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Progress in Arylpiperazine Synthesis by the Catalytic Amination Reaction

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Abstract—Careful base and solvent optimization for catalytic amination is described. A Pd-catalyzed amination between some arylbromide and unprotected piperazine (1 equiv) was efficiently carried out with Pd/BINAP catalyst in a toluene–DBU solvent system, which is useful for the one-pot preparation of unsymmetrical piperazine through amination and in-situ *N*-protection. Reaction with *N*-BOC-piperazine was also successful in toluene–DBU or more polar NMP with Cs_2CO_3 as a key base. No reports have previously reported such solvent and base optimization in arylpiperazine synthesis.

Introduction

Synthesis of arylamines and its congeners is obviously an important task in modern medicinal chemistry. Although a number of synthetic methods are available, there still exists a demand for improved protocol which allows an effective transformation in the presence of a wide range of functional groups. We have thus been interested in the application of some metal-catalyzed reactions to the synthesis of Aripiprazole and other drug substances.[1,2]

We have already described a simple method for the conversion of phenol into arylamine via the corresponding triflate.[3] In this study, coupling of the triflate (**1**) with the aniline derivative (**2**) revealed the superiority of the Pd catalyst over the Cu system. On the other hand, some reactions were successfully carried out by the Cu catalyst using the different substrates including the activated halide (**3**).

Our arylpiperazine study has also disclosed a modified Buchwald amination reaction with **4** and **5**, in which the addition of 18-crown-6 to Cs-promoted amination was fruitful, as shown in Scheme 1.[4]

Aripiprazole studies

Aripiprazole is an important arylpiperazine derivative developed by our company for the treatment of psychotic disease (structure shown in Scheme 1).[1] In relation to the study of its metabolite (**8**), Morita and Uchida have revealed some beneficial aspect of the catalytic amination over conventional routes.[5] In this study, a tetra-substituted arylpiperazine (**7**) was synthesized in the yield of 94% as shown in Scheme 2. This application clearly showed the superiority of Buchwald amination over classical methods based on the conversion from nitroaromatics. Furthermore, the precise study (shown in Scheme 2) indicated a preferable amount of the catalysts and selection of the amine reagent for the reaction of **9**.

Initial Studies

We then resumed our own process optimization for the arylpiperazine (**11**) in the presence of a metal catalyst under various base-solvent systems. A Cu-catalyzed amination of the bromide (**9**) either with *N*H-piperazine (**10a**) or *N*-Me piperazine (**10b**) afforded only less than 15% of the desired aryl piperazine as shown in Scheme 2. Albeit low yield, the utilization of the toluene–DBU–Cs_2CO_3 system was noteworthy, because almost no product was obtained from the reaction in toluene–Cs_2CO_3.

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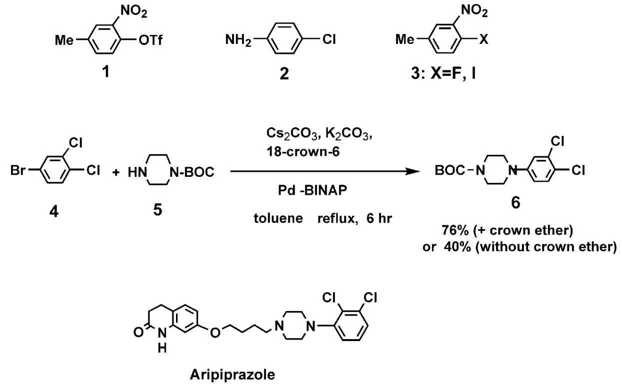
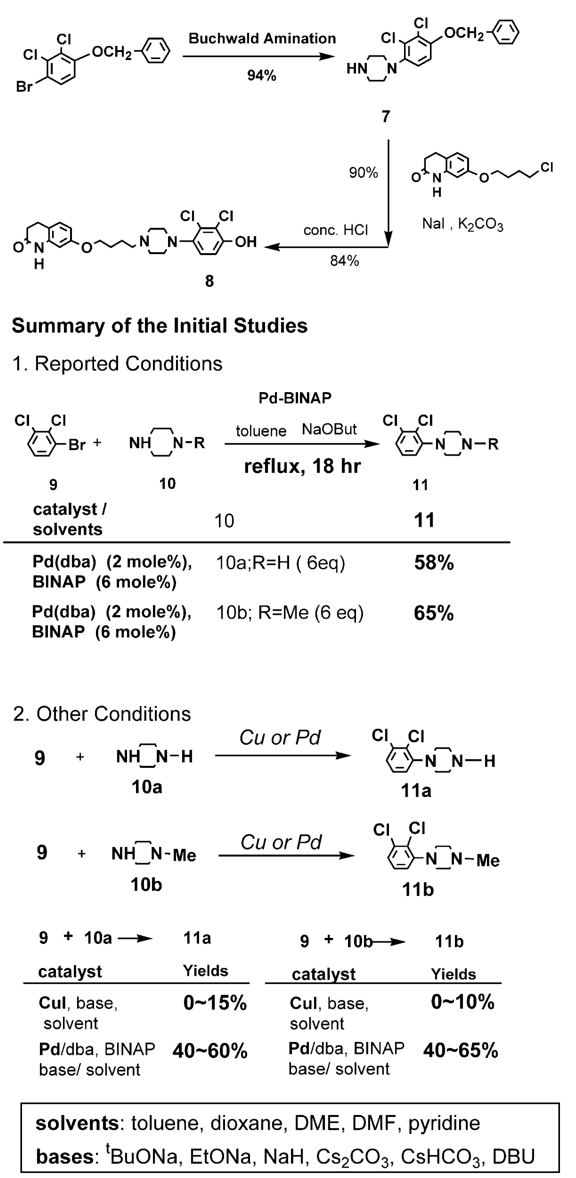
Contrary to the results with Cu catalyst, a survey with the Pd–BINAP system (Buchwald amination) demonstrated again the efficiency of the Pd catalyst. In the transformations shown above (**9**–**11**), 60% unoptimized yield was attained in the initial survey using the toluene–DBU–NaO^{t}Bu system with *excess* piperazines and Pd catalyst (5 mol%).



Scheme 1. Previous study.



Summary of the Initial Studies

1. Reported Conditions

catalyst / solvents	10	11
Pd(dba) (2 mole%), BINAP (6 mole%)	10a;R=H (6eq)	58%
Pd(dba) (2 mole%), BINAP (6 mole%)	10b; R=Me (6 eq)	65%

2. Other Conditions

9 + 10a → 11a

catalyst	Yields
CuI, base, solvent	0~15%
Pd/dba, BINAP base/ solvent	40~60%

9 + 10b → 11b

catalyst	Yields
CuI, base, solvent	0~10%
Pd/dba, BINAP base/ solvent	40~65%

solvents: toluene, dioxane, DME, DMF, pyridine
bases: ^{t}BuONa, EtONa, NaH, Cs_2CO_3, $CsHCO_3$, DBU

Scheme 2. Aripiprazole study.

Our study then focused on the Pd-catalyzed amination with nearly *1 equiv NH-piperazine with minimum catalyst loading (1 mol%).*

Amination with *N*H-Piperazine

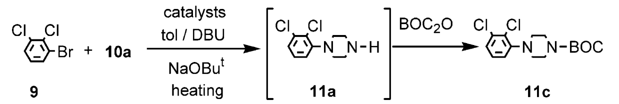
Careful surveying started with employing less than 1 mol% Pd catalyst. Selected results are summarized in Table 1. We were interested in the effect of added organic base such as DBU, which can form a clear solution and assist nuclephilic substitution by amines.

Compared with the previous results, this modification is particularly useful in a one-pot operation to unsymmetrical arylpiperazine. The notable features are as follows:

- Addition of DBU formed a colorless clear solution at first, which indicated DBU substrates (**9**, **10a**) interaction before reaction starts (see the structure shown in Scheme 3).
- Addition of ^{t}BuONa started reaction in exothermic way, but addition of ^{t}BuONa before the piperazine led to a messy and sluggish reaction (~45% yield with by-products).
- DBU could neither work as ligand nor as a key base like ^{t}BuONa. This indicated an interaction between *ligand–Pd–DBU(piperazine) complex* and ^{t}BuONa before reductive elimination as delineated in Scheme 3.

We noticed here that the interaction of the amine and Pd was an initial key factor for the successful conversion. The reactions were strongly dependent on the amine counterpart employed. Some unwanted complexation or further interaction between amine and the catalyst strongly affected the catalytic cycle. We thus tentatively

Table 1. Amination with 1 equiv NH-piperazine



9/**10a**	Catalysts	Base	**11c**
10 mM/12 mM	Pd(dba) (0.1 mM), BINAP (0.3 mM)	NaOBu^t (added last)	75%
	$Pd(OAc)_2$ (0.2 mM) BINAP (0.6 mM)	NaOBu^t (added last)	70%
	$Pd(OAc)_2$ (0.2 mM) BINAP (0.6 mM)	NaOBu^t (added before **10a**)	45%
	$Pd(OAc)_2$, BINAP (0.2/0.6)	Cs_2CO_3 (added last)	$<10\%$
	$Pd(OAc)_2$, BINAP (0.2/0.6)	Cs_2CO_3 (added last)	25%
	$Pd(OAc)_2$, $P(o\text{-}tol)_3$ (0.2/0.6)	NaOBu^t (added last)	Trace

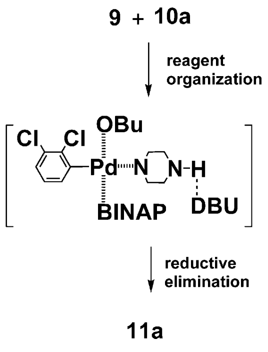
speculate that DBU might assist such proper interaction of the catalyst with one molar amine that can form a crucial intermediate shown in Scheme 3.

Whatever the true nature is, the reaction was a facile process which can afford the *N*-protected arylpiperazines in one step from arylbromide and *N*H-piperazine in ca. 75% overall yield through the sequential amination and protection in the same flask. Our protocol thus offers operational simplicity as well as efficient conversion in a short reaction time, which is superior to the existing protocols, usually requiring excess piperazine to prevent the formation of bis-piprazine by-products, and requiring long reaction time. None of the reported procedures attained such short time conversion with 1 equiv of *N*H-piperazine without the assistance of DBU as a co-solvent, which is summarized later for clarity.

Amination with *N*-BOC-Piperazine

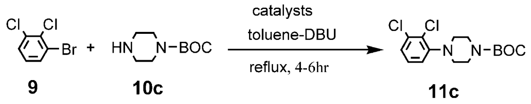
We further attempted an improved catalytic amination with mote bulky *N*-BOC piperazine (**10c**). The availability of this derivative in bulk quantity now prompted us to uncover its utility. As summarized in Table 2, the conversion again indicated the superiority of DBU-based protocol, especially in its fast and clean reaction in comparison with the Cu catalyst. As indicated in the last run, comparable reaction with Cu catalyst gave only 25% of the product with recovery of largely starting material.

Further reaction in more common polar solvents such as DMF, DMA and NMP (*N*-methyl piperidinone) indicated that a mixture of products was obtained with ^{t}BuONa as a base.



Scheme 3.

Table 2. Amination with N-BOC piperazine



Catalysts	10c	Reflux (h)	11c
Pd/dba (1 mol%) BINAP (3 mol%)	2 equiv	4	80%
Pd/dba (1 mol%) BINAP (3 mol%)	1.2 equiv	6	55%
CuI (20 mol%) $CuCO_3$ (120 mol%)	2 equiv	6	25%

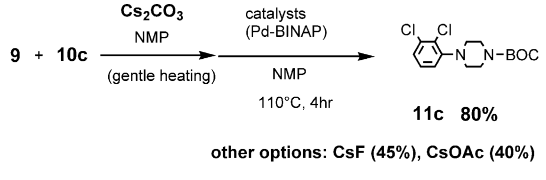
To overcome the messy reaction caused by alkoxide base (or NaH), we attempted the reaction of **9** and **10c** with Cs_2CO_3 in DMA and NMP. A recommended reaction sequence was shown (Scheme 4), in which a preformed cesium amide worked as a good precursor for this amination in 80% yield (see Experimental). It should be noted that crushed Cs salt was recommendable and the reactions were almost complete within 4 h with vigorous stirring under Ar atmosphere. Among the cesium salts examined, Cs_2CO_3 was superior to CsF, CsOH, $CsHCO_3$ and CsOAc.

Pd-Catalyzed Amination with DPPP or DPPB

It is also desirable to find a simple ligand that can replace expensive BINAP. Search for an alternative ligand is currently under active investigation, which highlighted the bulky trialkylphosphines or others.[6,7] Here, we did not focus on these special candidates, which sometimes require special precautions in handling or preparation. Instead, we have been interested in the simplest example of the chelating phosphines DPPP and DPPB.

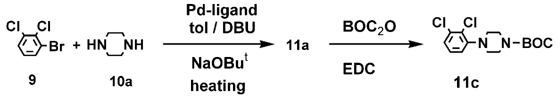
Results with such ligands as DPPP and DPPB in toluene–DBU media are summarized in Table 3, which clearly indicates that piperazine formation was successful only in moderate yields.

In all cases in Table 3, *o*-dichlorobenezene was obtained as a major product, which was also formed in the reaction with PPh_3 or P(*o*-Tol)$_3$. These results clearly indicated the bulkiness of phosphine is essential. In other words,



Scheme 4. Improved amination in NMP.

Table 3. Reaction with other ligands



9/10a	Catalyst/solvents	Conditions	11c
10 mM/12 mM	Pd/dba (0.05 mM), DPPP (0.12 mM) DBU/tol	70–120°, 6 h	45%
	Pd/dba (0.05 mM) BIPPB (0.12 mM) DBU/tol	70–120°; 6 h	30%
	Pd(OAc)2 (0.24 mM) BU_3P (0.29 mM) DPPP (0.24 mM) DBU/tol	70–120°; 46 h	30%

large aromatic ring (binaphtyl) is essential for key reductive coupling reaction. We are now searching for a readily available bulky phosphine, which has a tether that can interact with DBU such as COOH group.

As reviewed in a recent article, reactions in some ionic liquids or by the assistance of *N*-heterocyclic carbene ligands will open another avenue of the aryl amination and other important transformations.[11]

Related studies

Besides our study, many other studies have dealt with the same topics. Some of them should be summarized below for comparison with our protocols. The synthesis of arylpiperazines via Pd-catalyzed amination with unprotected piperazine (**10a**) was first reported in 1996 by Zhao (Roche),[8] in that the isolated yield of the product has reached 50% with 4 equiv excess of piperazine by $PdCl_2[P(o\text{-tol})_3]_2$–NaOt-Bu combination. The major problem was the bis-arylation reaction resulting in the formation of undesired *N,N*-disubstituted bisarylpiperazines.

In a search for the effective ligand for catalytic amination, Nishiyama (Tosoh)[9] discovered the new catalyst system: Pd(II)/P^tBu_3 in *o*-xylene (i.e., at higher reaction temperature), which shows high product (Ar–N/Ar–H) selectivity and high TON: 6400 (mol product/mol Pd). A wide variety of arylpiperazines including *N*-heteroarylpiperazines can be prepared using this system with an excess amount of NH-piperazine (2–6 equiv).

For the work on 5-HT_{1A} ligands, Thomas (Knoll Pharmaceuticals)[10] reported a convenient procedure for the bicyclic arylpiperazines, which involved the reaction of *N*-BOC-piperazine (**10c**) with bicyclic bromoarenes under Pd_2dba_3–$P(o\text{-tolyl})_3$ system, followed by deprotection of the BOC group by TFA. Yields were strongly dependent upon the nature of the bromoarene, ranging from 20 to 60%. This protocol has found wide unitity as a standard procedure in medicinal chemistry research.

Concluding Remarks

In our present study, we have briefly investigated and summarized some Cu and Pd catalyzed pathways to the important arylpiperazine intermediate for Aripiprazole and others. The simple and effective protocol was developed through a careful solvent optimization focusing on DBU, which can be easily removed in extractive workup (see Experimental). Among the amine additives examined, DBU was particularly noteworthy because it is effective in both Cu- and Pd-catalyzed reactions. DBU has previously been utilized as a good solvent and base for such Pd-catalyzed reaction as amidocarbonylation reaction, in which amine is a nucleophile involved. We thus assume that DBU might assist the *ligand–Pd–DBU(amine) complex* as depicted above. Thus, the order of the addition of reagents was an important factor, which governed this catalytic amination. The key base ^{t}BuONa should be added after all reagents were mixed [*ligand–Pd–DBU(amine) complex formation*] in the flask. Exothermic amination reaction immediately started on warming around 70 °C.

In the reaction with bulky and less reactive *N*-BOC-piperazine, solvent optimization was critical for the efficient conversion. We also found an optional system, in which DMA and NMP was a good solvent in combination with a Cs bases. In this reaction of Cs base, preformation of a Cs amide species was preferable. Thus, Cs base was first mixed with amine and substrate, before the addition of catalysts. In all reactions mentioned above, more solvated mixture was obtained than those reported before.

Obviously, further investigation is necessary to find the optimum ligand–solvent combination for the important arylpiperazines, and one promising direction was indicated in the aforementioned review article.[11] Progress along these lines will be reported in due course.

Experimental

Materials and instrumentation

Chemicals were purchased from the commercial firms indicated and used without further purification except for brief crushing prior to use. TLC analysis was carried out using Merck silica gel 60 F_{254} plate (Art 5715). ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, with tetramethylsilane (TMS) as the internal standard.

Pd-catalyzed amination with *N*H-piperazine (Table 1)

A well-dried flask (200 mL) was first charged with the starting bromide (**9**, 10 mM, TCI) and *N*H-piperazine (**10a**, 12 mM, Wako), which was evacuated and backfilled with argon through a balloon under gentle warming (40 °C). Solvent (dry toluene, 15 mL) was charged and the mixture was bubbled with Ar for ca. 10 min, before the two catalysts were delivered (BINAP and pd_2dba_3: the amount indicated in Table 1; BINAP was purchased from Kanto Chemical Co and pd_2dba_3 from Aldrich). After the addition of DBU (TCI, dried by MS 4A and flushed with Ar for 5 min; 1–2 mL) to the mixture, the clear solution was warmed at 60–70 °C while fine powder of ^{t}BuONa (Wako, 15 mM initially, or other bases shown in Table 1) was added in one portion to start amination. After being heated for a while (1–4 h), the dense colored mixture was monitored by tlc (AcOEt/*n*-hexane) to reveal the formation of the polar products. (Further amount of base was delivered if reaction was incomplete.)

After cooling to rt, the mixture was diluted with ethylene dichloride (dry reagent; 10–15 mL) and further treated with Boc_2O (TCI, 20–30 mM) to form a single less polar spot on the tlc. After dilution with AcOEt–H_2O, the products were extracted with AcOEt and extracts were washed well with H_2O to remove polar material. The crude products obtained after evaporation of the dried extracts was further passed through a SiO_2 short column to afford the very pure product as a faint yellow caramel in the yields indicated in Table 1.

For the structural identification, the initial *N*-Boc-aryl piperazine (**11c**) was further deprotected by the treatment of excess HCl in MeOH (most conveniently from AcCl + MeOH) to furnish the known hydrochloride, on evaporation of the mixture, as a white solid, which was identical with the commercially available sample from Lancaster Co.

Pd-catalyzed amination with *N*-BOC-piperazine (Table 2)

In a well-dried flask (200 mL) was first placed the starting bromide (**9**, 10 mM) and *N*-BOC-piperazine (**10b**, 12 mM, Lancaster), which was evacuated well and backfilled with argon through a balloon under gentle warming to melt the crystals (40–50 °C). Solvent (dry toluene, 15 mL) was charged and the mixture was well mixed and exchanged with Ar, before the two catalysts were delivered (BINAP and pd_2dba_3: the amount indicated in Table 2). After the addition of DBU (2 mL) to the mixture, the resulting clear solution was warmed at 60 °C while fine powder of ^{t}BuOK (14 mM) was added in one portion to start the reaction. After heating for 4 h, the mixture was monitored by tlc (AcOEt/*n*-hexane) to reveal the formation of the single polar product (**11c**). After cooling to rt, the mixture was diluted with AcOEt–H_2O, further extracted with AcOEt and extracts were washed well with H_2O to remove polar material. The crude products obtained after evaporation of the dried extracts was further passed through a SiO_2 column to afford the very pure product (**11c**) as caramel in the yields indicated in Table 2.

Pd-catalyzed amination with *N*-BOC-piperazine in NMP

In a well-dried flask (200 mL) was first placed the starting bromide (**9**, 10 mM) and *N*-BOC-piperazine (**10c**, 12 mM), which was evacuated and backfilled with argon through a balloon under gentle warming to melt the solids (40 °C). Solvent (dry **NMP**, 10 mL) was charged and crushed cesium carbonate (Aldrich, 15 mM; or other cesium salts such as CsF) was then added in one portion. The mixture was warmed further to form a purple solution, which was well mixed and exchanged with Ar, before the two catalysts were delivered (BINAP: 30 mg and pd_2dba_3: 20 mg). Resulting solution was warmed at 70–80 °C for 1 h to initiate the reaction. After further heating for 3 h at 110 °C with vigorous stirring, the dense colored mixture was monitored by tlc (AcOEt/*n*-hexane) to reveal the formation of the single polar product.

After cooling to rt, the mixture was diluted with AcOEt–H_2O, extracted with AcOEt and extracts were washed well with H_2O to remove polar material.

The crude products obtained after evaporation of the extracts gave a nearly pure material, which was further passed through a SiO_2 column to afford the very pure product (**11c**) as a yellow caramel in 80% yields.

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