d]	>99%

[a] Reaction conditions: aryl chloride (1 mmol), morpholine (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL), T = 50 °C. [b] Conversions are the average of at least two runs. [c] Isolated yields. [d] KO^{t}Bu (2.2 mmol), DME (2 mL), and conversions were measured by ^{1}H NMR.

temperature, unfortunately the reaction time was increased to three days to reach an 89% conversion (entry 4), and even under reoptimized conditions, the arylation proceeded poorly (entry 15). 1,2-Dimethoxyethane (DME) appeared to be a better solvent than dioxane for this N-arylation (entry 6). In isopropanol, only dehalogenation was observed (entry 9).[16,19] The reaction proceeded well with strong bases such as KO^{t}Bu or NaO^{t}Bu, whereas others were completely ineffective (NaOH and NaOMe, respectively, entries 11 and 12). The result presented in entry 10 emphasizes the importance of the counteranion of the base for the activation of the catalyst. Complete conversion was reached in only 5 min with KO^{t}Bu at 50 °C, while 1 h was necessary with NaO^{t}Bu. Finally, better catalytic performances were obtained with increasing reaction mixture concentration (entry 13). Thus, reaction conditions were improved compared to those reported for palladacycle-catalyzed Buchwald−Hartwig cross-coupling,[17] although they were found to be similar to the ones found for [(NHC)Pd(R-allyl)Cl][10] or Pd-PEPPSI catalysts.[12] Once again, the reactivity of **4** versus **2** was compared with the new conditions (entries 13 and 14). Compound **4** was slightly more efficient than **2**, but this difference is small.

Precatalyst 4 in the Buchwald−Hartwig Reaction. The arylation of the morpholine was extended to a range of unactivated and other aryl chlorides (Table 3). With typical arylamination substrates, all reactions proceeded with good GC conversions and reaction times ranged from 2 min to 3 h (entries 1−5). The system was tolerant of a variety of functional groups. The secondary cyclic amine was easily coupled with various aryl chlorides: activated (entry 3), neutral (entries 1 and 2), unactivated (entry 5) as well as heteroaromatic chlorides (entry 4). Sterically hindered aryl chlorides such as mono or di ortho-substituted chlorobenzene exhibited reactions slightly slower than those for nonhindered analogues (entries 2 and 5). In most cases, final compounds were isolated in excellent yields. Pyridine and *o*-methoxy derivatives were found to be volatile (entries 4, 5). Then, we explored more unusual (less commonly employed) aryl chlorides as partners for the Buchwald−Hartwig reaction (entries 6−9). 1-Chloro-4-nitrobenzene and 3-chlorothiophene were completely unreactive under our optimized reaction conditions (entries 6 and 7). Morpholinylbenzene compounds bearing an electron-withdrawing group such as carboxylic or amide group are useful building blocks in the synthesis of new drugs and are therefore of commercial value.[30] The morpholinobenzoic acids were previously prepared either via Pd-catalyzed amination from ethyl bromobenzoate or by direct nucleophilic aromatic substitution of fluorobenzonitrile with subsequent hydrolysis of the resulting intermediates.[30a,31] 4-Morpholinobenzamide was obtained by substitution of the 4-fluorobenzamide[31] or by Pd-mediated coupling of the polymer bound aryl bromide.[32] Although two equivalents of base were required, complex **4** appeared to catalyze, under mild conditions, the amination of 4-chlorobenzamide and 3-chlorobenzoic acid with good yields and without a side reaction (entries 8 and 9). No reaction occurred in both cases with only one equivalent of KO^{t}Bu; presumably, a faster deprotonation of the carboxylic function occurs over the generation of the active species and the productive cross-coupling reaction. Extending the scope to *N*-methylaniline as partner instead of the highly active morpholine also gave high yields using both activated and unactivated chlorides (Table 4). Nevertheless, compared to morpholine, the aniline reacted slightly slower (entries 1 and 5).

A range of amines was also tested as partners for the coupling reaction (Table 5). The less reactive and sterically hindered dibutylamine reacted smoothly with 2-chlorotoluene in high yields (entry 1). Primary amines appeared to be compatible with our catalytic system. The 1-chloro-3-fluorobenzene was rapidly coupled to the bulky 1-adamantylamine in quantitative yield (entry 2) without any formation of the diarylated product. Also, the primary amine, cyclohexylamine, straightforwardly produced the biologically interesting naphthylamine (entry 3). The diallylamine, absent from the previous *N*-arylation study, was unreactive under these conditions either with neutral or activated aryl chlorides (entries 4 and 5). Unfortunately, benzophenone imine could not be coupled with 4-chlorotoluene in DME (entry 6), and attempts performed in toluene also failed.

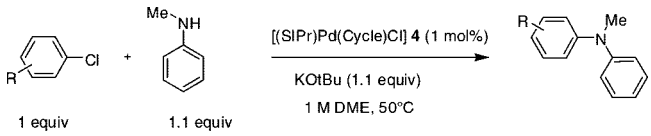
Application to the Synthesis of the *N*,*N*-Dimethylbiphenyl-2-amine Ligand. Economically and industrially, the reaction conditions obtained with [(NHC)Pd(palladacycle)Cl] systems are very appealing. However, the synthesis of the palladacycle biphenyl ligand requires harsh conditions and/or is low yielding, which is a significant hurdle. In the literature, the synthesis of the *N*,*N*-dimethylbiphenyl-2-amine was first described in 1939

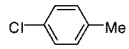
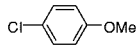
(30) (a) Brown, D. S.; Belfield, A. J.; Brown, G. R.; Campbell, D.; Foubister, A.; Masters, D. J.; Pike, K. G.; Snelson, W. L.; Wells, S. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5383–5387.

(31) (b) Oberboersch, S.; Schunk, S.; Reich, M.; Hees, S.; Jostock, R.; Engels, M.; Kless, A.; Christoph, T.; Schiene, K.; Germann, T.; Bijsterveld, E. PCT Int. Appl. WO2008040492, 2008. (c) Tian, W. PCT Int. Appl. WO0187865, 2001.

(32) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181–7184.

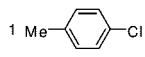
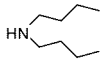
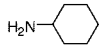
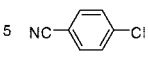
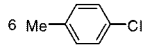
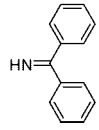
Table 4. Cross Coupling of Aniline and Various Aryl Halides Catalyzed by 4[a]



entry	Ar-Cl	time	conversion GC[b]	yield[c]
1		20 min	98%	97%
2		3 h	96%	93%
3		30 min	97%	94%
4		2 h	82%	81%
5		9 h	96%	94%

[a] Reaction conditions: aryl chloride (1 mmol), *N*-methylaniline (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol%), KOtBu (1.1 mmol), DME (1 mL), and $T = 50$ °C. [b] Conversions are the average of at least two runs. [c] Isolated yields.

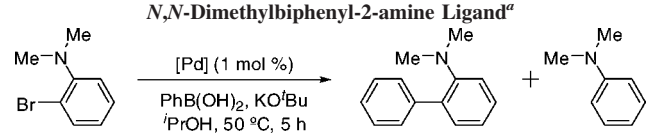
Table 5. Cross Coupling of Various Amines and Aryl Halides Mediated by 4[a]

entry	Ar-Cl	HNRR'	time	conversion GC[b]	yield[c]
1			4 h	98%	99%
2			30 min	97%	99%
3			4 h	98%	99%
4			24 h	0%	-
5			24 h	0%[d]	-
6			24 h	0%	-

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [(SIPr)Pd(Cycle)Cl] **4** (1 mol%), KO′Bu (1.1 mmol), DME (1 mL), and $T = 50$ °C. [b] Conversions are the average of at least two runs. [c] Isolated yields. [d] Decomposition of the 4-chlorobenzonitrile observed.

by Evans and Williams.[33] Beyond using the highly toxic methyl sulfate as methylating agent, they claimed to obtain the product in very good yield (94%) starting from the 2-aminodiphenyl. However, Popkin and co-workers reported in 1944 that the previously published yield was a mixture of the dimethyl and monomethyl compounds in a 66:34 ratio.[34] By conducting the methylation with methanol under high temperature and pressure, the product ratio was improved to 87:13 with a reduced yield of 85%. Other procedures also gave mixtures, and the product was usually isolated in poor yields.[35] Finally to date, the only appealing procedure to this ligand was reported in 2003 using formaldehyde and sulfuric acid at −10 °C to methylate 2-aminodiphenyl in good yield.[36] Here, we have synthesized *N*,*N*-dimethylbiphenyl-2-amine by employing Suzuki−Miyaura cross-coupling using one of our novel palladacycle-NHC complexes. In addition to representing an original catalytic application, this specific example represents an unusual strategy: *using a catalyst as a synthetic tool for the synthesis of a biaryl compound that is an organic moiety of this same catalyst*.

Table 6. Catalyst Screening for the Synthesis of the *N*,*N*-Dimethylbiphenyl-2-amine Ligand[a]



9 **10** **11**

entry	[Pd]	% conv[b]	ratio 10/11[b]
1	[(IPr)Pd(Cycle)Cl] **2**	92	1/1.5
2	[(SIMes)Pd(Cycle)Cl] **3**	92	1/1.0
3	[(SIPr)Pd(Cycle)Cl] **4**	91	1/1.1
4	[(IPr)Pd(ally)Cl]	83	1/7.3
5	[(SIPr)Pd(allyl)Cl]	79	1/1.1
6	[(SIPr)Pd(cin)Cl]	96	1/1.05
7	$[(SIPr)PdCl_2]_2$	95	1/1.8
8	[(IPr)Pd(acac)Cl]	>2	
9	$[(SIPr)Pd(OAc)_2(H_2O)]$	80	1/2.6

[a] Reaction conditions: 2-bromo-*N*,*N*′-dimethylaniline **9** (1 mmol), phenylboronic acid (1.1 mmol), [Pd] (1 mol %), KO′Bu (1 0.2 mmol), tech. grade ^{i}PrOH (2 mL), $T = 50$ °C, and time = 5 h. [b] Determined by ^{1}H NMR spectroscopy; average of two runs.

We first tested the feasibility of the coupling reaction with several catalysts synthesized in our laboratory (Table 6). Excluding the Pd-acac complex[13] that did not exhibit any activity in the desired cross-coupling reaction (entry 8), all catalysts tested allowed for good conversions to the desired product in 5 h. The main problem observed was the formation of byproduct **11**, resulting from the dehalogenation of the starting material, in significant amount (≥50%). The cycle-, allyl-,[10] and cinnamyl-(NHC)Pd[11] series, known for their high reactivity, showed the most interesting results with a ratio close to 1/1. Compared to the unsaturated congeners, the reduction/cross-coupling ratio was decreased when saturated NHCs were used ([(NHC)Pd(Cycle)Cl] or [(NHC)Pd(allyl)Cl], (entries 1 and 3−5). In order to improve these results, reaction conditions were re-examined using [(SIMes)Pd(Cycle)Cl] (**3**) (Table 7).

Different non- or protic, non- or coordinating solvents were tested, and surprisingly, the reaction could only be carried out in isopropanol (entry 1). The optimization of the base showed that carbonate bases were inefficient (entries 11 and 12). A smaller counteranion caused a conversion decrease in parallel with an increase in dehalogenation (entry 8). Finally, despite only moderate conversion after 5 h, an important change in the ratio in favor of **10** occurred using KOH and KOMe (entries 9 and 10). The optimized conditions were used for the synthesis

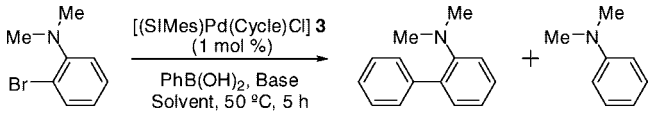
(33) Evans, D. P.; Williams, R. *J. Chem. Soc.* **1939**, 1199–1202.

(34) Popkin, A. H.; Perretta, G. M.; Selig, R. *J. Am. Chem. Soc.* **1944**, *66*, 833–834.

(35) (a) Chen, Q.; Li, Z. *J. Fluorine Chem.* **1994**, *66*, 59–62. (b) Creencia, E. C.; Horaguchi, T. *J. Heterocyclic Chem.* **2006**, *43*, 1441–1446.

(36) Azzena, U.; Cattari, M.; Melloni, G.; Pisano, L. *Synthesis* **2003**, 2811–2814.

Table 7. Solvent Ant Base Screening for the Synthesis of the *N,N*-Dimethylbiphenyl-2-amine Ligand[a]

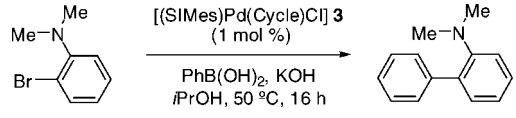


9 10 11

entry	solvent	base	% conv[b]	ratio 10/11[b]
1	^{i}PrOH	KO^{t}Bu	92	1/1.0
2	EtOH	KO^{t}Bu	>2	
3	MeOH	KO^{t}Bu	>2	
4	DME	KO^{t}Bu	>2	
5	dioxane	KO^{t}Bu	>2	
6	THF	KO^{t}Bu	>2	
7	Toluene	KO^{t}Bu	>2	
8	^{i}PrOH	NaO^{t}Bu	52	1/1.4
9	^{i}PrOH	KOMe	15	1/0.3
10	^{i}PrOH	KOH	66	1/0.2
11	^{i}PrOH	K_2CO_3	>2	
12	^{i}PrOH	Cs_2 CO_3	>2	

[a] Reaction conditions: 2-bromo-*N*,*N*′-dimethylaniline **9** (1 mmol), phenylboronic acid (1.1 mmol), [(SIMes)Pd (Cycle)Cl] **3** (1 mol %), base (1.2 mmol), solvent (2 mL), T = 50 °C, and time = 5 h. [b] Determined by^1 H NMR spectroscopy; average of two runs.

Scheme 2. Large Scale Synthesis of *N,N*-Dimethylbiphenyl-2-amine Ligand 10



9 10

88 % isolated yield
(10 mmol scale)

of **10** in large scale (Scheme 2). The reaction time was optimized to 16 h, and 88% of **10** was isolated, and the formation of **11** was greatly reduced.

In conclusion, two well-defined, air- and moisture-stable saturated NHC-containing *N*-*C*-palladacycle complexes were synthesized and fully characterized. Their reactivity was evaluated in the Buchwald−Hartwig amination of a range of unactivated and diverse aryl chlorides.[37] Both aryl and alkyl primary and secondary amines were well tolerated by the [(SIPr)Pd(Cycle)Cl] complex. Moreover, the catalytic system was found to be compatible with reactive functions such as carboxylic acid and amide. [(NHC)Pd(Cycle)Cl] complexes bearing saturated and unsaturated NHCs did not show any differences in terms of reactivity. In addition, the Suzuki−Miyaura cross-coupling using [(SIMes)Pd(Cycle)Cl] was applied to the synthesis of the biphenyl ligand employed to synthesize the catalyst. We hope this more accessible synthetic route will facilitate the development of further applications of these dimethylbiphenylamine palladacycle complexes.

Experimental Section

General Considerations. All reactions were performed under an inert atmosphere of argon or nitrogen using standard high-vacuum or Schlenk techniques or in an MBraun glovebox containing less than 1 ppm oxygen and water. Solvents were distilled from appropriate drying agents or were dispensed from a solvent purification system from Innovative Technology; other anhydrous solvents were purchased from Aldrich and degassed prior to use by purging with dry argon and were kept over molecular sieves. Flash column chromatography was performed on silica gel 60 (230−400 mesh). ^{1}H and ^{13}C, ^{19}F nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 Ultrashield NMR spectrometer. High resolution mass spectroscopy (HRMS) analyses were performed at the ICIQ. Elemental analyses were performed at Universidad Complutense de Madrid.

Synthesis of [(SIMes)Pd(cycle)Cl] (3). In a glovebox, a scintillation vial was charged with a stirring bar, 135 mg (0.2 mmol) of palladacycle dimer, 130 mg (0.42 mmol) of SIMes, and 10 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtered over a plug of celite, and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane; 220 mg (85% yield) of an off white solid was obtained.^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.25 (d, ^{3}J(H,H) = 6.8 Hz, 1H, H^{Ar}), 7.16 (dt, ^{3}J(H,H) = 7.7 Hz, ^{4}J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.11−7.07 (m, 2H, H^{Ar}), 7.04−6.99 (m, 1H, H^{Ar}), 6.97−6.90 (m, 5H, H^{Ar}), 6.48 (s, 2H, H^{Ar}), 4.02−3.97 (m, 1H, CH_2-CH$_2$), 3.94−3.83 (m, 1H, CH_2-CH$_2$), 3.74−3.69 (m, 2H, CH_2-CH$_2$), 2.90 (s, 3H, CH_3-N), 2.80 (s, 3H, CH_3-N), 2.53 (s, 3H, CH_3^{Mes}), 2.41 (s, 3H, CH_3^{Mes}), 2.36 (s, 3H, CH_3^{Mes}), 2.26 (s, 3H, CH_3^{Mes}), 2.17 (s, 3H, CH_3^{Mes}), 1.52 (s, 3H, CH_3^{Mes}). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 198.2 (C, N-*C*-N), 152.0 (C, C^{Ar}), 147.2 (C, C^{Ar}), 142.2 (C, C^{Ar}), 140.4 (C, C^{Ar}), 138.5 (C, C^{Ar}), 137.4 (C, C^{Ar}), 137.2 (CH, C^{Ar}), 137.1 (C, C^{Ar}), 136.6 (C, C^{Ar}), 136.4 (C, C^{Ar}), 136.0 (C, C^{Ar}), 135.4 (C, C^{Ar}), 135.3 (C, C^{Ar}), 129.6 (CH, C^{Ar}), 129.5 (CH, C^{Ar}), 129.3 (CH, C^{Ar}), 128.8 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 126.8 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 125.1 (CH, C^{Ar}), 124.1 (CH, C^{Ar}), 124.0 (CH, C^{Ar}), 115.9 (CH, C^{Ar}), 52.6 (CH$_2$, *C*H$_2$−CH$_2$), 51.1 (CH$_3$, *C*H$_3$−N), 50.4 (CH$_2$, *C*H$_2$−CH$_2$), 49.9 (CH$_3$, *C*H$_3$−N), 20.7 (CH$_3$, C^{Mes}), 20.5 (CH$_3$, C^{Mes}), 19.8 (CH$_3$, C^{Mes}), 17.5 (CH$_3$, C^{Mes}). HRMS (ESI): *m*/*z* calcd for $C_{35}H_{40}N_3Pd$: 608.2257 [M^+ − Cl]; found 608.2237. Anal. Calcd for $C_{35}H_{40}N_3ClPd$ (MW 644.59): C, 65.22; H, 6.25; N, 6.52. Found: C, 65.09; H, 6.46; N, 6.47.

Synthesis of [(SIPr)Pd(Cycle)Cl] (4). In a glovebox, a scintillation vial was charged with a stirring bar, 405 mg (0.6 mmol) of palladacycle dimer, 500 mg (1.26 mmol) of SIPr, and 20 mL of dry THF. The reaction mixture was stirred 2 h at room temperature. Outside of the glovebox, the reaction mixture was filtrated over a plug of celite, and solvent was evaporated *in vacuo*. The remaining solid was triturated with pentane, and the precipitate was collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane; 830 mg (95% yield) of an off white solid was obtained. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.44 (t, ^{3}J(H,H) = 7.5 Hz, 1H, H^{Ar}), 7.35 (d, ^{3}J(H,H) = 7.2 Hz, 1H, H^{Ar}), 7.28 (d, ^{3}J(H,H) = 7.4 Hz, 1H, H^{Ar}), 7.17−7.11 (m, 3H, H^{Ar}), 7.03−6.95 (m, 4H, H^{Ar}), 6.86−6.83 (m, 3H, H^{Ar}), 6.69 (d, ^{3}J(H,H) = 7.4 Hz, 1H, H^{Ar}), 4.19−4.10 (m, 2H, CH(CH$_3$)$_2$), 4.04−3.97 (m, 2H, CH_2-CH$_2$), 3.87−3.82 (m, 2H, CH_2-CH$_2$), 3.27 (septet, ^{3}J(H,H) = 6.6 Hz, 1H, CH(CH$_3$)$_2$), 2.86 (s, 3H, CH_3-N), 2.60 (septet, ^{3}J(H,H) = 6.4 Hz, 1H, CH(CH$_3$)$_2$), 2.06 (s, 3H, CH_3-N), 1.70 (d, ^{3}J(H,H) = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.58 (d, ^{3}J(H,H) = 6.6 Hz, 3H, CH(CH_3)$_2$), 1.44 (d, ^{3}J(H,H) = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.30 (d, ^{3}J(H,H) = 6.7 Hz, 3H, CH(CH_3)$_2$), 1.08 (d, ^{3}J(H,H) = 6.5 Hz, 3H, CH(CH_3)$_2$), 0.98 (d, ^{3}J(H,H) = 6.5 Hz, 3H, CH(CH_3)$_2$), 0.93 (d, ^{3}J(H,H) = 6.2 Hz, 3H, CH(CH_3)$_2$), 0.47 (d, ^{3}J(H,H) = 6.3 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 200.6 (C, N-*C*-N), 152.7 (C, C^{Ar}), 148.2 (C, C^{Ar}), 147.8 (C, C^{Ar}), 147.2 (C, C^{Ar}), 145.7 (C, C^{Ar}), 145.6 (C, C^{Ar}), 142.9 (C, C^{Ar}), 141.6 (C, C^{Ar}), 138.0 (C, C^{Ar}), 136.8 (C, C^{Ar}), 135.9 (CH, C^{Ar}), 129.6 (CH, C^{Ar}), 128.4 (CH, C^{Ar}), 128.2 (CH, C^{Ar}), 126.7 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 125.3 (CH, C^{Ar}), 124.7 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 124.4 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 122.8 (CH, C^{Ar}), 116.2 (CH, C^{Ar}), 55.5 (CH$_2$, *C*H$_2$−CH$_2$), 52.7 (CH$_2$, *C*H$_2$−CH$_2$), 50.6 (CH$_3$,

(37) The reactivity of [(SIPr)Pd(Cycle)Cl] (**4**) was also tested in the *O*-arylation of phenol with arylbromides and arylchlorides. Unfortunately, no coupling was observed in the few tests carried out.

*C*H$_3$−N), 50.3 (CH$_3$, *C*H$_3$−N), 29.0 (CH, *C*H(CH$_3$)$_2$), 28.7 (CH, *C*H(CH$_3$)$_2$), 28.3 (CH, *C*H(CH$_3$)$_2$), 28.2 (CH, *C*H(CH$_3$)$_2$), 27.2 (CH$_3$, CH(*C*H$_3$)$_2$), 26.9 (CH$_3$, CH(*C*H$_3$)$_2$), 26.0 (CH$_3$, CH(*C*H$_3$)$_2$), 25.5 (CH$_3$, CH(*C*H$_3$)$_2$) 24.7 (CH$_3$, CH(*C*H$_3$)$_2$), 24.1 (CH$_3$, CH(*C*H$_3$)$_2$), 23.3 (CH$_3$, CH(*C*H$_3$)$_2$), 22.9 (CH$_3$, CH(*C*H$_3$)$_2$). HRMS (ESI): *m*/*z* calcd for $C_{41}H_{52}N_3Pd$: 692.3196 [M^+ − Cl]; found 692.3178. Anal. Calcd for $C_{41}H_{52}N_3ClPd$ (MW 728.74): C, 67.57; H, 7.19; N, 5.77. Found: C, 67.74; H, 6.91; N, 5.60.

General Procedure for the Buchwald−Hartwig Cross-Coupling Reaction. In a glovebox, to a screw cap septum vial equipped with a magnetic stir bar were added in turn [(SIPr)Pd(Cycle)Cl] (1 mol %, 7.3 mg), potassium *tert*-butoxide (1.1 mmol, 120 mg), and anhydrous DME (1 mL). Outside the glovebox, the amine (1.1 mmol) and the aryl chloride (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was, before loading of the solvent, charged in the vial inside the glovebox. The reaction mixture was then stirred at 50 °C. When the reaction reached completion or no further conversion was observed by gas chromatography, the volatiles were removed *in vacuo*.

4-*p*-Tolylmorpholine (Table 3, Entry 1) CAS [3077-16-5]. The general procedure followed by silica gel chromatography (DCM) afforded 320 mg (91%) of the title compound as a white solid.

***N*-(2,6-Dimethylphenyl)morpholine (Table 3, Entry 2) CAS [255835-91-7].** The general procedure followed by silica gel chromatography (pentane/DCM 8/2) afforded 140 mg (74%) of the title compound as a white solid.

***N*-(4-Cyanophenyl)morpholine (Table 3, Entry 3) CAS [10282-31-2].** The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (90%) of the title compound as a white solid.

***N*-(3-Pyridyl)morpholine (Table 3, Entry 4) CAS [92670-29-6].** The general procedure followed by silica gel chromatography (EtOAc/MeOH 98/2) afforded 152 mg (95%) of the title compound as a clear volatile liquid.

***N*-(2-Methoxyphenyl)morpholine (Table 3, Entry 5) CAS [27347-13-3].** The general procedure followed by silica gel chromatography (DCM) afforded 130 mg (68%) of the title compound as a clear volatile liquid.

4-Morpholinobenzamide (Table 3, Entry 8) CAS [183557-77-9]. The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1 N HCl solution (20 mL). After adjusting the pH to 5 with a 3 N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9/1) afforded 128 mg (61%) of the title compound as a white solid.

3-Morpholinobenzoic acid (Table 3, Entry 9) CAS [215309-00-5]. The general procedure was followed using potassium *tert*-butoxide (2.2 mmol, 240 mg) and anhydrous DME (2 mL). The reaction mixture was then dissolved in 30 mL of EtOAc and washed once with a 0.1 N HCl solution (20 mL). After adjusting the pH to 5 with a 3 N NaOH solution, the aqueous phase was extracted six times with EtOAc. Subsequent flash chromatography on silica gel (EtOAc/MeOH 9/1) afforded 207 mg (>99%) of the title compound as a white solid.

***N*-Methyl-*N*-*p*-tolylaniline (Table 4, Entry 1) CAS [38158-65-5].** The general procedure followed by silica gel chromatography (pentane/DCM 98/2) afforded 192 mg (97%) of the title compound as a clear liquid.

***N*-Methyl-*N*-(2-methylphenyl)aniline (Table 4, Entry 2) CAS [6590-44-9].** The general procedure followed by silica gel chromatography (pentane) afforded 184 mg (93%) of the title compound as a clear liquid.

2-(*N*-Methylanilino)pyridine (Table 4, Entry 3) CAS [62093-17-8]. The general procedure followed by silica gel chromatography (DCM) afforded 170 mg (94%) of the title compound as a clear liquid.

***N*-Methyl-*N*-phenyl-4-methoxyaniline (Table 4, Entry 4) CAS [55251-46-2].** The general procedure followed by silica gel chromatography (pentane/DCM 5/5) afforded 170 mg (81%) of the title compound as a clear liquid.

***N*-Methyl-*N*-phenyl-2-methoxyaniline (Table 4, Entry 5) CAS [263917-74-4].** The general procedure followed by silica gel chromatography (pentane/DCM 5/5) afforded 200 mg (94%) of the title compound as a clear liquid.

Dibutyl(4-tolyl)amine (Table 5, Entry 1) CAS [31144-33-9]. The general procedure followed by silica gel chromatography (pentane/DCM 8/2) afforded 218 mg (99%) of the title compound as a clear liquid.

***N*-(3-Fluorophenyl)-1-adamantylamine (Table 5, Entry 2).** The general procedure followed by silica gel chromatography (pentane/DCM 6/4) afforded 243 mg (99%) of the title compound as a white precipitate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (q, 1H, J = 6.0 Hz), 6.50−6.46 (m, 2H), 6.43−6.38 (m, 1H), 3.49 (bs, 1H), 2.12 (bs, 3H), 1.90 (d, J = 2.8 Hz, 6H), 1.72−1.65 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, C, C^3), 148.2 (d, C, C^1), 129.9 (d, CH, C^5), 113.5 (d, CH, C^6), 104.6 (d, CH, C^4), 104.2 (d, CH, C^2), 52.3 (C), 43.3 (3CH$_2$), 36.63 (3CH$_2$), 29.83 (3CH). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.34 (s). HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}FN$ (M^+ + H) 246.1658, found 246.1667.

***N*-Cyclohexyl-1-naphthylamine (Table 5, Entry 3) CAS [26863-63-8].** The general procedure followed by silica gel chromatography (pentane/DCM 7/3) afforded 223 mg (99%) of the title compound as a white solid.

***N*,*N*-Dimethylbiphenyl-2-amine (10).** A Schlenk tube was charged with a stirring bar, 65 mg (0.1 mmol) of [(SIMes)Pd(Cycle)Cl] **3**, 1.34 g (11 mmol) of phenylboronic acid, 672 mg (12 mmol) of ground KOH, 1.3 mL (10 mmol) of 2-bromo-*N*,*N*-dimethylaniline, and 20 mL of *i*PrOH. The reaction mixture was stirred for 16 h at 50 °C and then filtrated over a plug a celite. Purification of crude mixture by silica gel chromatography (pentane/diethyl ether, 98/2) afforded the title product as a colorless oil (1.73 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, ^{3}J(H,H) = 8.0 Hz, ^{4}J(H,H) = 1.6 Hz, 2H, H^{Ar}), 7.46 (t, ^{3}J(H,H) = 7.6 Hz, 2H, H^{Ar}), 7.38−7.32 (m, 2H, H^{Ar}), 7.29 (dd, ^{3}J(H,H) = 7.6 Hz, ^{4}J(H,H) = 1.6 Hz, 1H, H^{Ar}), 7.12−7.08 (m, 2H, H^{Ar}), 2.62 (s, 6H, CH_3-N). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3 (C, C^{Ar}), 142.0 (C, C^{Ar}), 134.2 (C, C^{Ar}), 131.7 (CH, CH^{Ar}), 128.7 (CH, CH^{Ar}), 128.3 (CH, CH^{Ar}), 128.1 (CH, CH^{Ar}), 126.5 (CH, CH^{Ar}), 121.5 (CH, CH^{Ar}), 117.6 (CH, CH^{Ar}), 43.4 (CH$_3$, *C*H$_3$−N). HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}N$: 198.1283 [M^+]; found 198.1293.

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Supporting Information Available: CIF files of crystal structures **3** and **4** have been deposited with the CCDC, No. CCDC-688389 and 688388, respectively. Copies of the data can be obtained free of charge on applications to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336 033; http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk. This material is available free of charge via the Internet at http://pubs.acs.org.

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