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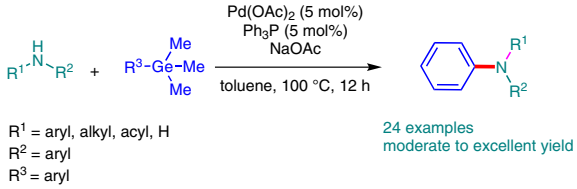
Palladium-Catalyzed N-Arylation of Amines and Amides with Aryltrimethylgermanes

Qiang Zhang*
Cunfang Liu
Juan Shi
Qiong Xu
Lingxia Jin*
Chaibin Zhao
Tianlei Zhang

School of Chemistry and Environmental Science, Shaanxi University of Technology, Shaanxi Province Key Laboratory of Catalytic Fundamentals & Applications, Hanzhong, 723001, P. R. of China
zhangqiang22@126.com
jinlingxia1982@126.com



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Abstract Described herein is a novel palladium-catalyzed C–N bond-formation reaction employing aryltrimethylgermanes as the new arylating reagents. Primary/secondary amines or even amides could be smoothly arylated to provide the corresponding N-arylation products in moderate to excellent yields.

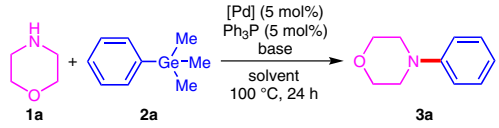
Key words N-arylation, amine, amide, aryltrimethylgermane

Owing to the ubiquity and diverse biological activities, N-containing molecules are of utmost importance. The construction of the C–N bond is of significant importance[1] as it paves the ways to the introduction of nitrogen in organic entities. Despite the significant achievements in this field, the construction of the C–N bond is still a major challenge for organic chemists. Thus, the development of more applicable methodologies toward the formation of C–N bonds[2] in an expedient fashion is still highly desirable. As the key components featuring the N-containing molecules, amines, and amides are ubiquitous structural motifs[1a] that have been widely found in many biologically active entities. Thus, syntheses of these compounds have attracted significant interest in organic community and pharmaceutical industry. During the last decade, significant advancement has been made. Notably, among all the methods developed, the palladium-catalyzed Buchwald–Hartwig amination[3,4] between aryl halides with amines has received the most attention in this arena because of its high efficacy and good substrate spectrum. Noteworthy, organoboron reagents[5] have recently been employed as the arylating agents for the metal-catalyzed C–N bond-formation event because of their indisputable advantages of relative stability under air and moisture conditions, commercial availability, good functional-group compatibility, low toxicity, and ease of synthesis. An alternative to such a transformation is the use of organogermane, which eliminates the purification difficulties associated with organoboron reagents, as well as the toxic byproducts along with the use of organolead and organotin[6] compounds. As far as we know, germanium, element 32, has lower carbon–metal bond energy and a larger covalent radius than the silicon counterpart in group IVA (group 14). Thus germylated arenes[7] are more susceptible to electrophilic substitution reactions than arylsilane[8] analogues. However, examples of employing organogermanes in N-arylation reaction have not yet been reported to date. Herein, we describe, for the first time, a palladium-catalyzed N-arylation of amines and amides employing aryltrimethylgermanes as substrates.

In the beginning, aryltrimethylgermane compounds were synthesized[7] via the corresponding bromobenzene through Grignard reaction. Then phenyltrimethylgermane (**2a**) and morpholine were used as substrates, and a series of catalysts, bases, and solvents were employed for optimization of reaction conditions. Since ligands always play a key role[9] in transition-metal-catalyzed chemistry, we firstly focused on the screening of ligands. In this transformation, bidentate phosphine ligands such as dppp, dppe, dppb, and dppf were proven to be less effective than the monodentate phosphine ligand Ph_3P.

To our delight, Ph_3P could promote N-arylation of phenyltrimethylgermane to provide the desired product with 17% yield. Then we embarked on the examination of different solvents. Xylene, dioxane, and 1,2-dimethoxyethane (DME) gave inferior yields or delivered no product (Table 1, entries 1–4). When using 5 mol% of $Pd(OAc)_2$ as the catalyst, 5 mol% Ph_3P as the ligand, and 2.0 equivalents of K_2CO_3 as the base at 100 °C in toluene under argon atmosphere produced the target product in 26% yield (Table 1, entry 3). Among all the bases, NaOAc was the best base, and the

Table 1 Screening of Parameters in the N-Arylation Reaction[a]



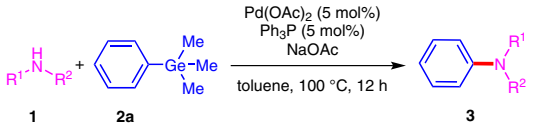
Entry	Pd source	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	K_2CO_3	xlyene	<5
2	$Pd(OAc)_2$	K_2CO_3	dioxane	<5
3	$Pd(OAc)_2$	K_2CO_3	toluene	26
4	$Pd(OAc)_2$	K_2CO_3	DME	<5
5	$Pd(OAc)_2$	Na_2CO_3	toluene	76
6	$Pd(OAc)_2$	Cs_2CO_3	toluene	65
7	$Pd(OAc)_2$	NaOAc	toluene	94
8	$Pd(OAc)_2$	KF	toluene	47
9	$Pd(OAc)_2$	K_3PO_4	toluene	37
9	$PdCl_2$	NaOAc	toluene	68
10	$PdCl_2$(dppf)	NaOAc	toluene	<5
11	$Pd(PPh_3)_4$	NaOAc	toluene	31

[a] Reaction conditions: morpholine (**1a** , 104.4 μL, 1.2 mmol), phenyltrimethylgermane (**2a**, 194.9 mg, 1.0 mmol), Pd source (5 mol%), Ph_3P (13.1 mg, 5 mol%), toluene (2.0 mL), under argon atmosphere at 100 °C for 12 h.
[b] Isolated yield.

product was isolated in 94% yield (Table 1, entry 7). The $Pd(OAc)_2$ exhibited the highest catalytic activity among $PdCl_2$, $Pd(OAc)_2$, $PdCl_2$(dppf), and $Pd(PPh_3)_4$. Further increasing or decreasing the amount of Ph_3P in the system did not increase the yield. It was worth pointing out that rigorous exclusion of air/moisture is not required in these transformations. Thus, we established the optimized reaction conditions as follows: amine or amide **1a** (1.2 mmol), phenyltrimethylgermane (**2a**, 1.0 mmol), $Pd(OAc)_2$ (5 mol%), Ph_3P (5 mol%), NaOAc (164.1 mg, 2.0 mmol), toluene (2.0 mL), 100 °C, 12 hours.

With the optimized conditions in hand, a variety of amines including primary and secondary aliphatic amines as well as anilines were systematically examined to explore the extent of the reaction. As expected, a variety of amines could be well tolerated in the reaction providing the N-arylation products in moderate to excellent yields. Anilines were expected to be good cross-coupling substrates under the model conditions to provide the diarylamines in good yields. It is worth noting that the hindrance of amines and amides had obvious effects on this reaction. For example, **3l** and **3n** were only isolated in 47% and 57% yield, respectively, while **3h** and **3m** were formed in 84% and 87% yield, respectively (Table 2, entries 8, 12, 13, 14). Interestingly, the 4-chlorobenzenamine **1j** could also be employed as the qualified substrate in the reaction and keep the chloro group untouched (Table 2, entry 10).

Table 2 N-Arylation of the Amines and Amides with $PhGeMe_3$[a]



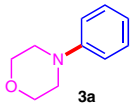
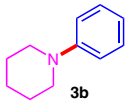
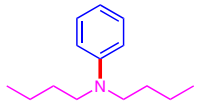
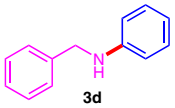
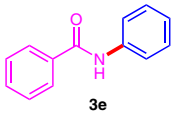
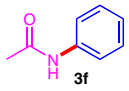
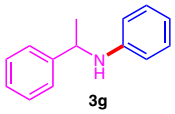
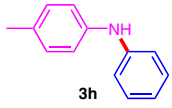
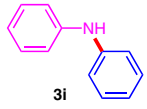
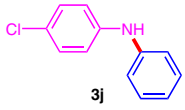
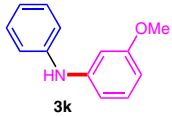
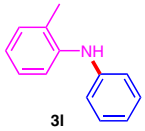
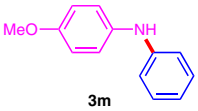
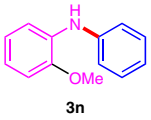
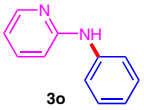
Entry	Product	Yield (%)[b]
1	 **3a**	94
2	 **3b**	75
3	 **3c**	77
4	 **3d**	64
5	 **3e**	37
6	 **3f**	56
7	 **3g**	66
8	 **3h**	84
9	 **3i**	83
10	 **3j**	81
11	 **3k**	75

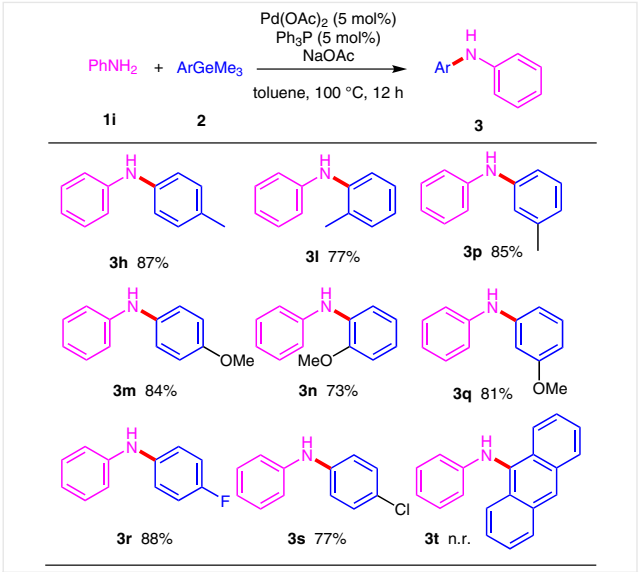
Table 2 (continued)

Entry	Product	Yield (%)[b]
12	 **3l**	47
13	 **3m**	87
14	 **3n**	57
15	 **3o**	35

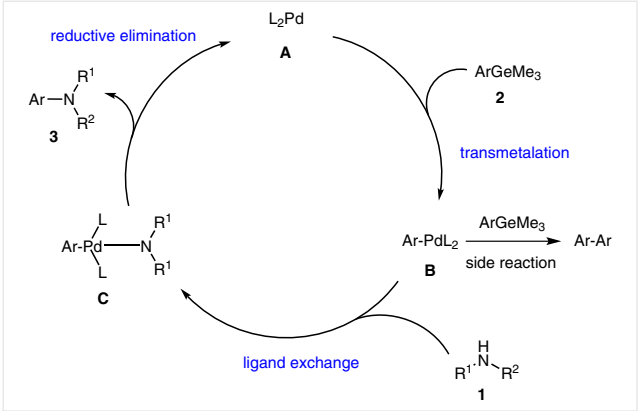
[a] Reaction conditions: amine or amide **1** (1.2 mmol), phenyltrimethylgermane (**2a**, 194.9 mg, 1.0 mmol), $Pd(OAc)_2$(11.2 mg, 5 mol%), Ph_3P (13.1 mg, 5 mol%), NaOAc (164.1 mg, 2.0 mmol), toluene (2.0 mL), under argon atmosphere at 100 °C for 12 h.[10]
[b] Isolated yield.

We next employed aryltrimethylgermanes possessing electron-donating groups or sterically hindered substrates to further expand the scope of the reaction. As expected, all reactions proceeded smoothly under our optimum conditions and no obvious electronic effect except highly hindered aryltrimethylgermane (Scheme 1). Of particular note, a mono substitution in the *ortho* position of aryltrimethylgermane reduced reactivity slightly. 4-Chloroaniline (**1j**) and 4-chlorophenyl- trimethylgermane (**2j**) could proceed smoothly with **3j** to afford **3s** in good yield and keep the chloro group untouched (Table 2, entry 10, Scheme 1).

To understand the mechanism in more detail, the crude reaction mixture between morpholine and phenyltrimethylgermane under optimized reaction conditions was examined by GC–MS. It showed that the 1,1′-biphenyl and as the byproduct was produced in situ except the 4-arylated phenylmorpholine and the reactants. Based upon the above experimental results, a plausible mechanism is outlined in Scheme 2. The catalytic cycle may contain three steps: 1) L_2Pd **A** undergoes transmetalation to form $ArPdL_2$ **B**, which may produce the byproduct Ar–Ar through cross-coupling reaction; 2) $ArPdL_2$ **B** exchange the partner with R^1R^2NH to form intermediate **C**; 3) intermediate **C** deliver the reductive elimination product **3**, and the true catalytic species **A** is regenerated.[2a]



Scheme 1 N-Arylation of $PhNH_2$ with aryltrimethylgermane



Scheme 2 A plausible mechanism

In conclusion, we describe for the first time a mild palladium-catalyzed N-arylation reaction of amines and amides via $ArGeMe_3$, The catalytic system provides N-arylation products in moderate to excellent yields. The reaction has a wide scope of substrate including amides, primary and secondary or aliphatic and aromatic amines, and may provide potential opportunities in the N-arylation of nitrogen-containing compounds. The applications of aryltrimethylgermane are the focus of ongoing efforts under way in our laboratory and will be reported in due course.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562104.

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(10) **Representative Procedure**

A Schlenk reaction tube was charged with phenyltrimethylgermane (**2a**, 194.9 mg, 1.0 mmol), 4-methoxyaniline (**1m**, 147.9 mg, 1.2 mmol), $Pd(OAc)_2$ (11.2 mg, 5 mol%), Ph_3P (13.1 mg, 5 mol%), NaOAc (164.1 mg, 2.0 mmol), toluene (2.0 mL), under argon atmosphere at 100 °C for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic layer was washed by water and dried by Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by a short column chromatography (silica gel 300–400 mesh, PE–EtOAc = 8:1) to give **3m** in 87% isolated yield (173 mg); mp 102–103 °C.

4-Methoxy-*N*-Phenylaniline (3m)

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.18 (m, 3 H), 7.09–7.05 (m, 2 H), 6.92–6.83 (m, 4 H), 5.49 (s, 1 H), 3.81 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7, 129.3, 124.3, 122.2, 119.5, 115.6, 114.6, 114.1, 55.6. MS (EI): *m/z* = 212. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.35; H, 6.59; N, 7.02. Found: C, 78.22; H, 6.41; N, 6.95.