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Transition metal-free amination of aryl halides—A simple and reliable method for the efficient and high-yielding synthesis of *N*-arylated amines

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ABSTRACT

A simple and reliable reaction protocol for the clean, fast, and high-yielding synthesis of various *N*-arylated amines derived from reactions of aryl halides with various (also sterically hindered) amines under transition metal-free reaction conditions is presented. Dioxane and $KN(Si(CH_3)_3)_2$ were found to be the ideal solvent and base for this transformation. The conversion rates and yields observed are excellent and in the majority of the reactions performed significantly higher than that obtained in their catalyzed versions. Furthermore, the selective synthesis of 6-halopyridin-2-amines and asymmetric pyridine-2,6-diamines (derived from consecutive reactions of 2,6-dibromopyridine and 2,6-dichloropyridine, respectively, with different amines) is possible in almost quantitative yields (relative to 2,6-dihalopyridine) within very short reaction times. Purification of the 6-halopyridin-2-amine intermediates is not necessary, allowing the synthesis of pyridine-2,6-diamines in 'one-pot'. However, catalysts are in many cases *not* required to efficiently and selectively couple aryl halides with amines, making transition metal-free versions of the Buchwald–Hartwig reaction extremely attractive for the synthesis of *N*-arylated amines with substrates containing substituents on the aryl halide, which either promote regioselectivity and/or do not require regioselective aminations.

1. Introduction

The *N*-aryl amination (Buchwald–Hartwig reaction) has attracted enormous interest over the last 20 years and belongs nowadays to an indispensable set of cross-coupling reactions, which finds its application in all areas of organic chemistry, ranging from the laboratory bench, the synthesis of pharmaceutical fine chemicals and the production of bulk chemicals.[1–3] Despite the existence of copper-, nickel-, and iron-catalyzed versions of the Buchwald–Hartwig reaction, palladium still remains the metal of choice for this transformation.[4–6] As a consequence, most research groups are focused on the development of palladium complexes with newly designed ligand systems in order to improve their efficiency, scope, and applicability as catalyst.[3] Thus, many palladium catalysts are known, of which some efficiently couple amines with electronically deactivated and sterically hindered aryl chlorides, occasionally even at room temperature and in some cases to completion within only few minutes. However, beside all the great advances achieved, a major drawback of the Buchwald–Hartwig reaction still includes the large amount of catalyst required (typically ~1 mol %) to promote this transformation efficiently. Thus, their separation from organic products, which is of particular importance for the synthesis of pharmaceutical fine chemicals because of their residual toxicity in the target compounds, is a central issue to consider. Moreover, transition metal-catalyzed reactions also generate hazardous waste (in particular in the case of copper-catalyzed versions), which is environmentally problematic and hence, should to be avoided wherever possible.[7] Although transition metal-free cross-coupling reactions between primary and secondary amines and aryl halides using microwave irradiation conditions were recently reported,[8] the development of more improved synthetic methods for the transition metal-free synthesis of aryl substituted amines is desirable. Therefore, if aryl halides are efficiently aminated under transition metal-free reaction conditions with competitive conversion rates and yields when compared with its catalyzed versions; this would greatly increase its attraction—also from economic and ecologic points of view.

We present here a new, convenient, generally applicable and reliable reaction protocol for the clean, fast, and high-yielding synthesis of *N*-arylated amines derived from reactions of aryl halides with amines under transition metal-free reaction conditions. Whereas dioxane and $KN(Si(CH_3)_3)_2$ were found to be the ideal solvent and base for this transformation, K_3PO_4 was the base of choice for the selective synthesis of 6-halopyridin-2-amines derived from reactions of 2,6-dihalopyridines with equimolar amounts of dialkylamines. However, the observed conversion rates

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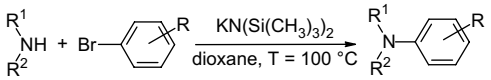
and yields are excellent and in the majority of the reactions performed significantly higher when compared with their catalyzed versions.[9] Although reports already exist, which successfully describe the transition metal-free amination of aryl halides with $NaNH_2$, KNH_2, $LiNH_2$, or NaH as base,[11] many of these reports describe reactions performed with specific substrates (e.g., fluorides) and/or are part of the synthesis of more complex organic molecules.[12] Moreover, it was found that the use of these bases often lead to significantly lower conversion rates and yields when compared to reactions performed with $KN(Si(CH_3)_3)_2$ as it is for instance generally the case when aryl halides are coupled with dialkylamines. In addition, whereas amination reactions performed with $KN(Si(CH_3)_3)_2$ generally are successful,[13] results obtained with, e.g., $NaNH_2$ or NaH were found to be much more substrate dependent.[14] However, an elegant method for transition metal-free aminations of aryl chlorides was recently reported with K^{t}BuO as base, generally giving the *N*-arylated amines in high yields.[15] Unfortunately, prolonged reaction times (36 h) and high reaction temperatures (135 °C) are required, refering to the need of more efficient methods for transition metal-free amination reactions.

2. Results and discussion

Exceedingly clean and efficient C–N bond formations with aryl bromides to yield the anilines in almost all cases quantitatively and occasionally within only a few minutes of reaction time were found to be possible (Table 1). For instance, when morpholine was allowed to react at 100 °C in dioxane with phenyl bromide in the presence of 1.2 equiv (relative to the aryl halide) of $KN(Si(CH_3)_3)_2$, quantitative conversion into 4-phenylmorpholine was observed within less than 10 min (Table 1, entry 1). Only slightly lower conversion rates were observed with dibenzylamine, dibutylamine, and *N*-methylaniline as coupling partners (Table 1, entries 2–4). Similarly, 3,5-dimethoxyanilines were almost exclusively formed and isolated in very high yields when 1-bromo-3,5-dimethoxybenzene was reacted for 20 min (or less) at 100 °C with amines, such as morpholine, dibenzylamine, dibutylamine and *N*-methylamine (Table 1, entries 5–8). Slightly lower conversion rates were noticed with sterically hindered 2-bromo-1,4-dimethylbenzene (Table 1, entries 9–12). For instance, its coupling with morpholine yielded 88% of 4-(2,5-dimethylphenyl)morpholine within 15 min. Reactions performed with dibenzylamine, dibutylamine, and *N*-methylaniline gave the coupling products in >95% yield within 90 and 45 min, respectively. Amination reactions performed with 1,3-dibromobenzene or 2,6-dibromopyridine in the presence of 2.2 equiv of amines and base yielded the 1,3-diaminobenzenes and 2,6-diaminopyridines at 100 °C, generally within only 30 min of reaction time (Table 1, entries 13–20). On the other hand, when dioxane solutions of *N*-methylaniline, 2,6-dimethylaniline, 2,6-di(propan-2-yl)aniline, or 3,4,5-trimethoxyaniline and $KN(Si(CH_3)_3)_2$ equimolar amounts of 2,6-dibromopyridine were added at 25 °C, quantitative formations of 6-bromopyridin-2-amines were obtained within only 20 min in all reactions examined (Table 1, entries 21–24), offering a simple and metal-free route for the high-yielding synthesis of 6-bromopyridin-2-amines and asymmetric pyridine-2,6-diamines, respectively, within very short reaction times in 'one-pot'.[16] Indeed, when to an exemplary reaction mixture of equimolar amounts of *N*-methylaniline and 2,6-dibromopyridine (stirred at 25 °C for 20 min) additional base and an amine, such as morpholine, piperidine, *cis*-2,6-dimethylpiperidine, 2,6-dimethylaniline, 2,6-di(propan-2-yl)aniline, or 3,4,5-trimethoxyaniline were added, >95% yield (relative to 2,6-dibromopyridine) of the corresponding

Table 1
Metal-free *N*-aryl amination using aryl bromides[a]



Entry	Aryl bromide	Amine	Conv.[b] [%]	*t* [min]
1	Bromobenzene	Morpholine	95	<10
2	Bromobenzene	Dibenzylamine	98	15
3	Bromobenzene	Dibutylamine	96	20
4	Bromobenzene	*N*-Methylaniline	99	10
5	1-Bromo-3,5-dimethoxybenzene	Morpholine	99	<10
6	1-Bromo-3,5-dimethoxybenzene	Dibenzylamine	98	15
7	1-Bromo-3,5-dimethoxybenzene	Dibutylamine	85	20
8	1-Bromo-3,5-dimethoxybenzene	*N*-Methylaniline	92	10
9	2-Bromo-1,4-dimethylbenzene	Morpholine	88	15
10	2-Bromo-1,4-dimethylbenzene	Dibenzylamine	97	90
11	2-Bromo-1,4-dimethylbenzene	Dibutylamine	95	90
12	2-Bromo-1,4-dimethylbenzene	*N*-Methylaniline	99	45
13[c]	2,6-Dibromopyridine	Morpholine	100	30
14[c]	2,6-Dibromopyridine	Dibenzylamine	100	30
15[c]	2,6-Dibromopyridine	Dibutylamine	95	30
16[c]	2,6-Dibromopyridine	*N*-Methylaniline	100	30
17[c]	1,3-Dibromobenzene	Morpholine	86	30
18[c]	1,3-Dibromobenzene	*cis*-2,6-Dimethylpiperidine	85	60
19[c]	1,3-Dibromobenzene	Dibenzylamine	96	90
20[c]	1,3-Dibromobenzene	*N*-Methylaniline	96	60
21[d]	2,6-Dibromopyridine	*N*-Methylaniline	100[e]	20
22[d]	2,6-Dibromopyridine	2,6-Dimethylaniline	100[e]	20
23[d]	2,6-Dibromopyridine	2,6-Di(propan-2-yl)aniline	99[e]	20
24[d]	2,6-Dibromopyridine	3,4,5-Trimethoxyaniline	100[e]	20

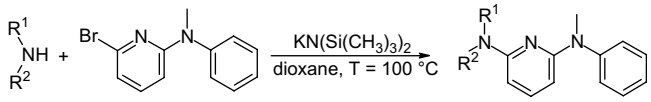
[a] Reaction conditions: 2.0 mmol aryl bromide, 1.2 equiv (relative to aryl bromide) amine, 1.2 equiv (relative to aryl bromide) $KN(Si(CH_3)_3)_2$, 6 ml dioxane, reactions performed at 100 °C under N_2 atmosphere.
[b] Determined by GC/MS, based on aryl halide.
[c] Reaction performed with 2.2 equiv (relative to aryl bromide) of amine and base.
[d] Reaction performed at 25 °C with 1.0 equiv (relative to aryl bromide) amine, 1.2 equiv (relative to aryl bromide) K_3PO_4.
[e] Refer to 6-bromopyridin-2-amine.

N-methyl-*N*-phenylpyridin-2,6-diamines were isolated in all cases after stirring the reaction mixtures for 30 min at 100 °C (Table 2).

In contrast to coupling reactions performed with equimolar amounts of 2,6-dibromopyridine and anilines, $KN(Si(CH_3)_3)_2$ were found to be not appropriate when dialkylamines, such as morpholine, piperidine, *N*-methylpiperazine, or dibutylamine were used as coupling partners. Only mixtures consisting of 2,6-dipromopyridine, 6-bromopyridin-2-amines, and pyridine-2,6-diamines were observed.[18] However, when K_3PO_4 was used instead, 6-bromopyridin-2-amines were exclusively and quantitatively formed when dialkylamines, such as morpholine, piperidine, and *N*-methylpiperazine were coupled with 2,6-dibromopyridine at 100 °C within 5 or 6 h, respectively. Reactions performed with dibutylamine exhibit significantly lower conversion rates but still lead to the quantitative formation of 6-bromo-*N*,*N*-dibutylpyridin-2-amine after 60 h.[19,20] Filtration of the resulting reaction mixtures (in order to remove K_2HPO_4) and subsequent addition of equimolar amounts of $KN(Si(CH_3)_3)_2$ and another amine, such as morpholine, piperidine, *N*-methylpiperazine or *N*-methylaniline exclusively yielded the corresponding 2,6-diaminopyridines within only 30 min at 100 °C in almost quantitative overall yields (Table 3). Almost identical conversion rates and yields were obtained with 2,6-dichloropyridine as coupling partner. Exemplary reactions of 2,6-dichloropyridine and morpholine or piperidine with K_3PO_4 as base at 100 °C exclusively yielded 4-(6-chloropyridin-2-yl)morpholine and 2-chloro-6-piperidin-1-ylpyridine, respectively, within 5 h. Filtration of the reaction mixtures and subsequent addition of equimolar amounts of $KN(Si(CH_3)_3)_2$ and dibenzylamine or dibutylamine quantitatively yielded *N*,*N*-dibenzyl-6-morpholin-4-ylpyridin-2-amine and *N*,*N*-dibutyl-6-piperidin-1-ylpyridin-2-amine, respectively, within only 30 min at 100 °C (Table 3, entries 4 and 8).[19]

Excellent conversion rates and yields were also obtained in the reactions performed with various aryl chlorides as well (Table 4). For instance, when 2-chloronicotinonitrile was reacted with morpholine, piperidine, and *N*-methylpiperazine in the presence of K_3PO_4,[21] the anilines were cleanly formed in >90% yield within only 30 min or less (Table 4, entries 1–3). Significantly lower conversion rates were observed with dibutylamine as coupling partner: 7 h were required to fully convert 2-chloronicotinonitrile into 2-(dibutylamino)pyridine-3-carbonitrile. On the other hand, complete conversion was achieved within only 10 min when *N*-methylaniline was coupled with 2-chloronicotinonitrile in presence of $KN(Si(CH_3)_3)_2$ (Table 4, entries 4 and 5). Exceptional high conversion rates were observed with chlorobenzene (Table 4, entries 6–11) and 2-chloro-1,4-dimethoxybenzene (Table 4, entries

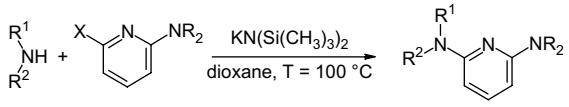
Table 2
Metal-free *N*-aryl amination of 6-bromo-*N*-methyl-*N*-phenylpyridine-2-amine[a]



Entry	Aryl bromide	Amine	Conv.[b] [%]	*t* [min]
1	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	Morpholine	99	30
2	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	Piperidine	98	30
3	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	*cis*-2,6-Dimethylpiperidine	95	30
4	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	Dibenzylamine	99	30
5	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	Dibutylamine	96	30
6	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	2,6-Dimethylaniline	96	30
7	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	2,6-Diisopropylaniline	96	30
8	6-Bromo-*N*-methyl-*N*-phenylpyridine-2-amine	3,4,5-Trimethoxyaniline	99	30

[a] Reaction conditions: 2.0 mmol aryl bromide, 1.2 equiv (relative to aryl bromide) amine, 1.2 equiv (relative to aryl bromide) $KN(Si(CH_3)_3)_2$, 6 ml dioxane, reaction performed at 100 °C under N_2 atmosphere.
[b] Determined by GC/MS, based on aryl halide.

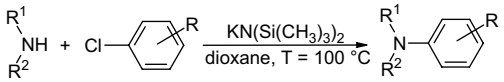
Table 3
Metal-free *N*-aryl amination of 6-halopyridin-2-amines[a]



Entry	Aryl halide	Amine	Conv.[b] [%]	*t* [min]
1	4-(6-Bromopyridin-2-yl)morpholine[c]	Morpholine	99	30
2	4-(6-Bromopyridin-2-yl)morpholine[c]	*N*-Methylaniline	100	30
3	4-(6-Bromopyridin-2-yl)morpholine[c]	Dibenzylamine	99	30
4	4-(6-Chloropyridin-2-yl)morpholine[c]	Dibenzylamine	100	30
5	2-Bromo-6-piperidin-1-ylpyridine[c]	Piperidine	97	30
6	2-Bromo-6-piperidin-1-ylpyridine[c]	*N*-Methylaniline	98	30
7	2-Bromo-6-piperidin-1-ylpyridine[c]	Dibutylamine	98	30
8	2-Chloro-6-piperidin-1-ylpyridine[c]	Dibutylamine	97	30
9	1-(6-Bromopyridin-2-yl)-4-methylpiperazine[c]	Piperidine	95	30
10	6-Bromo-*N*,*N*-dibutylpyridin-2-amine[c]	Dibenzylamine	98	30

[a] Reaction conditions: 2.0 mmol aryl bromide, 1.2 equiv (relative to aryl halide) amine, 1.2 equiv (relative to aryl halide) $KN(Si(CH_3)_3)_2$, 6 ml dioxane, reaction performed at 100 °C under N_2 atmosphere.
[b] Determined by GC/MS, based on aryl halide.
[c] 6-Bromopyridin-2-amines and 6-chloropyridin-2-amines were prepared by reactions of equimolar amounts of the appropriate amine and 2,6-dibromopyridine and 2,6-dichloropyridine, respectively, at 100 °C with 2.0 equiv (relative to 2,6-dihalopyridine) of K_3PO_4.

Table 4
Metal-free *N*-aryl amination using aryl chlorides[a]



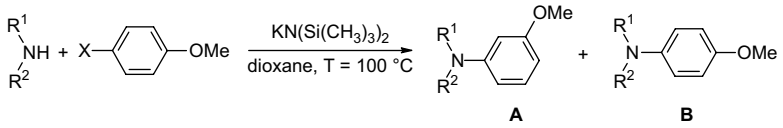
Entry	Aryl chloride	Amine	Conv.[b] [%]	*t* [min]
1[c]	2-Chloronicotinonitrile	Morpholine	93	30
2[c]	2-Chloronicotinonitrile	Piperidine	100	15
3[c]	2-Chloronicotinonitrile	*N*-Methylpiperazine	98	30
4[c]	2-Chloronicotinonitrile	Dibutylamine	88	420
5	2-Chloronicotinonitrile	*N*-Methylaniline	100	<10
6	Chlorobenzene	Morpholine	100	<10
7	Chlorobenzene	Piperidine	97	15
8	Chlorobenzene	*cis*-2,6-Dimethylpiperidine	92	30
9	Chlorobenzene	*N*-Methylpiperazine	98	10
10	Chlorobenzene	Diphenylamine	67	30
11	Chlorobenzene	Dibenzylamine	92	10
12	2-Chloro-1,4-dimethoxy-benzene	Morpholine	100	<10
13	2-Chloro-1,4-dimethoxy-benzene	Piperidine	100	<10
14	2-Chloro-1,4-dimethoxy-benzene	Dibenzylamine	100	<10
15	2-Chloro-1,4-dimethoxy-benzene	Dibutylamine	100	<10
16	2-Chloro-1,4-dimethoxy-benzene	*N*-Methylaniline	100	<10
17[d]	2-Chloro-1,4-dimethoxy-benzene	Benzylamine	96[e]	30
18[d]	2-Chloro-1,4-dimethoxy-benzene	2,6-Diisopropylaniline	94[e]	30
19[d]	2-Chloro-1,4-dimethoxy-benzene	3,4,5-Trimethoxyaniline	92[e]	30
20	2-Chloro-1,4-dimethyl-benzene	Morpholine	97	30
21	2-Chloro-1,4-dimethyl-benzene	Piperidine	83	30
22	2-Chloro-1,4-dimethyl-benzene	*N*-Methylpiperazine	97	30
23	2-Chloro-1,4-dimethyl-benzene	Dibenzylamine	93	60
24	2-Chloro-3-methoxybenzonitrile	Morpholine	100	60
25	2-Chloro-3-methoxybenzonitrile	Piperidine	91	60
26	2-Chloro-3-methoxybenzonitrile	*N*-Methylaniline	99	20
27	2-Chloro-3-methoxybenzonitrile	3,4,5-Trimethoxyaniline	99	30
28	1,3,5-Trichlorobenzene	Morpholine	93	90
29	1,3,5-Trichlorobenzene	*N*-Methylpiperazine	92	270
30	1,3,5-Trichlorobenzene	*N*-Methylaniline	95	90

[a] Reaction conditions: 2.0 mmol aryl chloride, 1.2 equiv (relative to aryl chloride) amine, 1.2 equiv (relative to aryl chloride) $KN(Si(CH_3)_3)_2$, 6 ml dioxane, reaction performed at 100 °C under N_2 atmosphere.
[b] Determined by GC/MS, based on aryl halide.
[c] Reaction performed with 2.0 mmol K_3PO_4.
[d] Reaction performed with 2 equiv (relative to amine) aryl chloride.
[e] Refer to the formation of the tertiary anilines.

12–19). Impressively, in almost all the reactions performed the anilines were formed in >90% yield in less than 20 min. For example, when 2-chloro-1,4-dimethoxybenzene was coupled with piperidine, dibenzylamine, dibutylamine, or *N*-methylamine, respectively, full conversions into their tertiary anilines was achieved in all the reactions within less than 10 min. Exemplary reactions performed with 2 equiv (relative to amine) of 2-chloro-1,4-dimethoxybenzene yielded the tertiary anilines quantitatively within only 30 min when primary amines, such as benzylamine, 2,6-diisopropylaniline, and 3,4,5-trimethoxyaniline were used as coupling partner. High conversion rates and yields were also obtained with 2-chloro-1,4-dimethylbenzene as coupling partner (Table 4, entries 20–23). For instance, its coupling with *N*-methylpiperazine yielded 97% of 1-(2,5-dimethylphenyl)-4-methylpiperazine within 30 min; 93% conversion within 1 h was obtained with dibenzylamine. In contrast to 2,6-alkylated aryl halides, which are inert toward transition metal-free amination,[22] high conversions were observed with 2-chloro-3-methoxybenzonitrile (Table 4, entries 24–27); >90% yield within less than 1 h was achieved with morpholine, piperidine, *N*-methylaniline, and 3,4,5-trimethoxyaniline as coupling partners. Smooth C-N bond formations were also observed with polychlorinated substrates. Exemplary reactions were carried out with 1,3,5-trichlorobenzene (Table 4, entries 28–30). Its treatment with 3.4 equiv of amine, gave the products in >90% yield within only 90 min of reaction time when morpholine and *N*-methylaniline were used as coupling partners; with *N*-methylpiperazine, 4.5 h were required to get 95% of the aniline.

Overall, non-catalyzed versions of the Buchwald–Hartwig were shown to selectively yield the desired coupling products when reactions were performed with bromobenzene, 1,4-bissubstituted haloaromatic compounds or substrates possessing directing groups, such as 1,3-dibromobenzene, 1-bromo-3,5-dimethoxybenzene, 2-chloronicotinonitrile, 2-chloro-3-methoxybenzonitrile, 1-chloro-3,5-dimethylbenzene 1,3,5-trichlorobenzene, or 2,6-dichloropyridine.[11] Since aryne-type mechanisms are operative in transition metal-free versions of the Buchwald–Hartwig reaction the substitution pattern of the aryl halide is of significant importance for regioselective product formation. Thus, non-selective product formation was expected to be obtained when substrates, such as 1-bromo-4-methoxybenzene (Table 5), 2-chlorotoluene, 4-bromobiphenyl or 4-chlorobenzonitrile were used as coupling partners.[9,23] Indeed, when, for example, 1-bromo-4-methoxybenzene or 1-chloro-4-methoxybenzene were coupled with morpholine, piperidine, *cis*-2,6-dimethylpiperidine, dibenzylamine, dibutylamine, *N*-methylpiperazine or *N*-methylamine overall yields of >90% but mixtures containing 3-methoxyanilines and 4-methoxyanilines were obtained within less than 30 min. In fact the product distribution corresponds to those expected for aryne-type mechanisms.[14] Similarly, when 2-bromotoluene or 2-chlorotoluene was coupled with amines, reaction mixtures containing 2-methylanilines and 3-methylanilines were obtained,[23] of which the latter ones were dominant, confirming the involvement of cyclohexa-1,3-dien-5-ynes intermediates further. In addition, the nature of the amine has only a minor effect

Table 5
Metal-free *N*-aryl amination using 4-bromoanisole and 4-chloroanisole[a]



Entry	Aryl halide	Amine	**A**	**B**	Conv.[b] [%]	*t* [min]
1	4-Bromoanisole	Morpholine	53	47	95	<10
2	4-Bromoanisole	Piperidine	51	49	97	<10
3	4-Bromoanisole	*cis*-2,6-Dimethylpiperidine	45	55	96	30
4	4-Bromoanisole	Dibenzylamine	58	42	92	20
4	4-Bromoanisole	Dibutylamine	53	47	93	20
5	4-Bromoanisole	*N*-Methylaniline	56	44	99	10
6	4-Chloroanisole	Morpholine	54	46	91	<10
7	4-Chloroanisole	Piperidine	54	46	96	<10
8	4-Chloroanisole	*cis*-2,6-Dimethylpiperidine	46	54	98	90
9	4-Chloroanisole	*N*-Methylpiperazine	55	45	92	<10
10	4-Chloroanisole	Dibutylamine	56	44	93	<10
11	4-Chloroanisole	*N*-Methylaniline	57	43	99	<10

[a] Reaction conditions: 2.0 mmol aryl chloride, 1.2 equiv (relative to aryl halide) amine, 1.2 equiv (relative to aryl chloride) $KN(Si(CH_3)_3)_2$, 6 ml dioxane, reaction performed at 100 °C under N_2 atmosphere; product distributions refer relative GC-yields.
[b] Determined by GC/MS, based on aryl halide.

on the product distribution, which is also characteristic for aryne-type mechanisms.[11,14,23]

In conclusion, although aryne-type mechanisms are operative in transition metal-free versions of the Buchwald–Hartwig reaction, and hence the substitution pattern of the aryl halide is of importance for selective product formations catalysts are in many cases *not* required to efficiently and selectively couple aryl halides with amines. A wide variety of amines were found to undergo exceedingly clean and efficient C–N bond formation with electronically activated, deactivated and even sterically hindered aryl halides, to give the desired *N*-arylated amines in almost quantitative yields occasionally even within only a few minutes of reaction time. Furthermore, reactions performed with 2,6-dibromopyridine and 2,6-dichloropyridine allow the selective synthesis of 6-halopyridin-2-amines and asymmetric pyridine-2,6-diamines, respectively, in very high overall yields generally within short reaction times. Purification of the 6-halopyridin-2-amine intermediates is not required for the synthesis of asymmetric pyridine-2,6-diamines. The conversion rates and yields obtained under transition metal-free reaction conditions are generally excellent, making the transition metal-free version of the Buchwald–Hartwig reaction extremely attractive for substrates with substituents on the aryl halide, which either promote regioselectivity and/or do not require regioselective aminations for selective product formations.

3. Experimental section

3.1. General procedures

All synthetic operations were carried out in oven-dried glassware using a combination of glovebox (M. Braun 150B-G-II) and Schlenk techniques under a dinitrogen atmosphere. Solvents were reagent grade or better, freshly distilled under N_2 atmosphere by standard procedures, and degassed before use. Deuterated solvents were purchased from Armar. All the chemicals were purchased from Aldrich Chemical Co., Acros Organics, ABCR or Fluka and used as received.

3.2. Analysis

^1H and $^{13}C\{^1H\}$ NMR data were recorded at 300.0 and 75.4 MHz on a Varian Gemini 300 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) coupling constants (J) are in hertz. The ^1H and ^{13}C NMR chemical shifts are reported relative to tetramethylsilane; the resonance of the residual protons of the solvent was used as internal standard for ^1H (δ 7.26 chloroform, 3.58 and 1.73 THF-d_8) and all-d solvent signals for ^{13}C (δ 77.0 chloroform, 67.4 and 25.2 THF-d_8). All measurements were carried out at 298 K. Abbreviations used in the description of NMR data are as follows: s, singlet; d, duplet; t, triplet; sept, septet; m, multiplet. Elemental analyses were performed on a Leco CHNS-932 analysator at the University of Zurich, Switzerland.

3.3. General procedure for the amination of aryl halides

In a Young Schlenk with dioxane (6 ml) were placed appropriate amounts of the amine, $KN(Si(CH_3)_3)_2$ (or K_3PO_4), followed by the aryl halide (2.0 mmol). Then the reaction mixture was stirred vigorously at 25 °C or placed in a preheated 100 °C oil bath. Samples taken from the reaction mixture were quenched with water. The products were extracted with diethyl ether/THF (1:1) mixtures and analyzed by GC/MS. At the end of the reaction the mixtures were allowed to cool to room temperature, quenched with water and extracted with 30–50 ml of diethyl ether/THF (1:1) mixtures. The combined extracts were washed with 1 M Na_2CO_3 (3×50 ml), dried over $MgSO_4$, filtrated, and evaporated to dryness. Where necessary, the product was purified by flash chromatography on silica gel or on alumina. The identities of known products were confirmed by comparison with data reported in the literature.

3.3.1. *N,N,N′,N′-Tetrabenzylpyridine-2,6-diamine (Table 1, entry 14)*

The title compound was obtained after flash chromatography on silica gel (toluene) as pale brown oil, which solidified upon standing. Yield: 97%.

^1H NMR (300 MHz, $CDCl_3$) δ=7.31–7.01 (m, 21H), 5.75 (d, J=8.1 Hz, 2H), 4.62 (s, 8H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ=158.1, 139.8, 129.0, 128.6, 127.8, 127.2, 94.3, 51.5. Anal. Calcd (%) for $C_{33}H_{31}N_3$: C, 84.40; H, 6.65; N, 8.95. Found: C, 84.55; H, 6.70; N, 8.99.

3.3.2. *N,N,N′,N′-Tetrabutylpyridine-2,6-diamine (Table 1, entry 15)*

The title compound was obtained after flash chromatography on silica gel (toluene) as a pale brown oil, which solidified upon standing. Yield: 93%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.46 (t, J=8.1 Hz, 1H), 5.95 (d, J=8.1 Hz, 2H), 3.65 (t, J=7.7 Hz, 8H), 1.91–1.81 (m, 8H), 1.67–1.55 (m, 8H), 1.22 (t, J=7.3 Hz, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=156.9, 138.1, 91.7, 48.6, 30.2, 20.5, 14.1. Anal. Calcd (%) for $C_{21}H_{39}N_3$: C, 75.62; H, 11.78; N, 12.60. Found: C, 75.69; H, 11.74; N, 12.66.

3.3.3. *N,N′-Dimethyl-N,N′-diphenylpyridine-2,6-diamine (Table 1, entry 16)*

The title compound was obtained after flash chromatography on silica gel (toluene) as colorless powder. Yield: 99%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.64–7.48 (m, 8H), 7.40 (tt, ^3J=7.1 Hz, ^4J=1.5 Hz, 2H), 7.29 (t, J=7.3 Hz, 1H), 6.13 (d, J=8.0 Hz, 2H), 3.73 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.5, 147.0, 137.7, 129.1, 126.1, 124.7, 97.3, 38.0. Anal. Calcd (%) for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found: C, 78.97; H, 6.59; N, 14.66.

3.3.4. *6-Bromo-N-methyl-N-phenylpyridine-2-amine (Table 1, entry 21)*

The title compound was obtained as pale yellow oil. Yield: 98%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.41–7.37 (m, 2H), 7.25–7.19 (m, 3H), 7.05 (dd, J=8.4, 7.4 Hz, 1H), 6.70 (d, J=7.4 Hz, 1H), 6.34 (d, J=8.4 Hz, 1H), 3.43 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.7, 145.7, 140.0, 138.5, 129.9, 126.5, 126.2, 115.8, 106.9, 38.4. Anal. Calcd (%) for $C_{12}H_{11}BrN_2$: C, 54.77; H, 4.21; N, 10.65. Found: C, 54.85; H, 4.17; N, 10.69.

3.3.5. *6-Bromo-N-(2,6-dimethylphenyl)-N-methylpyridin-2-amine (Table 1, entry 22)*

The title compound was obtained as off-white powder. Yield: 97%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.26–7.14 (m, 4H), 6.78 (dd, ^3J=7.4 Hz, ^4J=0.6 Hz, 1H), 6.33 (br s, 1H), 5.05 (dd, ^3J=8.3 Hz, ^4J=0.6 Hz, 1H), 2.22 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.0, 140.3, 140.0, 136.9, 135.5, 128.7, 127.3, 116.7, 103.6, 18.3. Anal. Calcd (%) for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 56.29; H, 4.76; N, 10.07.

3.3.6. *N-[2,6-Bis(1-methylethyl)phenyl]-6-bromo-N-methylpyridin-2-amine (Table 1, entry 23)*

The title compound was obtained as colorless powder. Yield: 98%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.43–7.38 (m, 1H), 7.32–7.28 (m, 2H), 7.21 (t, J=7.8 Hz, 1H), 6.80 (dd, ^3J=7.5 Hz, ^4J=0.5 Hz, 1H), 6.72 (br s, 1H), 5.93 (d, J=8.2 Hz, 1H), 3.25 (sept, J=6.9 Hz, 2H), 1.20 (d, J=6.9 Hz, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.4, 145.6, 138.0, 137.5, 130.4, 126.2, 121.8, 114.1, 101.6, 26.1, 21.6. Anal. Calcd (%) for $C_{17}H_{21}BrN_2$: C, 61.27; H, 6.35; N, 8.41. Found: C, 61.30; H, 6.40; N, 8.47.

3.3.7. *6-Bromo-N-methyl-N-(3,4,5-trimethoxyphenyl)pyridin-2-amine (Table 1, entry 24)*

The title compound was obtained as colorless powder after flash chromatography on silica gel (first using methylene chloride in order to remove 2,6-dibromopyridine and then ethyl acetate as the eluent). Yield: 98%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.31 (dd, J=8.2, 7.6 Hz, 1H), 6.74 (dd, ^3J=7.6 Hz, ^4J=0.6 Hz, 1H), 6.69 (dd, ^3J=8.2 Hz, ^4J=0.6 Hz, 1H), 6.61 (s, 2H), 6.54 (br s, 1H), 3.84 (s, 6H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=156.3, 153.6, 139.9, 139.6, 135.5, 134.4, 117.7, 106.3, 99.0, 60.9, 56.0. Anal. Calcd (%) for $C_{14}H_{15}BrO_3N_2$: C, 49.58; H, 4.46; N, 8.26. Found: C, 49.63; H, 4.39; N, 8.37.

3.3.8. *N-Methyl-6-morpholin-4-yl-N-phenylpyridin-2-amine (Table 2, entry 1)*

The title compound was obtained as pale yellow solid. Yield: 97%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.30–7.21 (m, 2H), 7.20–7.11 (m, 2H), 7.10–7.04 (m, 2H), 5.86 (d, J=7.9 Hz, 1H), 5.84 (d, J=8.1 Hz, 1H), 3.74–3.71 (m, 4H), 3.40–3.37 (m, 4H), 3.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.5, 156.6, 146.0, 137.4, 128.3, 125.3, 123.9, 97.5, 94.0, 65.9, 44.7, 37.0. Anal. Calcd (%) for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.50; H, 7.45; N, 15.57.

3.3.9. *N-Methyl-N-phenyl-6-piperidin-1-ylpyridin-2-amine (Table 2, entry 2)*

The title compound was obtained after filtration over silica gel (toluene) as brown oil. Yield: 96%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.71–7.60 (m, 4H), 7.53–7.45 (m, 2H), 6.33 (d, J=8.0 Hz, 1H), 6.23 (dd, ^3J=8.0 Hz, ^4J=1.7 Hz, 1H), 3.84 (br s, 4H), 3.81 (s, 3H), 1.98 (br s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.6, 157.5, 147.2, 138.2, 129.1, 126.2, 124.5, 97.3, 95.4, 46.2, 37.9, 25.5, 24.9. Anal. Calcd (%) for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.28; H, 7.91; N, 15.69.

3.3.10. *6-[(2R,6S)-2,6-Dimethylpiperidin-1-yl]-N-methyl-N-phenylpyridin-2-amine (Table 2, entry 3)*

The title compound was obtained as pale yellow solid. Yield: 94%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.31–7.02 (m, 6H), 5.84 (d, J=7.9 Hz, 1H), 5.76 (d, J=7.8 Hz, 1H), 4.46 (br s, 2H), 3.36 (s, 3H), 1.85–1.42 (m, 6H), 1.12 (d, J=6.8 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.6, 156.7, 147.4, 138.0, 129.0, 126.1, 124.3, 95.9, 95.2, 45.2, 37.9, 30.8, 19.0, 14.7. Anal. Calcd (%) for $C_{19}H_{25}N_3$: C, 77.25; H, 8.53; N, 14.22. Found: C, 77.17; H, 8.49; N, 14.22.

3.3.11. *N,N-Dibenzyl-N′-methyl-N′-phenylpyridine-2,6-diamine (Table 2, entry 4)*

The title compound was obtained after flash chromatography on silica gel (toluene) as brownish oil. Yield: 97%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.68–7.50 (m, 14H), 7.48–7.41 (m, 2H), 6.22 (d, J=8.0 Hz, 1H), 6.18 (d, J=8.0 Hz, 1H), 5.10 (s, 4H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.5, 147.2, 139.3, 138.4, 129.2, 128.4, 128.1, 127.3, 126.7, 126.3, 124.7, 96.6, 94.4, 51.0, 38.1. Anal. Calcd (%) for $C_{26}H_{25}N_3$: C, 82.29; H, 6.64; N, 11.07. Found: C, 82.22; H, 6.59; N, 11.11.

3.3.12. *N,N-Dibutyl-N′-methyl-N′-phenylpyridine-2,6-diamine (Table 2, entry 5)*

The title compound was obtained after filtration over silica gel (toluene) as pale brownish oil. Yield: 94%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.28–7.15 (m, 4H), 7.08–7.02 (m, 2H), 5.73–5.68 (m, 2H), 3.35 (s, 3H), 3.34–3.29 (m, 4H), 1.56–1.46 (m, 4H), 1.32–1.19 (m, 4H), 0.86 (t, J=7.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.6, 156.8, 147.4, 137.8, 129.0, 126.2, 124.3, 94.9, 94.0, 48.5, 37.9, 30.0, 20.4, 14.0. Anal. Calcd (%) for $C_{20}H_{29}N_3$: C, 77.12; H, 9.38; N, 13.49. Found: C, 77.23; H, 9.29; N, 13.52.

3.3.13. *N′-(2,6-Dimethylphenyl)-N-methyl-N-phenylpyridine-2,6-diamine (Table 2, entry 6)*

The title compound was obtained after flash chromatography on silica gel (toluene) as brown oil. Yield: 94%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.48–7.04 (m, 9H), 5.98 (dd, ^3J=8.1 Hz, ^4J=0.6 Hz, 1H), 5.93 (br s, 1H), 5.42 (dd, ^3J=7.8 Hz, ^4J=0.6 Hz, 1H), 3.54 (s, 3H), 2.34 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.4, 156.6, 147.2, 138.5, 137.2, 136.7, 129.4, 128.4, 126.4, 126.2, 124.9, 98.9, 94.3, 38.2, 18.6. Anal. Calcd (%) for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.07; H, 7.06; N, 13.92.

3.3.14. *N′-[2,6-Bis(1-methylethyl)phenyl]-N-methyl-N-phenylpyridine-2,6-diamine (Table 2, entry 7)*

The title compound was obtained after flash chromatography on silica gel (toluene) as off-white powder. Yield: 95%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.44–7.10 (m, 8H), 7.03 (t, J=8.0 Hz, 1H), 5.90 (dd, ^3J=8.0 Hz, ^4J=0.6 Hz, 1H), 5.78 (br s, 1H), 5.31 (dd, ^3J=7.8 Hz, ^4J=0.6 Hz, 1H), 3.50 (s, 3H), 3.30 (sept, J=6.8 Hz, 2H), 1.39 (d, J=6.8 Hz, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.3, 147.9, 147.2, 143.2, 138.3, 134.1, 129.3, 127.6, 126.1, 124.7, 123.8, 98.6, 94.4, 38.1, 28.2, 24.0. Anal. Calcd (%) for $C_{24}H_{29}N_3$: C, 80.18; H, 8.13; N, 11.69. Found: C, 79.99; H, 8.02; N, 11.61.

3.3.15. *N-Methyl-N-phenyl-N′-(3,4,5-trimethoxyphenyl)pyridine-2,6-diamine (Table 2, entry 8)*

The title compound was obtained after flash chromatography on silica gel (toluene) as off-white powder. Yield: 96%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.29–7.22 (m, 2H), 7.19–7.14 (m, 2H), 7.12–7.05 (m, 2H), 6.62 (s, 2H), 6.40 (br s, 1H), 6.01 (d, J=7.8 Hz, 1H), 5.87 (d, J=8.1 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 6H), 3.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.1, 154.7, 153.3, 146.9, 138.3, 137.3, 133.0, 129.6, 126.2, 125.1, 99.5, 97.5, 97.5, 60.9, 55.9, 38.5. Anal. Calcd (%) for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.07; H, 6.39; N, 11.53.

3.3.16. *6-Bromo-N,N-dibutylpyridin-2-amine*

The title compound was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1). The pure product was obtained as a colorless oil. Yield: 97%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.04 (dd, ^3J=8.4 Hz, ^3J=7.4 Hz, 1H), 6.44 (d, ^3J=7.4 Hz, 1H), 6.15 (d, ^3J=8.4 Hz, 1H), 3.25 (t, ^3J=7.5 Hz, 4H), 1.46–1.36 (m, 4H), 1.26–1.13 (m, 4H), 0.81 (t, ^3J=7.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.0, 139.3, 137.9, 112.5, 102.6, 47.4, 28.6, 19.3, 13.0. Anal. Calcd (%) for $C_{13}H_{21}BrN_2$: C, 54.74; H, 7.42; N, 9.82. Found: C, 54.71; H, 7.37; N, 9.74.

3.3.17. *N,N-Dibenzyl-6-morpholin-4-ylpyridin-2-amine (Table 3, entry 3)*

The title compound was purified by flash chromatography on silica gel (methylene chloride). The pure product was obtained as pale yellow oil, which solidified upon standing, giving a colorless powder. Yield: 99%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.42–7.26 (m, 11H), 6.03 (d, ^3J=7.8 Hz, 1H), 6.00 (d, ^3J=8.0 Hz, 1H), 4.83 (s, 4H), 3.84 (t, ^3J=4.8 Hz, 4H), 3.51 (t, ^3J=4.8 Hz, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.6, 157.5, 139.3, 139.2, 128.6, 127.2, 126.9, 95.6, 94.6, 66.9, 51.0, 45.8. Anal. Calcd for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 76.84; H, 6.94; N, 11.65.

3.3.18. *N,N-Dibutyl-6-piperidin-1-ylpyridin-2-amine (Table 3, entry 6)*

The title compound was purified by flash chromatography on silica gel (toluene). The pure product was obtained as pale yellow oil, which solidified upon standing. Yield: 96%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.22 (dd, ^3J=8.0 Hz, ^3J=7.9 Hz, 1H), 5.85 (d, ^3J=7.9 Hz, 1H), 5.75 (d, ^3J=8.0 Hz, 1H), 3.46 (br s, 4H), 3.36 (t, ^3J=7.4 Hz, 4H), 1.59 (br s, 6H) overlapped with 1.61–1.51 (m, 4H), 1.38–1.27 (m, 4H), 0.92 (t, ^3J=7.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=158.6, 156.8, 138.3, 93.7, 93.0, 48.5, 46.2, 29.9, 25.4, 24.9, 20.4, 13.9. Anal. Calcd (%) for $C_{18}H_{31}N_3$: C, 74.69; H, 10.79; N, 14.52. Found: C, 74.43; H, 10.75; N, 14.49.

3.3.19. *1-Methyl-4-(6-piperidin-1-ylpyridin-2-yl)piperazine (Table 3, entry 7)*

The title compound was purified by flash chromatography on alumina (ethyl acetate). Pure product: pale yellow oil. Yield: 97%.

^{1}H NMR (300 MHz, THF-d_8) δ=7.09 (dd, ^3J=8.1 Hz, ^3J=8.0 Hz, 1H), 5.85 (d, ^3J=8.1 Hz, 1H), 5.81 (d, ^3J=8.0 Hz, 1H), 3.44–3.31 (m, 8H), 2.30–2.25 (m, 4H), 2.12 (s, 3H), 1.48 (br s, 6H); ^{13}C{^{1}H} NMR (75 MHz, d^8-THF) δ=158.3, 158.2, 138.1, 95.2, 94.5, 54.9, 45.8, 45.5, 44.9, 25.4, 24.6. Anal. Calcd (%) for $C_{15}H_{24}N_4$: C, 69.19; H, 9.29; N, 21.52. Found: C, 69.08; H, 9.26; N, 21.60.

3.3.20. *2-(Dibutylamino)pyridine-3-carbonitrile (Table 4, entry 4)*

The title compound was purified by flash chromatography on silica gel (methylene chloride). The pure product was obtained as a colorless oil. Yield: 86%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=8.24 (dd, ^3J=4.6 Hz, ^4J=2.0 Hz, 1H), 7.65 (dd, ^3J=7.6 Hz, ^4J=2.0 Hz, 1H), 6.51 (dd, ^3J=7.6 Hz, ^3J=4.6 Hz, 1H), 3.61 (t, ^3J=7.8 Hz, 4H), 1.67–1.57 (m, 4H), 1.42–1.29 (m, 4H), 0.93 (t, ^3J=7.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=156.5, 151.0, 143.7, 118.4, 110.1, 88.7, 48.8, 29.1, 18.8, 12.8. Anal. Calcd (%) for $C_{14}H_{21}N_3$: C, 72.69; H, 9.15; N, 18.16. Found: C, 72.64; H, 9.11; N, 18.15.

3.3.21. *N-Benzyl-N-(2,5-dimethoxyphenyl)-2,5-dimethoxyaniline (Table 4, entry 17)*

The title compound was purified by flash chromatography on silica gel (methylene chloride). The pure product was obtained as pale yellow oil. Yield: 95%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.73–7.70 (m, 2H), 7.55–7.43 (m, 3H), 7.07–7.03 (m, 2H), 6.84–6.82 (m, 2H), 6.78–6.73 (m, 4H), 5.11 (s, 2H), 3.93 (s, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=152.3, 145.9, 138.2, 138.0, 126.3, 125.9, 124.7, 112.3, 108.5, 105.2, 55.0, 54.4, 53.8. Anal. Calcd (%) for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.89; H, 6.63; N, 3.65.

3.3.22. *N-[2,6-Bis(1-methylethyl)phenyl]-N-(2,5-dimethoxyphenyl)-2,5-dimethoxyaniline (Table 4, entry 18)*

The title compound was purified by flash chromatography on silica gel (toluene). The pure product was obtained as a colorless powder. Yield: 92%.

^{1}H NMR (200 MHz, $CDCl_3$) δ=7.35–7.21 (m, 4H), 6.92–6.87 (m, 2H), 6.82–6.79 (m, 2H), 5.83 (s, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.49 (s, 3H), 3.24 (sept, ^3J=6.9 Hz, 2H), 1.19 (d, ^3J=6.9 Hz, 12H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=153.3, 151.8, 151.5, 147.6, 140.2, 138.1, 135.1, 129.3, 127.1, 123.7, 117.7, 114.7, 113.3, 112.6, 112.4, 96.9, 56.6, 56.5, 56.3, 55.7, 28.1, 24.1. Anal. Calcd (%) for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.67; H, 7.79; N, 3.15.

3.3.23. *N,N-Bis(2,5-dimethoxyphenyl)-3,4,5-trimethoxyaniline (Table 4, entry 19)*

The title compound was purified by flash chromatography on silica gel (diethyl ether). The pure product was obtained as pale yellow oil, which solidified upon standing. Yield: 90%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.25–6.69 (m, 6H), 6.26 (s, 2H), 4.19–3.87 (m, overlapping methoxy signals, 21H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=154.9, 153.0, 149.2, 144.3, 136.8, 133.8, 114.0, 113.8, 110.0, 97.0, 60.9, 56.4, 55.9, 55.6. Anal. Calcd (%) for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.07. Found: C, 65.75; H, 6.40; N, 2.99.

3.3.24. *3-Methoxy-2-[methyl(phenyl)amino]benzonitrile (Table 3, entry 26)*

The title compound was obtained after flash chromatography on silica gel (methylene chloride) as colorless powder. Yield: 98%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.68–7.55 (m, 2H), 7.54–7.48 (m, 3H), 7.09 (tt, ^3J=7.3 Hz, ^4J=1.0 Hz, 1H), 6.90–6.86 (m, 2H), 4.05 (s, 3H), 3.61 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ=157.4, 148.2, 139.1, 128.9, 128.0, 125.2, 118.0, 117.0, 115.0, 112.8, 55.9, 38.5. Anal. Calcd (%) for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.80; H, 5.98; N, 11.84.

3.3.25. *3-Methoxy-2-[methyl(3,4,5-trimethoxyphenyl)amino]-benzonitrile (Table 4, entry 27)*

The title compound was purified by flash chromatography on silica gel (diethyl ether). The pure product was obtained as pale brown oil, which solidified upon standing. Yield: 96%.

^{1}H NMR (300 MHz, $CDCl_3$) δ=7.03 (dd, ^3J=7.7 Hz, ^4J=1.4 Hz, 1H), 6.93 (dd, ^3J=8.1 Hz, ^4J=1.4 Hz, 1H), 6.85 (dd, ^3J=8.1 Hz, ^3J=7.7 Hz,

1H), 6.09 (s, 2H), 6.06 (br s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.68 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ=153.5, 150.6, 138.2, 136.2, 134.1, 125.4, 121.5, 117.1, 114.3, 102.7, 97.5, 60.9, 56.0 (two overlapping signals). Anal. Calcd (%) for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.99; H, 5.80; N, 8.81.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.072.

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13. The higher conversion rates and yields observed with $KN(Si(CH_3)_3)_2$ as base when compared with, e.g., $NaNH_2$ or NaH were attributed to a combination of its higher solubility, lower nucleophilicity and stronger basicity.
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16. Selective aminations of 2,6-dihalopyridines are generally difficult to perform and often lead to reaction mixtures consistent of 2,6-dibromopyridine, 6-bromopyridin-2-amines, and pyridine-2,6-diamines.[17] However, selective formations of asymmetric 2,6-diaminopyridines (via nickel-catalyzed aminations of 2,6-dihalopyridines) have recently been reported.[5e]
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18. The change of reaction conditions, such as the reaction temperature, reaction time or concentration had no effect on the product distributions.
19. See, Section 3
20. Asymmetrically substituted *N*,*N*-dibutylpyridine-2,6-diamines are preferably prepared by introducing the other amine first, since the product formation is significantly faster.
21. K_3PO_4 was used as base, because 2-chloronicotinonitrile instantly reacted with $KN(Si(CH_3)_3)_2$, leading in an insoluble black precipitate.
22. Cyclohexa-1,3-dien-5-yne intermediates cannot be formed with 2-bromo-1,3-dimethylbenzene, explaining why 2-halo-1,3-dialkylbenzenes are, in contrast to transition metal-catalyzed versions of the Buchwald–Hartwig reaction, inert toward amination.
23. See Tables S2–S4 in Supplementary data.