



Modulation of the Cs_2CO_3 -Promoted Catalytic Amination by a Crown Ether

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Abstract—The catalytic addition of 18-Crown-6 in some Cs_2CO_3 -promoted amination of triflates and bromides was beneficial to improve sluggish reaction with suppression of the unwanted side products. The protocol was useful for the preparation of chlorinated aryl piperazines from phenol derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

The pioneering work of both Buchwald and Hartwig now offers an expedient amination protocol with non-activated aryl halides and triflates.^{1,2} Notable improvements have also been reported by the fine-tuning of the catalyst system.³ Besides the choice of ligand phosphine, the base employed was also crucial for further improvement. While cesium salts are often recommended because of its greater functional group tolerance,^{3,4} recent reports suggested the superiority of the Rb_2CO_3 , K_2CO_3 and NaOMe over Cs_2CO_3 and NaO-Bu[†] as the base in some *N*-arylation reactions.^{5,6} During our investigation on some aryl amines⁷ and especially aryl piperazines related to OPC-14597⁸ and OPC-14523,⁹ we investigated the Buchwald amination of triflates employing Cs_2CO_3 as a key base component. It is of special interest to expand such catalytic amination to the substrates containing both bromide (or triflate) and chloride(s) in the benzene ring. In our survey, however, the Cs_2CO_3 protocol still suffered from sluggish reaction and moderate isolated yields, producing some side products, especially in larger-scale operations. We were thus interested in the effective additive that could modulate the Cs_2CO_3 -promoted amination.

We now wish to describe the results of our improvement on the Buchwald Cs_2CO_3 -promoted amination by the addition of catalytic Crown ether, with an application of this protocol to the preparation of some bis-piperazine derivative.

Depicted in Scheme 1 is our initial experimentation on the amination of the triflate (**1**) with *N*-BOC piperazine

(**2**), which showed rapid and clean reaction with $\text{Pd}_2\text{dba}_3/\text{BINAP}/\text{Cs}_2\text{CO}_3/18\text{-Crown-6}$ system after 2 h reflux. No significant byproducts were detected in the mixture except a small amount of arene byproduct (i.e. 1,2-dichlorobenzene, DCB; ~5%). In the reaction without Crown ether, we isolated a byproduct which was identified as bis-*N*-BOC piperazine derivative (**4**, 5~10%). Standard catalytic amination required much longer time (>10 h), while in our polychlorinated substrate (**1**), longer reaction time caused the unwanted polyamination product as reported previously.^{8b}

Further experimentation with aryl bromide (**5**) gave a satisfactory amination with $\text{BINAP}/\text{Cs}_2\text{CO}_3/18\text{-Crown-6}$ system, although arene byproduct (DCB) was always formed along with recovered bromide (ca. 10%) after 2 h reflux. Reaction with other phosphine ligands such as PPh_3 or (*o*-Tol)₃P gave no coupling products in the presence of the Crown ether, which indicated that Crown ether could not work as a ligand like BINAP.

We further observed, in the comparative experiments, that no better yields were obtained by the use of K_2CO_3 or K_2CO_3 -Crown ether. We also observed that conversion of **5** to **3** was possible by the use of catalytic Cs_2CO_3 (0.3–0.5 equiv) and K_2CO_3 (1.0–1.5 equiv) in the presence of Crown ether (10 mol%) as shown.

As has been emphasized before,¹ Cs_2CO_3 protocol was most effective in the reaction of triflate as substrate. In accord with this observation, usefulness of our Cs_2CO_3 /Crown ether system was further demonstrated with the case of bis-triflate (**7**), which was regarded as a sluggish substrate without any activating group in the benzene ring. Addition of 18-Crown-6 was proven to be beneficial as shown in Table 1; otherwise, sluggish reactions

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with less satisfactory yields were observed. In the reactions without Crown ether, substantial amounts of interrupted intermediates such as **9** and **10** have been isolated.

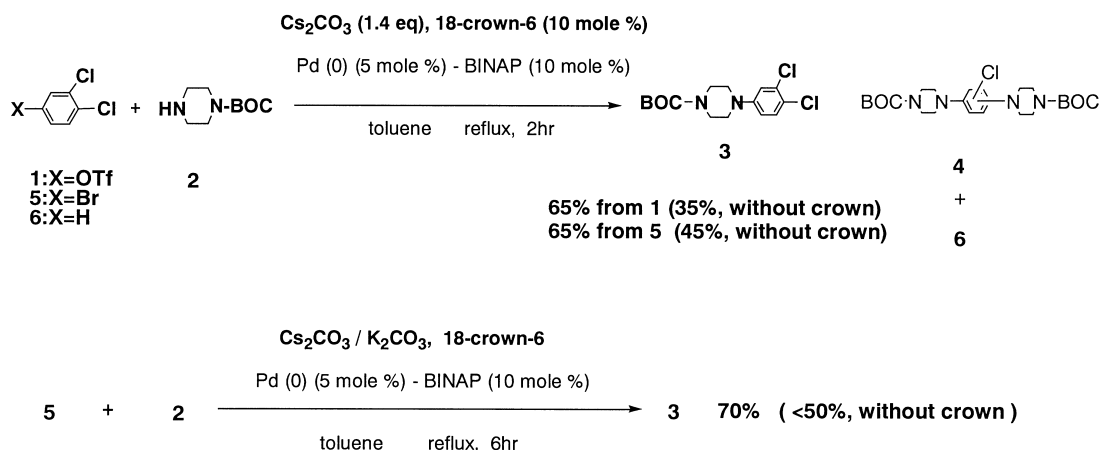
Reaction of **7** was almost complete within 4 h with 6 mol% Pd_2dba_3 while being somewhat incomplete and sluggish with less than 4 mol% of Pd(0) (optimized reaction is presented in run 2). The use of the Cs/Crown system was critical because no coupling products were detected in the reaction with *t*-BuONa as a base, in which hydrolysis of triflate was a major reaction path.

Concerning the effect of Crown ether on the amination reaction, Buchwald described an intriguing result with 18-Crown-6 (stoichiometric amount addition) in the room temperature amination of aryl iodides several years ago.¹⁰ An explanation was made later that Crown ether could facilitate the exchange of the halide with amine in the intermediate palladium complex, which resulted in the overall rate acceleration.^{1c}

In our reaction, Crown ether (catalytic amount) could interact with the more soluble Cs salt and facilitate the catalytic amination; an interaction between metal (Cs)–Crown–metal (Pd) was more probable. Such stabilization

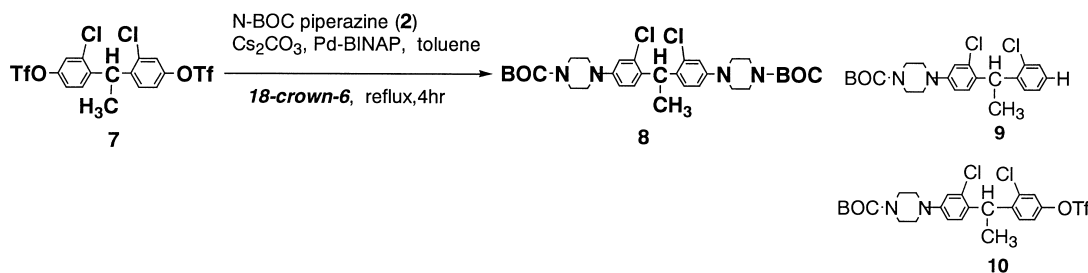
of the intermediate might result in acceleration of the reaction and suppress the byproduct formation.^{11,12} Similar assistance through Cs–(OH₂)–Pd(II) interaction was observed in our research on catalytic carbonylation.¹³ In other cases, some aza-crown compounds were prepared by the catalytic amination reaction, in which interesting ligand preference was observed; bulky monophosphines $\text{P}(o\text{-Tol})_3$ and $\text{P}(t\text{-Bu})_3$ gave only moderate (or low) yield, while sterically small ligand PPh_3 with $\text{Pd}(\text{OAc})_2$ gave best results.¹⁴ From these results and other reports,¹² we can assume some subtle interaction between Crown ether and metals present during catalytic amination in boiling toluene.

In summary, the effect of catalytic 18-Crown-6 on the Cs_2CO_3 -promoted Buchwald amination was investigated and summarized to reveal some beneficial assistance in the coupling reaction of aryl triflates (or bromide) with *N*-BOC piperazine, a sequence of special interests for the preparation of functionalized aryl piperazines starting from phenols. Further assessment of the effect associated with different types of Crown ether¹⁵ as well as a search for an option towards cost effective catalytic process are now in progress in our laboratory.



Scheme 1.

Table 1.



Run	7	Pd	Cs_2CO_3	18-Crown-6	8	9	10
1	5.5 mM	$\text{Pd}(\text{OAc})_2$ (1.0 mM)	11 mM	1.9 mM	61%	Trace	Trace
2	16.5 mM	Pd_2dba_3 (1.0 mM)	35 mM	3.78 mM	79%	Trace	Trace
3	11.0 mM	Pd_2dba_3 (1.1 mM)	22 mM + K_2CO_3	None	24%	20%	5%
4	5.5 mM	Pd_2dba_3 (0.9 mM)	<i>t</i> -BuONa (10 mM) + K_2CO_3	None	0%	Present in reaction mixture	

References and Notes

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15. We selected here 18-Crown-6 as a representative Crown ether based on our previous study (ref 12b).