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An improved synthesis of *N*-aryl and *N*-heteroaryl substituted piperidones

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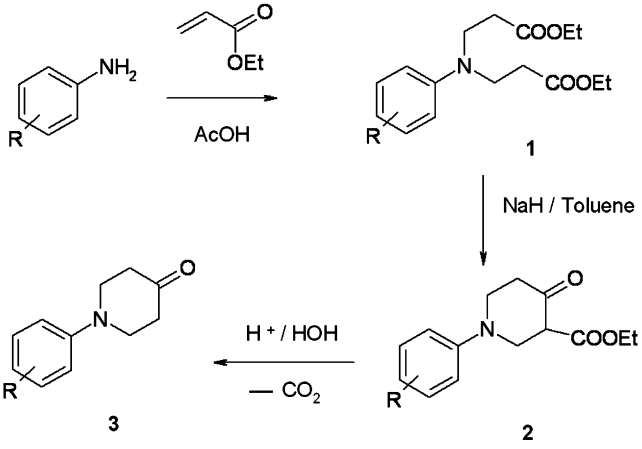
Abstract—An efficient Pd(0)-catalyzed protocol for the rapid and efficient preparation of *N*-aryl and *N*-heteroaryl substituted piperidones is described. The two step syntheses proceed with an overall yield of 50–70% using X-Phos as optimal ligand for the Pd(0)-catalyzed Buchwald–Hartwig amination followed by subsequent hydrolysis of resulted ketals.

The arylpiperidine scaffold is a key element involved in binding to a variety of receptors and therefore can be described as a privileged structure.[1] As part of our ongoing research programs, we were interested in the synthesis of 4-arylpiperidones as precursor for further variations. Therefore, a high-throughput synthesis of this structural class would be of benefit in lead finding and lead optimization stages in the drug discovery process. In this Letter, we disclose the synthesis of *N*-aryl and *N*-heteroarylpiperidones which relies on thermal as well as microwave heating to facilitate production of compounds in a parallel manner.

A general method for preparing 4-arylpiperidones **3** is the Dieckmann cyclization of suitable amino diesters such as **1**, which in turn is produced by the Michael addition of ethyl acrylate with substituted anilines, in glacial acetic acid (Scheme 1).[2] These reactions result in very poor yields and also require long reaction times, even though the Dieckmann condensation is a well documented synthetic strategy. The reaction conditions involve the use of moisture sensitive reagents, such as sodium hydride. Although, sodium alkoxide and other bases are also known to affect Dieckmann condensation, the yields of the resultant piperidones often are quite low.



Scheme 1. Dieckmann cyclization approach.

For some electron deficient systems, nucleophilic substitution reactions are described.[3] But in order not to limit the synthetic scope, our particular focus concentrated on a more general approach without any limitations concerning the substituent pattern.

In 2003 Quach and Batey[4] described a Cu-catalyzed protocol for the cross-coupling of arylboronic acids and potassium aryltrifluoroborate salts with primary and secondary aliphatic amines, using 1,4-dioxo-8-aza-spiro[4,5]decane as well. As boronic acids very often are synthesized via the corresponding aryl halides, we were interested to prepare N-substituted piperidones directly from aryl halides by adapting Buchwald–Hartwig

Keywords: Buchwald–Hartwig amination; X-Phos; Palladium; Microwave; 4-Arylpiperidones.
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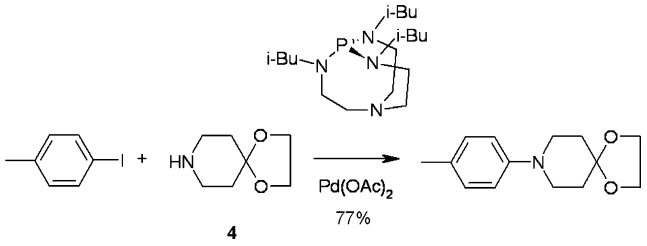


Scheme 2. Verkade approach. Reagents and conditions: 1 equiv of aryl iodide, 1.2 equiv of amine, 1.5 equiv of Cs_2CO_3, cat. $Pd(OAc)_2$, cat. bicyclic triaminophosphine ligand, toluene, 80 °C for 15–20 h.

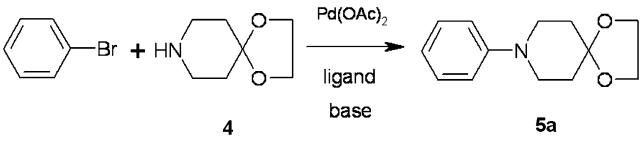
C–N bond coupling methodology[5] starting with 4-piperidone or with the corresponding 4-piperidone ethylene ketal.

Verkade et al. published data on the application of bicyclic triaminophosphine ligands in Pd-catalyzed Buchwald–Hartwig amination reactions of aryl halides under inert conditions.[6] For instance, 1,4-dioxo-8-azaspiro[4,5]decane **4** has been used as well (Scheme 2).

As we were interested in conditions that can also be used for parallel synthetic applications, we searched for simple general reaction conditions to be used for aromatic as well as heteroaromatic halides. Here we describe our attempts on the synthesis of this class of compounds by palladium-catalyzed amination of different aryl and heteroaryl halides according to the following general scheme (Scheme 3).

As the reaction of 4-piperidone monohydrochloride monohydrate with aryl halides would result in the desired product in one step, as indicated in Scheme 3, we attempted the amination reactions with different aryl halides, but yields did not exceed 30–40%. So, we carried out the synthesis by an alternate approach using 1,4-dioxo-8-azaspiro[4,5]decane **4** (4-piperidone ethylene ketal) followed by hydrolysis of the resulting *N*-aryl/heteroaryl-4-piperidone ethylene ketal which gave *N*-aryl/heteroaryl-4-piperidone.

Thus, we started a program to optimize the reaction conditions for the synthesis of *N*-aryl and *N*-heteroaryl



Scheme 4. Buchwald–Hartwig standard reaction.

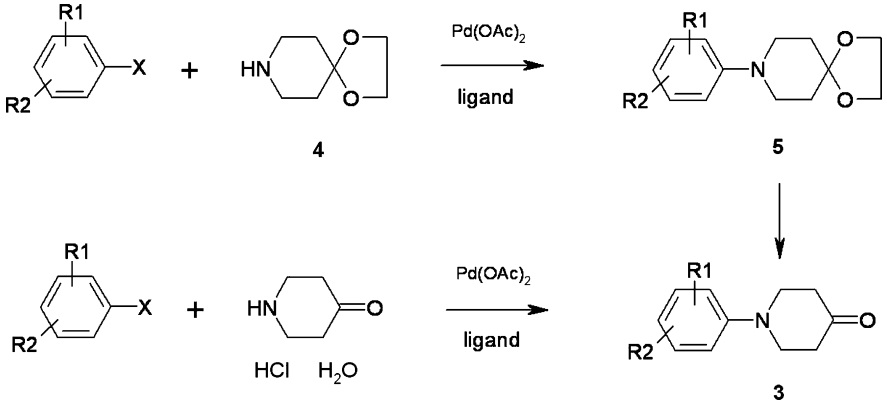
substituted piperidones using different ligands, bases and solvents at different temperatures. Our experimental results are presented and discussed below.

In a first step, we tried to identify the best Buchwald–Hartwig conditions for the coupling between 1,4-dioxo-8-azaspiro[4,5]decane and bromobenzene as a standard reaction (Scheme 4).

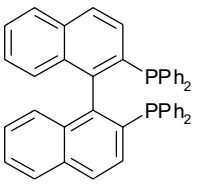
Our work began with the intention to identify the best phosphine ligand for the C–N coupling reaction. In a typical experiment, bromobenzene was subjected to Pd(0)-catalyzed amination in the presence of 12 different phosphine ligands (Scheme 5), KO-*t*-Bu in toluene/*t*-BuOH (5:1) at 120 °C for 18 h. The results of this ligand screening are listed in Table 1.

Of the twelve ligands screened (Scheme 5), the highest yield was achieved by using X-Phos (L8) while other ligands gave moderate yields and the bidentate ligand Xantphos (L2) and the ferrocene derivative dppf (L3) were essentially ineffective.

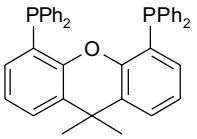
Furthermore, we explored the influence of different solvent system (see Table 2). In order to collect knowledge of how the Buchwald amination behaves in classical solvents, the reaction was first carried out in toluene and 1,4-dioxane. As the base Cs_2CO_3 is not dissolved in these solvents the reaction was performed under heterogeneous conditions, while in toluene the reaction proceeded well, it failed in 1,4-dioxane. Therefore, we carried out the amination in aprotic solvents such as NMP, DMF, and DMA. Under these conditions, bases such as Cs_2CO_3 dissolve to a higher extent compared to nonpolar solvents. However, we observed either no reaction or only low yields in these solvents and finally decided to continue with toluene/*t*-BuOH (5:1), a sol-



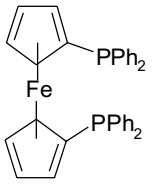
Scheme 3. Buchwald–Hartwig approach.



L1 (BINAP)

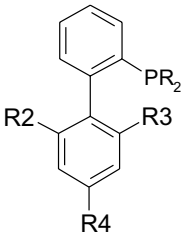


L2 (Xantphos)

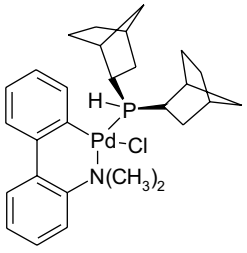


L3 (dppf)

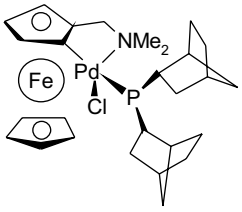
L4



	R	R2	R3	R4	
L5	C_6H_{11}	$N(CH_3)_2$	H	H	DavePhos
L6	C_6H_{11}	OCH_3	OCH_3	H	S-Phos
L7	C_6H_{11}	$OCH(CH_3)_2$	$OCH(CH_3)_2$	H	RuPhos
L8	C_6H_{11}	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	X-Phos
L9	$C(CH_3)_3$	H	H	H	JohnPhos
L10	C_6H_5	$N(CH_3)_2$	H	H	



11 (SK-CC01-A)



12 (SK-CC02-A)

Scheme 5. Ligands screened.

Table 1. Ligand effect on palladium-catalyzed amination reaction[a]

Ligand	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
Yield (%)	35[c]	0	0	37[b,d]	78[c]	51[c]	65[c]	96[c], 82[b]	69[c]	81[c]	79[c]	78[c]

[a] Reagents and conditions: 1,4-dioxa-8-azaspiro[4,5]decane (1 equiv), bromobenzene (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (5 mol %), toluene/*t*-BuOH (5:1), 120 °C, 18 h.
[b] Isolated yield.
[c] LC–MS yield.
[d] Without $Pd(OAc)_2$.

Table 2. Solvent effect on palladium-catalyzed amination reaction[a]

Solvent	Temperature (°C)	Yield[b] (%)
Toluene	120	71
1,4-Dioxane	100	No reaction
DMF	160	<15
NMP	100	No reaction
DMA	160	<15
Toluene/*t*-BuOH (5:1)	120	82

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), bromobenzene (1.1 equiv), Cs_2CO_3 (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), 120 °C, 18 h.
[b] Isolated yield.

vent mixture which has been generally used for the amination of aryl sulfonates.[7]

In the next step, the use of other bases like Et_3N, K_2CO_3, K_3PO_4, KO-*t*-Bu, Cs_2CO_3, and NaO-*t*-Bu was investigated and the results are summarized in Table 3. By using K_2CO_3, K_3PO_4 or KO-*t*-Bu the product was obtained in lower yields, whereas in the presence of Cs_2CO_3 and NaO-*t*-Bu the amination proceeded well and the product was isolated in 82% and 98%, respectively.

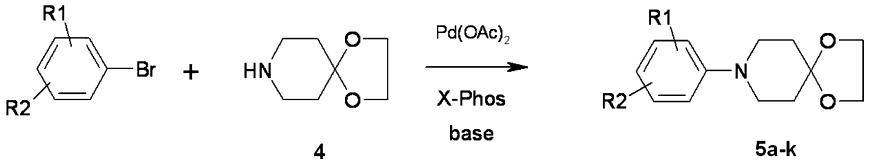
As summarized in Table 4, we successfully prepared eleven different aryl substituted piperidone ketals, using these optimized conditions (i.e., 1,4-dioxa-8-azaspiro[4,5]decane (1 equiv), aryl halide (1.1 equiv), NaO-*t*-Bu (1 equiv), X-Phos (5 mol %), $Pd(OAc)_2$ (5 mol %) in toluene/*t*-BuOH (5:1) at 120 °C for 10 h).[8]

Table 3. Effect of different bases on Buchwald–Hartwig amination[a]

Base	NEt_3	K_2CO_3	Cs_2CO_3	K_3PO_4	KO-*t*-Bu	NaO-*t*-Bu
Yield[b] (%)	0	68	82	73	60	98

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), bromobenzene (1.1 equiv), base (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), 120 °C, 18 h.
[b] Isolated yield.

Table 4. Synthesis of *N*-aryl-4-piperidone ethylene ketals[a]

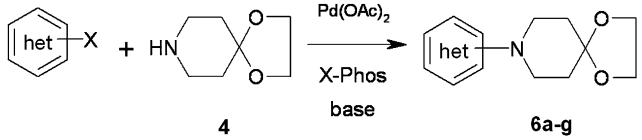


4 5a-k

No.	R1, R2	Base	Time (h)	Yield[b] (%)
5a	H	Cs_2CO_3	18	82
		NaO-*t*-Bu	8	98
5b	4-OMe	Cs_2CO_3	18	75
		NaO-*t*-Bu	10	97
5c	4-CF_3	Cs_2CO_3	18	64
		NaO-*t*-Bu	10	99
5d	4-F	Cs_2CO_3	18	84
		NaO-*t*-Bu	10	95
5e	3-CF_3, 4-Cl	Cs_2CO_3	18	83
		NaO-*t*-Bu	10	93
5f	4-CN	Cs_2CO_3	18	81
		NaO-*t*-Bu	10	82
5g	4-CHO	Cs_2CO_3	18	78
		NaO-*t*-Bu	10	72
5h	3-Cl	Cs_2CO_3	18	52
		NaO-*t*-Bu	10	73
5i	3-OMe	Cs_2CO_3	18	64
		NaO-*t*-Bu	10	98
5j	1-Naphthyl	Cs_2CO_3	18	75
		NaO-*t*-Bu	8	77
5k	3,4-OCH_2–CH_2O	NaO-*t*-Bu	13	82

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), aryl halides (1.1 equiv), Cs_2CO_3 or NaO-*t*-Bu (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), 120 °C, 8–18 h.
[b] Isolated yield.

Table 5. Synthesis of *N*-aza-heteroaryl-4-piperidone ethylene ketals[a]



4 6a-g

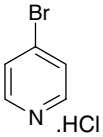
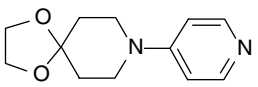
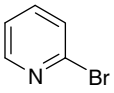
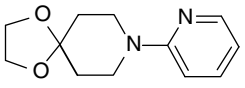
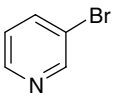
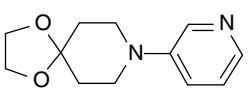
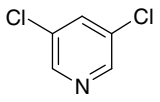
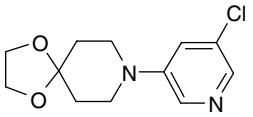
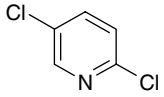
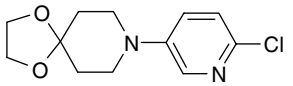
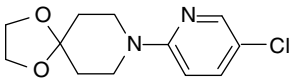
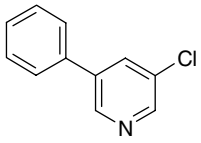
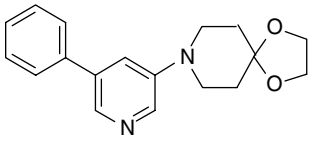
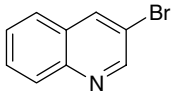
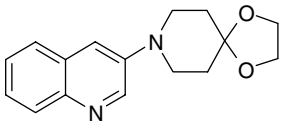
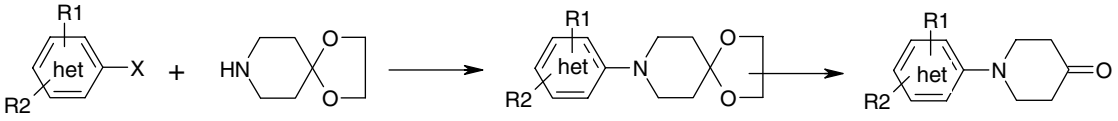
No.	Halide	Product	Base	Time (h)	Yield[b] (%)
6a			Cs_2CO_3	18	65
			NaO-*t*-Bu	8	76
6b			Cs_2CO_3	18	35
			NaO-*t*-Bu	16	55
6c			NaO-*t*-Bu	18	98

Table 5 (*continued*)

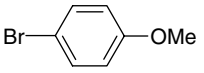
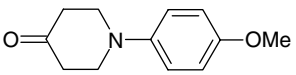
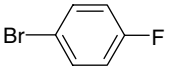
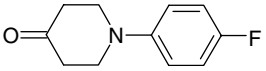
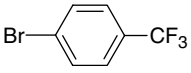
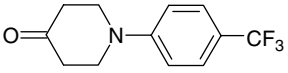
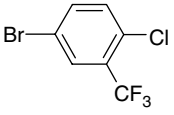
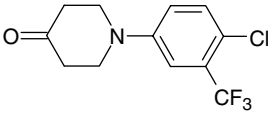
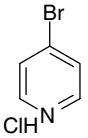
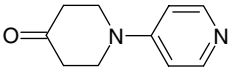
No.	Halide	Product	Base	Time (h)	Yield[b] (%)
6d			NaO-*t*-Bu	14	93
6e			NaO-*t*-Bu	14	38
					32
6f			NaO-*t*-Bu	18	70
6g			NaO-*t*-Bu	13	82

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), heteroaryl halides (1.1 equiv), Cs_2CO_3 or NaO-*t*-Bu (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), 120 °C, 10–18 h.
[b] Isolated yield.

Table 6. Upscaled synthesis of substituted *N*-aryl/heteroarylpiperidones[a]

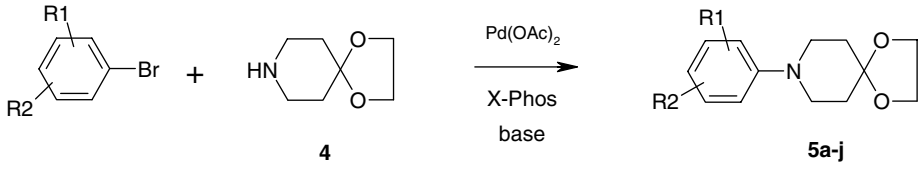


5 **3**

No.	Substrate	Product	Yield[b] (%) (**5**)	Yield[b] (%) (**3**)	Overall yield[b]
3a			97	74	71
3b			95	72	68
3c			99	70	70
3d			93	71	66
3e			76	75	57

[a] Reagents and conditions: (1) 1,4-dioxoazaspiro[4,5]decane (1 equiv), aryl/aza-heteroaryl halides (1.1 equiv), NaO-*t*-Bu (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), conventional heating at 120 °C for 10–18 h; (2) 5 N HCl at 100 °C for 2–3 h.
[b] Isolated yield.

Table 7a. Synthesis of *N*-aryl-4-piperidone ethylene ketals **5** under microwave conditions[a]



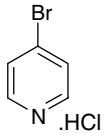
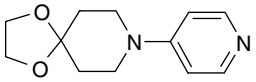
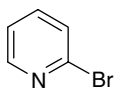
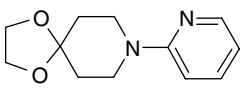
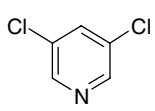
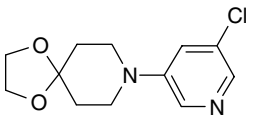
	5a	5c	5d	5e	5f	5g	5h	5i	5j
R1, R2	H	4-CF_3	4-F	3-CF_3,4-Cl	4-CN	4-CHO	3-Cl	3-OMe	1-Naphthyl
Yield (%)	100[b]	84[b]	87[b]	79[b]	73[b]	100[b]	85[b]	81[b]	51[b]
	94[c]	76[c]						80[c]	

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), aryl halides (1.1 equiv), NaO-*t*-Bu (1 equiv), $Pd(OAc)_2$ (5 mol %) X-Phos (5 mol %), toluene/*t*-BuOH (5:1), microwave heating at 160 °C for 10 min.
[b] LC–MS.
[c] Isolated yield.

The above results prompted us to explore the scope and limitations by applying our optimized condition for the synthesis of seven different hetero aryl derivatives of piperidone ethylene ketal. As summarized in Table 5, these different chloropyridines, bromopyridines, and 3-bromoquinoline gave the aminated products in moderate to good isolated yield.

Next, scale-up of the palladium-catalyzed amination reaction was evaluated and thus we applied our optimized conventional conditions (1 equiv of 1,4-dioxo-8-azaspiro[4,5]decane, 1.1 equiv of aryl halide, NaO-*t*-Bu (5 mol %), X-Phos (5 mol %), $Pd(OAc)_2$ in toluene/*t*-BuOH (5:1) at 120 °C) for 10–18 h in a sealed bomb for the synthesis of five different *N*-aryl-4-piperidones ketals. These substituted 4-piperidone ketals are prepared in 20–25 g scale. Furthermore, aryl substituted 4-piperidone ketals upon hydrolysis in 5 N HCl at 100 °C for 2–3 h gave the corresponding aryl substituted 4-piperidones in good yields. The results are summarized in Table 6.[8,9]

Table 7b. Synthesis of *N*-aza-heteroaryl-4-piperidone ethylene ketals 6 under microwave conditions[a]

No.	Halide	Product	Yield[b] (%)
6a			72
6b			57
6d			78

[a] Reagents and conditions: 1,4-dioxoazaspiro[4,5]decane (1 equiv), aza-heteroaryl halides (1.1 equiv), NaO-*t*-Bu (1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), toluene/*t*-BuOH (5:1), microwave heating at 160 °C for 10 min.
[b] LC–MS.

Though we were in principle able to synthesize the *N*-aryl/heteroarylpiperidone ketals, we searched for conditions to reduce the lengthy reaction times by shifting from conventional heating to microwave acceleration.[10] Under microwave irradiation conditions a better reproducibility with often higher yields and less side reactions has been encountered.

Though several reports of microwave assisted Pd-catalyzed aryl aminations have appeared in the literature,[11] to the best of our knowledge, no examples have been reported for *N*-aryl/heteroarylpiperidone ketals.

Therefore, we continued our study on the synthesis of the above target entities with microwave assisted Buchwald–Hartwig amination of aryl and heteroaryl halides with 1,4-dioxo-8-azaspiro-[4,5]decane. Once again, bromobenzene was chosen as test substrate, 1,4-dioxo-8-azaspiro[4,5]decane as amine, toluene/*t*-BuOH as solvent system and NaO-*t*-Bu as base in combination with 5 mol % $Pd(OAc)_2$, X-Phos (5 mol %) as pre-catalyst. When heating this mixture in a sealed tube at 160 °C for 10 min under temperature-controlled microwave irradiation using an initial power of 300 W, according to LC–MS results a complete reaction was observed. The optimized conditions were then applied on several activated as well as unactivated aryl bromides, aryl chlorides and aza-heteroaryl chlorides yielding the desired products (Tables 7a and 7b) in good to excellent yields (LC–MS).[12,13] In three representative examples (**5a**, **5c**, **5i**), the products have been isolated and the corresponding yields are given in Table 7a. Compared to conventional heating the rate of conversion is accelerated by a factor of 60.

Currently the microwave assisted scale-up is investigated and the results will be discussed in a separate publication.

In conclusion, we described a convenient protocol for the efficient preparation of *N*-aryl-4-piperidone ethylene ketals and *N*-heteroaryl-4-piperidone ethylene ketals under thermal condition as well as under microwave condition. Most of the coupling products are obtained in sufficiently good yields and isolation of the products

is easily achieved by column chromatography. The simplicity of this short and clean procedure and generally satisfactory yields render this method particularly attractive. The presence of diverse range of substituents and functional groups in aryl and heteroarylpiperidones suggests also an opportunity to acquire many other derivatives by adopting this synthetic strategy.

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8. General procedure for the palladium-catalyzed amination of aryl bromides under conventional conditions: In an oven dried reaction tube, $Pd(OAc)_2$ (5 mol %), ligand X-Phos (5 mol %), and Cs_2CO_3 or NaO-*t*-Bu (1 equiv) were taken in toluene/*t*-BuOH (5:1). The reaction was purged with nitrogen and the tube was capped with a rubber septum. After stirring for 1 min, 4-piperidone ketal (1 equiv), aryl bromide (1.1 equiv) in toluene/*t*-BuOH (5:1, 20 mg of ketal/ml) were added separately via a syringe. Then, the septum was replaced with a Teflon screw cap and the resulting mixture was flushed with nitrogen for an additional 2 min with stirring and it was heated at 120 °C in an oil bath for about 10–18 h. The reaction mixture was cooled to room temperature and filtered over celite and rinsed well with ethyl acetate. The filtrate was subsequently evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel.
9. General procedure for the ketal hydrolysis of aryl substituted 4-piperidone ketal: 1 g of substituted 4-piperidone ketal is taken up in a 50 ml flask fitted with a water condenser. 10–15 ml of 5 N HCl was added and the reaction mixture was heated at 100 °C for 2–3 h. The reaction mixture was cooled to room temperature and subsequently made basic with a 10% NaOH solution and extracted with ethyl acetate (2×100 ml). The ethyl acetate layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel.
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12. Emrys™ Optimizer from Biotage (formely Personal Chemistry) was used for all experiments described here (power 300 W).
13. General procedure for the microwave palladium-catalyzed amination of aryl bromides: A pressure vial (10 ml) was charged with 5 mol % of $Pd(OAc)_2$, 5 mol % of X-Phos and NaO-*t*-Bu (1 equiv), then the vial was flushed with nitrogen and was capped with a rubber septum and stirred for 5 min. 4-Piperidone ketal (1 equiv) and aryl bromide (1.1 equiv) were added into the vial using a syringe in toluene/*t*-BuOH (5:1, 20 mg of ketal/ml), The septum was replaced with a sealed cap and the reaction tube was heated to 160 °C under microwave conditions. The total heating time of all reactions was between 8 and 10 min. After the reaction vials were cooled to room temperature and filtered over celite, they were rinsed well with ethyl acetate. The filtrate was subsequently evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel.