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Variation of xanthene-based bidentate ligands in the palladium-catalyzed arylation of ureas

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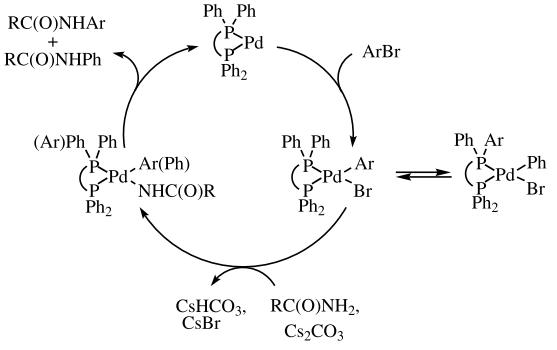
Abstract—A series of xanthene-based bidentate ligands containing various substituents on diphenylphosphino groups were synthesized and tested in the palladium-catalyzed arylation reaction of urea with unactivated aryl bromides. It was found that both steric and electronic properties of the ligands have a pronounced effect on the yields and ratios of the products. Arylation of urea and phenylurea with unactivated aryl bromides in the presence of $Pd_2dba_3{\cdot}CHCl_3$/3,5-$(CF_3)_2$Xantphos and Cs_2CO_3 as base in dioxane at 100°C gave the corresponding *N*,*N*′-diarylureas in 62–98% yields.

Arylureas have numerous applications such as drugs,[1] pesticides,[1] selective anion-binding receptors[2] and polymer materials.[3] Common methods for the synthesis of arylureas include the reactions of arylamines with isocyanates or phosgene.[1] Alternative routes to these substances include the reductive carbonylation of nitroarenes[4] or oxidative carbonylation of amines.[5] It is evident that most of these methods utilize hazardous and toxic reagents.

Recently, the palladium-catalyzed arylation of amines (Buchwald–Hartwig reaction)[6] became a convenient and efficient method for C–N bond formation. Even more recent expansions in the scope of this method allowed one to perform arylation of amides,[7–10] sulfonamides[8,9] and ureas[11] under rather mild conditions tolerating various functional groups. One of the most powerful ligands used in such palladium-catalyzed reactions is *Xantphos*.[8–11] However, the utility of this ligand is mainly limited to the amidation of electron-deficient aryl halides. Reactions with unactivated aryl halides usually require higher catalyst loadings and give much lower product yields.[8–11] In many cases, especially when an electron donating group like methoxy is present in the aryl halide, the reaction fails.[8,10] Recently we encountered a similar problem in the arylation of urea: reactions with activated aryl bromides afforded the corresponding *N*,*N*′-diarylureas in high yields, whereas arylation of urea with *p*-bromotoluene proceeded with incomplete conversion, gave a low yield of the desired product, and was accompanied with the formation of *N*-phenylation products: *N*,*N*′-diphenyl- and *N*-phenyl-*N*′-*p*-tolylurea.



Scheme 1.

Buchwald has recently reported an effective arylation of amides both with activated and unactivated aryl halides in the presence of a copper catalyst and diamine ligand.[12] However, our attempts to carry out the arylation of urea under these conditions were unsuccessful.

A catalytic cycle for the palladium-catalyzed amidation reaction is presented in Scheme 1. Oxidative addition to Pd(0) even of unactivated aryl bromides, takes place under very mild conditions. For instance, the amination of bromobenzene can be performed at room temperature in the presence of *Xantphos* ligand.[13] Amidation of unactivated aryl bromides requires harsher conditions (100–110°C).[8–10] Therefore it may be supposed that the

Keywords: palladium-catalyzed; ligands; amidation; aryl halides; urea.

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rate-determining steps in the amidation reaction of unactivated aryl bromides involve either substitution of halogen for amide or reductive elimination. The rate of C–N bond forming reductive elimination decreases with the increase of the donor ability of the substituent in the aryl group bound to palladium.[14] A considerable deceleration of the stages following the oxidative addition can give way to side processes, such as an exchange of the aryl group bound to palladium and the phenyl group of the ligand in the $PdL_2(Ar)Br$ complex, resulting in *N*-phenylated side products. Such an exchange process becomes more evident when electron-rich aryl halides are employed (Fig. 1).[8,9,11,15]

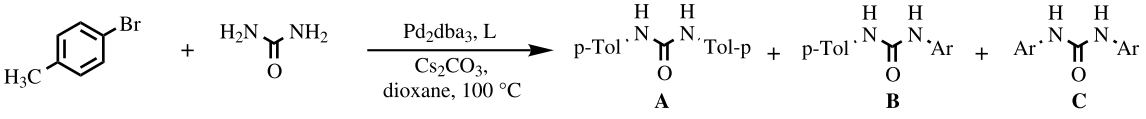
For this reason aryl–aryl exchange and catalyst deactivation represent urgent problems in the reactions of amides and ureas with unactivated aryl bromides. Taking into account that the rate of reductive elimination increases both with the decrease of electron density on the palladium atom[16] and with the increase of the steric bulk of the ligand,[17] one may expect that a bulky phosphine ligand bearing electron-withdrawing substituents will be of key importance for a successful amidation of unactivated aryl halides.

To test this supposition we synthesized a number of bidentate ligands based on the *Xantphos* backbone having various steric and electronic properties. Tuning of steric and electronic properties of the ligands was achieved by introducing acceptor and donor substituents into various positions of the phenyl rings of the ligand and by replacing phosphorus atoms with arsenic. The ligands were synthesized via metallation of dimethylxanthene and subsequent addition of diarylchlorophosphine (diphenylchloroarsine) at low temperature.[18]

Ar :		
	o-MeC_6H_4	*o-MeXantphos*
	p-$MeOC_6H_4$	*p-MeOXantphos*
	C_6H_5	*Xantphos*
	3,5-$(CF_3)_2C_6H_3$	*3,5-(CF3)2Xantphos*
	C_6F_5	*FluoroXantphos*

Xantharsine

Figure 1.



Thus, among the synthesized ligands on the *Xantphos* backbone the only efficient one for arylation of urea

Table 1. Variation of xanthene-based ligands in the palladium-catalyzed arylation of urea with *p*-bromotoluene[a]

Entry	Ligand	Pd (mol%)	Time (h)	Conversion (%)[b]	Yield (%)		
					A	**B**	**C**
1	*p-MeOXantphos*	4	2.5	34			
			24	47	8	4	
2	*Xantphos*	4	20	62	7	10	5
3	*3,5-(CF3)2Xantphos*	4	2.5	100	62	4	
4	*o-MeXantphos*	4	20	9			
5	*FluoroXantphos*	2.5	20	5			
6	*Xantharsine*	2.5	20	8			

[a] The reactions were carried out with 1 mmol of aryl halide, 0.65 mmol of urea, 1.25–2 mol% of $Pd_2dba_3{\cdot}CHCl_3$ (2.5–4 mol% Pd), 3.75–6 mol% of the ligand, 1.4 mmol Cs_2CO_3 in 4 ml of dioxane at 100°C under argon to the point when the conversion of the aryl bromide (as shown by GC) did not increase further.

[b] Corresponding diarylamines were formed as side products.

with *p*-bromotoluene is *3,5-$(CF_3)_2$Xantphos*. We utilized this ligand for the arylation of urea with unactivated aryl bromides.[21]

From the data presented in Table 2 one can clearly see the advantages of using *3,5-$(CF_3)_2$Xantphos* instead of *Xantphos*. In the presence of this ligand it is possible to carry out the arylation of urea with unactivated aryl halides with yields of 62–98%. *ortho*-Substituted aryl bromides react more readily than the corresponding *para*-isomers and give *ortho*-substituted ureas in 80–98% yields. By contrast, in the presence of *Xantphos* the reaction with *o*-bromochlorobenzene, besides di(*o*-chlorophenyl)urea, (57%), gave a substantial amount of (*o*-chlorophenyl)amine (35%) and in the reaction with *o*-bromotoluene di(*o*-tolyl)amine becomes the main product (77%). Thus, changing one ligand for another may alter the course of the reaction. It is worth noting, that the arylation of urea with *p*-bromochlorobenzene and *p*-bromotoluene in the presence of *3,5-*

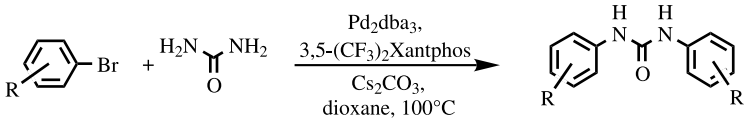
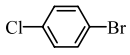
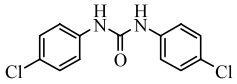
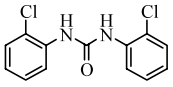
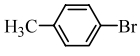
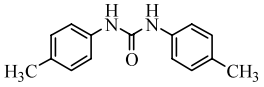
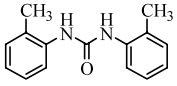
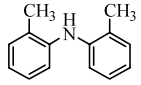
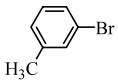
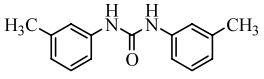
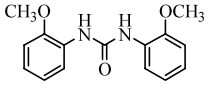
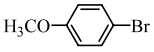


Table 2. Palladium-catalyzed arylation of urea with unactivated aryl bromides in the presence of *3,5-$(CF_3)_2$Xantphos* and *Xantphos*[a]

Entry	Aryl bromide	Ligand	Mol % of Pd	Time, h	Product	Conversion,%	Yield, %[b]
1		*3,5-$(CF_3)_2$Xantphos*	2	2		100	81
2		*Xantphos*	4	10		100	64
3		*3,5-$(CF_3)_2$Xantphos*	1	5		100	91
4		*Xantphos*	4	11		100	57
5		*3,5-$(CF_3)_2$Xantphos*	4	2.5		100	62
6		*Xantphos*	4	20		62	7
7		*3,5-$(CF_3)_2$Xantphos*	1	4		100	98
8		*Xantphos*	4	36		94	77[c]
9		*3,5-$(CF_3)_2$Xantphos*	2	4		100	71
10		*3,5-$(CF_3)_2$Xantphos*	3	4		100	80
11		*3,5-$(CF_3)_2$Xantphos*	2.5	2	-	29	-[d]
12		*3,5-$(CF_3)_2$Xantphos*	4	4.5	-	15	-[d,e]
13		*3,5-$(CF_3)_2$Xantphos*	4	5	-	27	-[d]

(a)The reactions were carried out with 1 mmol of aryl halide, 0.65 mmol of urea, 0.5-2 mol% of $Pd_2dba_3 \cdot CHCl_3$ (1-4 mol% Pd), 1.5 - 6 mol% of the ligand, 1.4 mmol Cs_2CO_3 in 4 ml of dioxane at 100°C under argon to the point when the conversion of aryl bromide (as shown by GC) did not increase further. (b) Presented in the Table are the yields of pure isolated compounds (except entries 6,8), purified by column chromatography on silica gel 40-63 μm. All of the substances were characterised by ^{1}H NMR. (c) The product contained about 7% of impurity. (d) The isolation of the products was not attempted. (e) *t*-BuONa was used as the base.

$(CF_3)_2$Xantphos requires lower catalyst loadings and results in higher product yields in comparison to the reaction with *Xantphos*.

Thus, the use of *3,5-$(CF_3)_2$Xantphos* as a ligand allowed us to accomplish a series of reactions of urea both with poorly activated and unactivated aryl bromides, which in the presence of *Xantphos* gave much less satisfactory yields of diarylureas. However, the scope of this electron-poor ligand also has some limitations: the reaction of urea with *p*-bromoanisole even with 2.5 mol% of the catalyst proceeds with low conversion. The use of a stronger base, *t*-BuONa instead of Cs_2CO_3, did not improve the result. It should be emphasized that *o*-bromoanisole, under the same conditions, gave the product in 80% yield. *o*-Bromo-*N*,*N*′-dimethylaniline proved to be an unreactive substrate.

In a previous paper we reported the arylation of phenylurea with activated aryl halides in the presence of *Xantphos* to give unsymmetrical *N*-aryl-*N*′-phenylureas in high yields.[11] The reaction is accompanied by formation of symmetrical *N*,*N*′-diarylureas and *N*,*N*′-diphenylurea, which arise from the disproportionation of the main product. The amount of symmetrical ureas increases with increased reaction time. Since the reaction of urea with unactivated aryl halides proceeds rather slowly, it is difficult to obtain unsymmetrical diarylureas with electron donor substituents under these conditions. However the use of *3,5-$(CF_3)_2$Xantphos* allowed us, in a number of cases, to obtain such ureas in high yields (Table 3). The quantity of the catalyst was increased to reduce the reaction time and hence to suppress the disproportionation side reaction. Again, the *ortho*-substituted aryl halides proved to be the most reactive substrates as in the arylation reaction of urea. The greater efficiency of *3,5-$(CF_3)_2$Xantphos* compared to *Xantphos* is evident from the reaction with *o*-bromotoluene (entries 5 and 6). Reaction in the presence of *Xantphos* proceeds with low conversion and gives a much lower yield of the product. In fact it proceeds slower than the reaction with *p*-isomer of bromotoluene, this being in sharp contrast to the reactions in the presence of *3,5-$(CF_3)_2$Xantphos*.

In summary, we have found that the electron-poor ligand *3,5-$(CF_3)_2$Xantphos* allows the palladium-catalyzed arylation of urea and phenylurea with unactivated

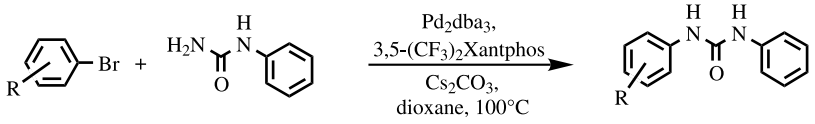
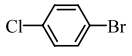
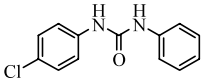
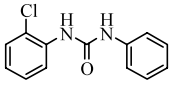
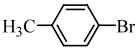
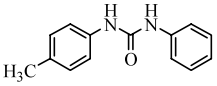
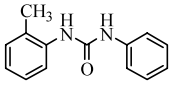
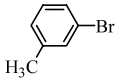
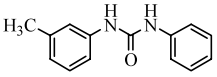
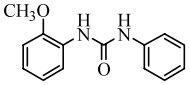


Table 3. Palladium-catalyzed arylation of phenylurea with unactivated aryl bromides in the presence of *3,5-CF_3Xantphos* and *Xantphos*[a]

Entry	Aryl bromide	Ligand	Mol % of Pd	Time, h	Product	Conversion,%	Yield, %[b]
1		*3,5-$(CF_3)_2$Xantphos*	2	1		100	72[c]
2		*3,5-$(CF_3)_2$Xantphos*	1	1		100	95
3		*3,5-$(CF_3)_2$Xantphos*	3.5	1		100	80
4		*Xantphos*	4	1.5		63	39[d]
5		*3,5-$(CF_3)_2$Xantphos*	2.5	1		100	95
6		*Xantphos*	4	1.5		30	18[e]
7		*3,5-$(CF_3)_2$Xantphos*	2	1		100	81
8		*3,5-$(CF_3)_2$Xantphos*	4	1		100	91

(a) The reactions were carried out with 0.60 mmol of aryl bromide, 0.60 mmol of phenylurea, 0.25-1 mol% of $Pd_2dba_3{\cdot}CHCl_3$ (0.5-2 mol% Pd), 0.75-3 mol% of the ligand, 0.84 mmol Cs_2CO_3 in 3 ml of dioxane at 100°C under argon to the point when the conversion of aryl bromide (as shown by GC) did not increase further. (b) Presented in the Table are the yields of pure isolated compounds, purified by column chromatography on silica gel 40-63 μm. All of the substances were characterized by ^{1}H NMR. (c) 7% of *N,N*`-diphenylurea and 7% of *N,N*`-di(*p*-chlorophenyl)urea were obtained as side products. (d) 17% of *N,N*`-diphenylurea was isolated as a side product. (e) 10% of *N,N*`-diphenylurea was isolated as a side product.

aryl bromides in high yields. The reactions in the presence of this ligand require lower catalyst loadings and give higher yields of the products than those with *Xantphos*.

Acknowledgements

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18. Preparation of *3,5-$(CF_3)_2$Xantphos*. To a mixture of 0.39 g (1.85 mmol) of 9,9-dimethylxanthene, 0.7 ml (0.54 g, 4.63 mmol) of TMEDA in 14 ml of heptane was added 2.75 ml (4.67 mmol) 1.67 M solution of *n*-BuLi in petroleum ether (65–70°C). The mixture was refluxed for 30 min, cooled to −65°C and 2.28 g (4.62 mmol) of bis[3,5-bis-(trifluoromethyl)phenyl]chlorophosphine[20] in 7 ml of THF was added dropwise over a period of 20 min. The reaction mixture was heated to room temperature and stirred for 16 h. The mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was then dried over $MgSO_4$, evaporated to dryness in vacuo and the residue was purified first by flash chromatography eluting with EtOAc:petroleum ether (1:6). The solid was then recrystallized from a mixture of MeOH:$CHCl_3$ (10:1) to give 0.755 g of the product as a white crystal. Mp 165–166°C. ^{1}H NMR ($CDCl_3$), δ 7.88 (s, 4H), 7.61 (s, 8H), 7.57 (d, 2H, 7.7 Hz), 7.12 (t, 2H, 7.7 Hz), 6.40 (d, 2H, 7.7 Hz), 1.67 (s, 6H). ^{31}P NMR ($CDCl_3$), δ −14.36. ^{19}F NMR ($CDCl_3$), δ −64.25. Anal. calcd for $C_{47}H_{24}F_{24}OP_2$: C, 50.22; H 2.03. Found: C, 50.29; H, 2.15.
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21. Representative procedure, *N*-(2-methoxyphenyl)-*N′*-phenylurea: 94 mg *o*-bromoanisole (0.5 mmol), 69 mg of phenylurea (0.5 mmol), 11 mg of $Pd_2dba_3{\cdot}CHCl_3$ (10.6×10^{-3} mmol), 33.9 mg of *3,5-$(CF_3)_2$Xantphos* (30.2×10^{-3} mmol), 225 mg of dried Cs_2CO_3 (0.83 mmol), and 2.5 ml of dioxane purged with argon were placed into an argon filled reactor. The reaction mixture was degassed by several freeze–pump–thaw cycles and the reactor was filled with argon. The reaction was carried out with stirring at 100°C under positive argon pressure. After 1 h TLC showed the absence of the starting phenylurea. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 ml), filtered and evaporated to dryness. The residue was chromatographed on silica gel 40–63 μm, eluting with ethyl acetate: light petroleum ether mixture (v/v 1:2), to give 111 mg (91%) of a white solid. Mp 148–149°C (lit 148–149°C[22]). ^{1}H NMR (DMSO-d_6), δ 9.3 (bs, 1H), 8.22 (bs, 1H), 8.12 (d, 1H, 7.8 Hz), 7.45 (d, 2H, 8.0 Hz), 7.27 (dd, 2H, 7.8 Hz, 8.0 Hz), 6.85–7.04 (m, 4H), 3.87 (s, 3H).
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