



Amination of aryl chlorides and fluorides toward the synthesis of aromatic amines by palladium-catalyzed route or transition metal free way: Scopes and limitations

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ABSTRACT

This paper presents the application of zeolite (NaY) supported Pd and Cu catalysts in amination reactions of aryl chlorides. Using 0.1 mol% Pd, good yields could be achieved in the coupling of 4-chloroacetophenone and piperidine after 6 h at 140 °C. In the second part, we demonstrate two different pathways for transition metal free amination of activated aryl chlorides and fluorides, and, respectively, non- and deactivated aryl chlorides. These reactions were performed with excellent yields in short reaction time without any transition metal catalyst under optimized reaction conditions. Activated aryl halides react smoothly using 2.1 equiv. amine without additional base whereas deactivated aryl halides require the use of a strong base (KO^tBu) for high conversion. DFT calculations were performed to study the surprising influence of substituents at the aromatic ring on selectivity in metal free aminations found in this work.

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1. Introduction

Aromatic amines are important substructures commonly encountered in biologically relevant natural or synthetic pharmaceutical compounds, in xerographic and photographic materials or in conducting polymers. Traditionally, the preparation of secondary or tertiary aromatic amines has been performed by the reductive amination of aniline derivatives or aryl nitration/reduction sequences. While being often effective, these methods could not be extended to a large variety of substrates and they suffer from a lack of tolerance towards functional groups. Additionally, these synthetic strategies require in many cases several reaction steps or the use of expensive reagents in stoichiometric amounts.

As an answer to these limitations, the transition metal catalyzed amination reaction of aryl halides was developed and is today often recognized as a powerful tool for synthetic organic chemists. The first approach was reported by Kosugi et al. [1] who described an effective palladium-catalyzed synthesis of aromatic tertiary amines from aryl bromides using organotin amides. A major improvement was achieved by Buchwald [2] and Hartwig [3] in the middle 1990s using palladium phosphine complexes to promote the reaction.

Using $[P(o-C_6H_4Me)_3]_2PdCl_2$ as catalyst in the presence of a strong base, these authors could perform the coupling reaction of aryl bromides with secondary amines in high yields. By their contribution to that field, the substrate range for the palladium-catalyzed amination of aryl halides has been considerably expanded, and several improvements were made at the catalyst level by mechanistic understanding and ligand design [4–9].

Recent investigations on the direct amination of aryl halides focused on substitution of Pd catalysts by Ni [10–14] or Cu [15–17] systems. Generally, expensive and often sensitive ligands are necessary to activate the metal center and to stabilize the complex during the reaction in order to prevent agglomeration. In most cases separation and recovery of homogeneous catalysts from the reaction mixture are difficult or even impossible. To solve such problems, Weigand et al. reported on palladium-catalyzed aminations using solid amine sources; however, the examples remained limited to the synthesis of aniline derivatives due to the restrictive choice of compatible amine sources [18]. Further attempts were made by several authors using supported heterogeneous catalysts. Buchmeiser et al. presented the heterogenization of a dichloropalladium di(pyrid-2-yl)amide complex on polymeric material. These catalysts were applied to various cross-coupling reactions including the amination of aryl bromides, but generally low yields (i.e. 10–63%) were obtained [19,20]. Following the Buchwald–Hartwig procedures, Djakovitch and co-workers reported on the heterogeneously Pd-catalyzed amination of aryl bromides using either Pd(0), Pd(II) or $[Pd(NH_3)_4]^{2+}$ in NaY zeolite or Pd(0) on metal oxides. However, this procedure was rather limited due to competitive uncatalyzed

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reactions that prevent high selectivity [21]. Basu et al. introduced a procedure using $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ intimately admixed with KF-alumina for the amination of aryl bromides [22]. Recently, Kiil and co-workers presented the use of FibreCatTM catalysts (i.e. $\text{Pd}(\text{OAc})_2$ or PdCl_2 immobilized by grafted triphenylphosphine on polymeric fibres). While good rates for the desired amination reaction were observed, a significant number and amount of side products (i.e. dehalogenation and aryl halide homocoupling) has been observed with these catalysts. Furthermore, the catalysts could not be recycled without reactivation due to a high rate of palladium leaching preventing broader applications [23]. As in homogeneous catalysis, other catalytic metals were used in heterogeneous systems. Lipshutz and co-workers gave an account of a procedure for the heterogeneous amination of aryl chlorides using Ni nanoparticles supported on charcoal. Generally, good to high yields were achieved for various aryl chlorides; however, the interest of this methodology was strongly limited as it required the use of expensive phosphine ligands (i.e. dppf) in quite high concentrations (Ni/dppf up to 1:20), long reaction times (up to 52 h) and high catalyst loading (5 mol%) [12,14,24]. Likhar et al. presented a Cu/Al-HT catalyzed amination of aryl chlorides with primary and secondary aromatic amines leading generally to good yields [25]. However, despite all efforts that were made (metal sources, support influence, added ligands, ...) to achieve high yield in target compounds, the interest in these heterogeneous catalysts remained limited since their activities are, generally, by orders of magnitude lower than those reported for homogeneous systems and required further developments.

An alternative way to solve the problem of noble metal separation from the products consists in applying a transition metal free amination protocol, a strategy of additional interest regarding economical and ecological reasons. Several authors described the direct amination of aryl halides by primary or secondary amines without any transition metal. However, most of these coupling reactions were performed under drastic conditions like microwave heating [26–28]. Milder conditions (toluene, KO^tBu , 135 °C) were successfully applied by Beller et al., though they needed longer reaction times (ca. 36 h) to achieve high conversions [29]. Yadav et al. reported on high conversions for the coupling of activated aryl halides and secondary amines at room temperature without any transition metal catalyst in ionic liquids. However, as outlined by the authors, it seems that the success of these reactions results from the use of hexafluorophosphate or tetrafluoroborate salts [30]. The Lewis acidic properties of these ionic liquids activate, most probably, the aromatic substrates for the coupling reaction. Nevertheless, although interesting, these methodologies remained linked to a narrow choice of the aromatic compounds and amines, and of the right reaction conditions to achieve high conversions.

To our knowledge, no general efficient, environmentally friendly, and cheap methodologies have been reported for the synthesis of aromatic amines from aryl halides and primary or secondary amines. In the present contribution, we describe two different new and complementally routes: an efficient methodology for the direct amination of activated aryl halides using heterogeneous Pd catalysts, and alternatively, a transition metal free coupling of aryl chlorides and fluorides with secondary amines. The methodology to use with its associated reaction conditions depends on the level of activation of the carbon–halide bond in the aromatic halide that is determined by the nature of the substituents.

2. Experimental

All manipulations were conducted under air atmosphere. All glassware was base- and acid-washed and oven dried. All chemicals were used as received from the supplier. The heterogeneous catalysts $[\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NaY}$ (1 wt% Pd), $[\text{Cu}(\text{NH}_3)_4]^{2+}/\text{NaY}$ (5 wt% Cu)

and Pd/Cu/NaY (3.5 wt% Pd, 2.2 wt% Cu) were prepared according to a method described in the literature [31].

2.1. Palladium-catalyzed aminations

10 mmol aryl chloride, 21 mmol amine, 10 mmol LiBr, 0.1 mol% Pd or Cu catalyst and 6 ml NMP were put in a sealed pressure tube and reacted for 6 h at 140 °C.

2.2. Transition metal free aminations of activated aryl chlorides and fluorides

10 mmol aryl chloride, 21 mmol amine, 10 mmol LiBr (only for aryl chlorides) and 6 ml NMP were put in a sealed pressure tube and reacted for 6 h at 140 °C.

2.3. Transition metal free aminations of deactivated aryl chlorides

10 mmol aryl halide, 21 mmol amine, 12 mmol KO^tBu and 6 ml NMP were put in a sealed pressure tube and reacted for 6 h at 140 °C.

Filtered samples were extracted with water/ CH_2Cl_2 and dried over MgSO_4 . Products were identified by GC/MS and NMR. Conversions and yields were quantified by GC using diethylene glycol dibutylether as internal standard ($\Delta_{\text{rel}} = \pm 5\%$).

2.4. Computational details

All calculations were performed with GAUSSIAN-03 [32] using the density functional/Hartree-Fock hybrid model Becke3LYP [33–36] and the split valence double- ζ (DZ) basis set 6-31G* [37]. No symmetry or internal coordinate constraints were applied during optimizations. All reported intermediates were verified as being true minima by the absence of negative eigenvalues in the vibrational frequency analysis. Transition state structures (indicated by TS) were located using the Berny algorithm [38] until the Hessian matrix had only one imaginary eigenvalue. The identities of all transition states were confirmed by IRC calculations, and by animating the negative eigenvector coordinate with MOLDEN [39] and GaussView [40].

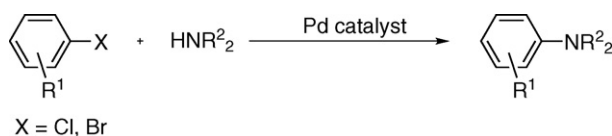
Approximate free energies (ΔG) and enthalpies (ΔH) were obtained through thermochemical analysis of frequency calculations, using the thermal correction to Gibbs free energy as reported by GAUSSIAN-03. This takes into account zero-point effects, thermal enthalpy corrections, and entropy. All energies reported in this paper, unless otherwise noted, are free energies or enthalpies at 298 K, using unscaled frequencies. All transition states are maxima on the electronic potential energy surface (PES), which may not correspond to maxima on the free energy surface.

3. Results and discussion

3.1. Palladium-catalyzed aminations

In contrast to homogeneous Pd catalyst systems which are commonly used, heterogeneous systems exhibit significant advantages like easy separation and recovery of the catalyst as well as high stability against air and moisture. However, the main drawback of all supported systems known so far is that their activity is by orders of magnitude lower. In the first part of this contribution, we present an application of transition metal containing zeolites (NaY), which feature high activity in C–C [41–44] and C–N [45] coupling reactions, for amination of aryl chlorides (Scheme 1).

In a first series of experiments, we applied “standard reaction conditions” (toluene as solvent, NaO^tBu or KO^tBu as bases, ΔT , compare [5]) known from homogeneous systems in the coupling of 4-chloroacetophenone and piperidine. Using these parameters,



Scheme 1. Buchwald–Hartwig amination of aryl halides and secondary amines.

Table 1

Comparison of different supported transition metal catalysts in the amination of 4-chloroacetophenone and piperidine.

Entry	Catalyst	Cat. amount (mol%)	Conversion (%)	Yield (%)
1	Pd/NaY	0.1	46	46
2	Pd/Cu/NaY	0.1 Pd, 0.1 Cu	21	16
3	Cu/NaY	1	18	14

Reaction conditions: 10 mmol 4-chloroacetophenone, 21 mmol piperidine, 6 mL NMP, 140 °C, 6 h.

Pd/NaY led to complete dehalogenation of the aryl chloride and no formation of the desired coupling product was observed.

Screening of several solvents revealed that *N*-methylpyrrolidone (NMP), which is known as a common solvent in several other coupling reactions, was most suitable. Interestingly, due to the basic properties of NMP addition of a base could be renounced. Using 0.1 mol% of Pd/NaY a yield of 46% 4-piperidylacetophenone was observed after 6 h at 140 °C without formation of any byproduct. Cu/NaY and a mixed Pd/Cu/NaY catalyst showed a significantly lower performance (Table 1).

Obviously, in this reaction system Cu is an inhibitory component. Variation of the amount of Pd/NaY from 0.001 to 1 mol% showed only a slight influence on the product yield. Beller et al. reported on the necessity of LiBr addition to convert activated aryl chlorides with palladacycles [46]. LiBr showed also a promoting effect in the presented system. Conversion of the aryl halide and yield of the coupling product could be enhanced with increasing LiBr amount. In presence of 12 mmol of the additive, a conversion of 75% yielding 74% of target 4-piperidylacetophenone was achieved after 6 h at 140 °C (Fig. 1). The role played by this additive in the palladium-catalyzed amination is still not clear today. As for all other C–C and C–N cross-coupling reactions (although we did not perform specific experiments), we assume that the reactions are catalyzed by soluble palladium or copper species resulting from leaching. This assumption is supported by the strong inhibiting effect observed when adding Cu/NaY as catalyst to the palladium-catalyzed reaction. In that case, the best explanation regarding the role played

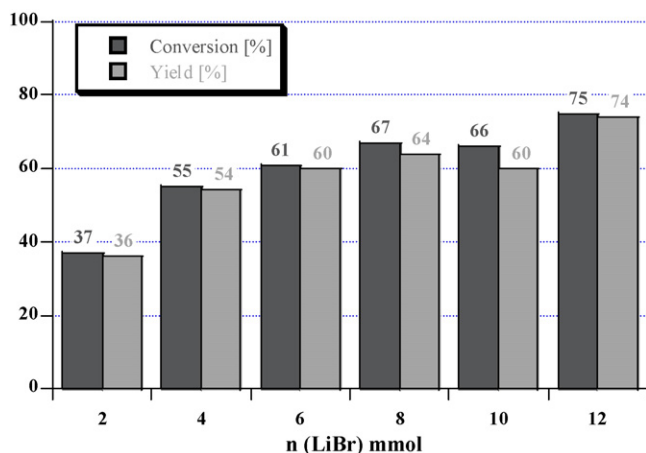


Fig. 1. Influence of LiBr on the Pd-catalyzed amination of 4-chloroacetophenone and piperidine. Reaction conditions: 10 mmol 4-chloroacetophenone, 21 mmol piperidine, 6 mL NMP, 6 h, 140 °C, 0.1 mol% Pd/NaY, LiBr as additive.

by LiBr is its role in stabilizing the dissolved Pd species in solution [47–49]. However, we cannot exclude that LiBr alone promotes the coupling reaction through the S_NAr mechanism as outlined below.

The reaction procedure described for the coupling of 4-chloroacetophenone was not effective for the amination of non- and deactivated aryl chlorides (chlorobenzene, 4-chlorotoluene, and 4-chloroanisole). Therefore our efforts focused on alternative, transition metal free procedures.

3.2. Transition metal free aminations

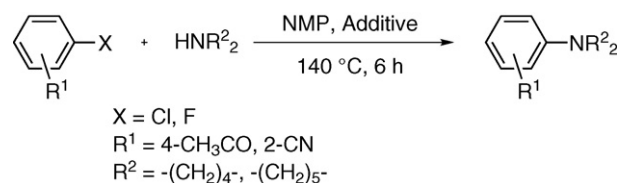
3.2.1. Activated aryl halides

Transition metal free amination reactions of aryl halides represent an important area in the pharmaceutical industry. For example, one of the key steps in the synthesis of fluoroquinolone antibacterials/antimicrobials is the selective amination of activated fluoroarenes [50,51]. However, most of these reactions gave limited isolated yields (<60%); therefore, developing new protocols for the transition metal free amination of aryl halides represents an attractive area which might be interesting for both academic and industrial chemists.

Initially, the reaction of 4-chloroacetophenone with piperidine was used to evaluate the applicability of the transition metal free protocol (Scheme 2). The reaction was unsuccessful under the reaction conditions usually described in the literature (toluene as solvent, KO^tBu as base, 135 °C). Modifications of the procedure, i.e. using NMP as solvent, no base and 2.1 equiv. secondary amine, gave high conversions (up to 70%). In the presence of LiBr as a promoter, the conversion of the 4-chloroacetophenone was increased up to 82%.

Comparing the Pd-catalyzed and the transition metal free amination of 4-chloroacetophenone at different temperatures under standard reaction conditions (1 equiv. LiBr, 2.1 equiv. amine/aryl halide, NMP), it was found that below 80 °C no reaction occurs, independently of the presence or absence of a Pd catalyst. As expected, an increase of the reaction temperature increased the conversions (Fig. 2). The slight enhance in product yields (<10%) observed at 160 °C compared to that at 140 °C did not justify such an increased consumption of energy; therefore 140 °C was set as the standard temperature for the following experiments. Below 160 °C, no differences in conversions were observed between the two protocols suggesting that the Pd-catalyst does not play a determining role in the amination reaction under these conditions. However, at 160 °C a slight increase of conversion is observed in presence of palladium catalyst. This observation supports that leaching of palladium species into solution occurs, as expected, in particular at increased reaction temperatures. In all reactions, the selectivity toward the expected product was 100%.

According to previous reports, we postulated that the LiBr used in those experiments promotes efficiently the amination reaction, encouraging us in evaluating other promoting agents (Fig. 3). As expected, all alkali halides promote the amination reaction, however, not as good as the LiBr does, suggesting that the activation of the 4-chloroacetophenone toward the amination results from the combination of the lithium and the bromide. Using LiOH as a co-base increased the conversion significantly (up to 97%).



Scheme 2. Amination of activated aryl halides.

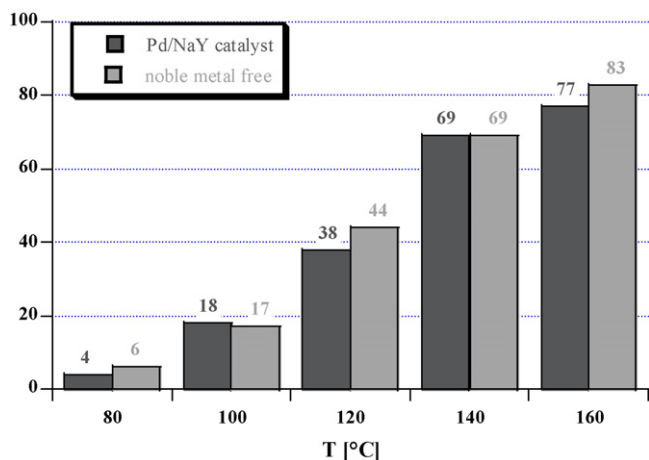


Fig. 2. Influence of the reaction temperature on the Pd-catalyzed and transition metal free amination. Reaction conditions: 10 mmol 4-chloroacetophenone, 21 mmol piperidine, 10 mmol LiBr, 6 mL NMP, 6 h.

Interestingly, the reactivity of aryl halides under these reaction conditions follow the reverse order than that usually reported for the Pd-catalyzed reactions: $F > Cl > Br$ (Table 2). Experiments monitoring conversion versus time showed that the reaction rate of 4-fluoroacetophenone is clearly higher than that of 4-chloroacetophenone. 50% of the initial 4-fluoroacetophenone was converted over 50 min whereas only 25% of the corresponding aryl chloride gave the expected amine (Fig. 4). Such differences in reactivity were equally observed by measuring the initial reaction rate for both substrates under strictly identical reaction conditions: 0.5 mmol/min for 4-fluoroacetophenone and 0.03 mmol/min for 4-chloroacetophenone.

Such variations of reactivity were also observed for other substrates (Table 2). While the aryl fluorides gave a complete conversion within 6 h, the corresponding aryl chlorides gave only 80% conversion, except for 2-chlorobenzonitrile that led to a limited conversion of 42%. These results are in good agreement with a reaction mechanism by nucleophilic aromatic substitution.

While the mechanism of these transition metal free coupling reaction is actually not yet fully understood, the high selectivity observed for the coupling reactions can be attributed to electronic factors. Actually, a great difference of reactivity was observed depending on the addition of LiBr as a promoter in the reaction media. While the reaction of 4-chloroacetophenone with pyrrolidine

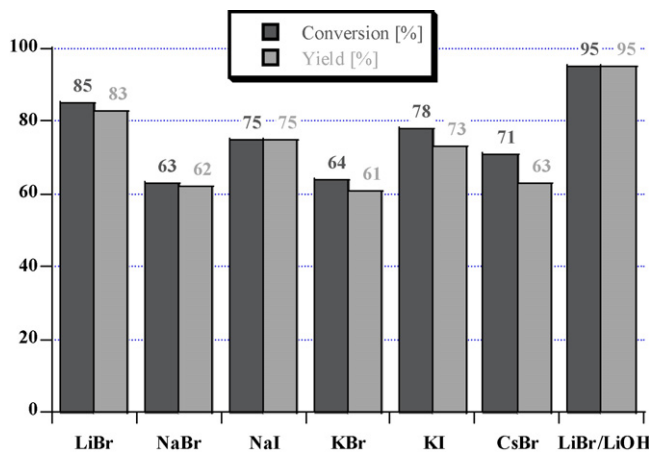


Fig. 3. Transition metal free amination of 4-chloroacetophenone und pyrrolidine using different additives. Reaction conditions: 10 mmol 4-chloroacetophenone, 21 mmol pyrrolidine, 10 mmol additive, 6 mL NMP, 6 h, 140 °C.

Table 2
Transition metal free amination of activated aryl halides.

Entry	Aryl halide	Amine	Conversion (%)	Yield (%)
1			61	60
2			81 ^a	80 ^a
3			82 ^a	80 ^a
4			42 ^a	38 ^a
5			100	100
6			100	100
7			100	100
8			100	100

Reaction conditions: 10 mmol aryl halide, 21 mmol amine, 6 mL NMP, 140 °C, 6 h.

^a 10 mmol LiBr were added as promoter.

dine gave 63% conversion within 6 h when 1 equiv. LiBr was added, only 30% conversion was achieved in absence of promoter. This observation can be reasonably explained by the coordination of the lithium cation to the carbonyl group of the 4-chloroacetophenone, resulting in an activation through resonance structures of the nucleophilic aromatic substitution at the *ipso*-position of the chloride atom by the secondary amine (Scheme 3). Such activation was not

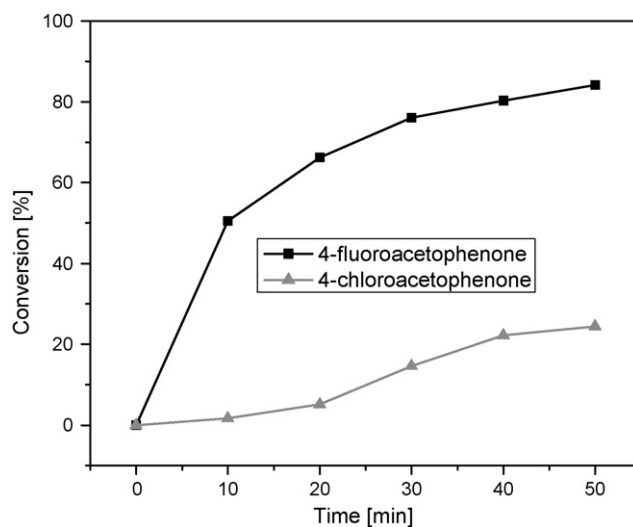
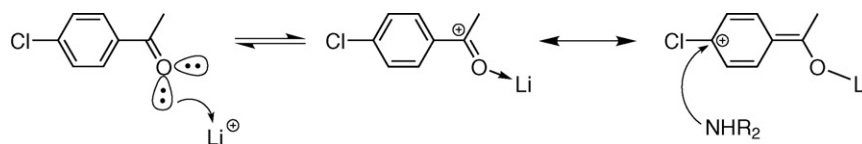
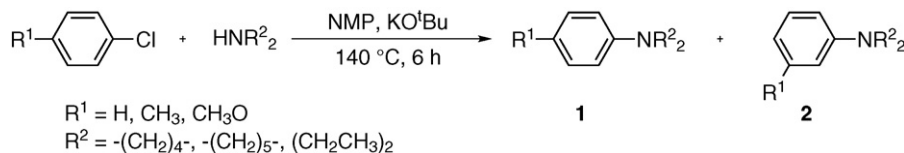


Fig. 4. Kinetic investigation of the reaction of 4-fluoro- and 4-chloroacetophenone with piperidine. Reaction conditions: 10 mmol aryl halide, 21 mmol piperidine, 6 mL NMP, 140 °C.



Scheme 3. Proposed mechanism for the activation of 4-chloroacetophenone by LiBr.



Scheme 4. Amination of non- and de-activated aryl halides.

observed using 2-chlorobenzonitrile which is reasonable, because a coordination of the lithium cation is not possible at this substrate.

All these results can be expected when considering the generally reported S_NAr mechanism, for which the rate-limiting step is the nucleophilic attack at the positively charged carbon atom of the C–X bond. The rate of the reaction increases with decreasing electron density at the aromatic system, which correlates with increasing electronegativity of the halogen ($F > Cl > Br$). In addition, coordination of Li ions to the aromatic compound either at the ring or its substituents (acetyl group) leads to a lowered electron density and, thus, activates the substrate.

3.2.2. Non- and deactivated aryl halides

While trying to extend the transition metal free protocol to other aryl halides, we discovered that the reaction conditions described above were not applicable to non- or deactivated aryl chlorides, like chlorobenzene, 4-chlorotoluene or 4-chloroanisole. For these substrates, the use of a strong base, i.e. KO^tBu , was found to be essential to achieve high conversions (Scheme 4, Table 3).

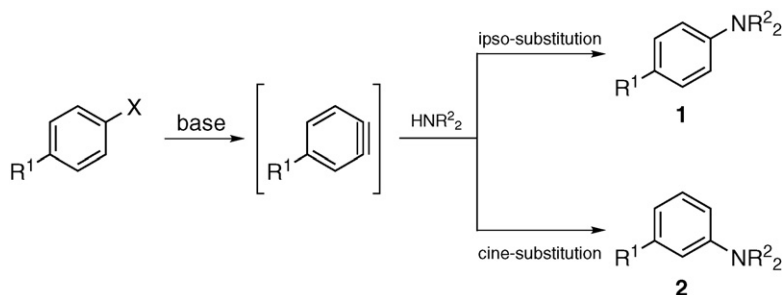
Compared to the other procedure described above, the most reasonable explanation for this base dependence is given by the so-called “aryne mechanism” proposed by several authors for similar amination reactions (Scheme 5) [52]. According to this mechanism, an aryne intermediate is generated by the base-induced elimination of the halogen atom. In the next step, the nucleophilic addition of the amine takes place at this aryne intermediate. Since the nucleophilic attack of the amine is possible at both carbon atoms of the triple bond a product mixture should be expected, leading either to the *ipso*-substitution or alternatively, to the *cine*-(*ortho*)-substitution. After optimization of the reaction conditions (NMP, 1.2 equiv. KO^tBu , 140°C), all non- and deactivated aryl chlorides reached up to 80% conversion within 6 h at 140°C , independent of the secondary amine used. While 100% selectivity towards the *cine*-(*ortho*)-substituted product was achieved for the coupling reaction of 4-chlorotoluene with piperidine, pyrrolidine or *N,N*-diethylamine, the amination of 4-chloroanisole resulted in a 50:50 product mixture of the *cine*-(*ortho*)- and *ipso*-substituted corresponding aryl amines (Table 3).

Table 3

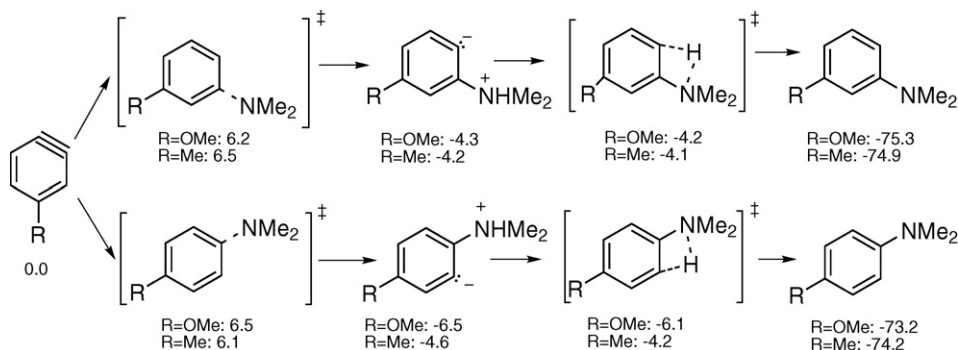
Transition metal free amination of non- and deactivated aryl halides.

Entry	Aryl halide	Amine	Conversion (%)	Yield 1 (%)	Yield 2 (%)
1			82	82	
2			78	78	
3			73	73	
4			65	65	0
5			62	62	0
6			63	63	0
7			75	38	37
8			76	38	38
9			73	36	37

Reaction conditions: 10 mmol aryl halide, 21 mmol amine, 12 mmol KO^tBu , 6 mL NMP, 140°C .



Scheme 5. "Aryne mechanism" for base-dependent substrates.



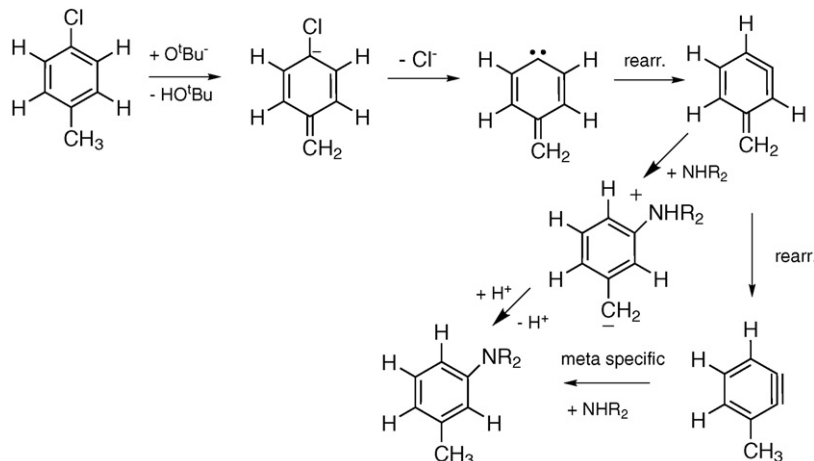
Scheme 6. DFT-results for the free energies (ΔG in kcal/mol) of the *para* and *meta* addition of dimethyl amine to the corresponding benzyne intermediate (B3LYP/6-31G*)—relative to benzyne and amine.

In order to explain these surprising selectivities, DFT calculations were performed to look for the corresponding energies of the aryne mechanism (Scheme 5). As selectivity is only induced during the second step; i.e. addition of the amine to the benzyne intermediate, we only looked at the transition states and the thermodynamics of the products in relation to the benzyne intermediate. Dimethyl amine was used as the model amine compound. Scheme 6 shows the occurring points on the potential energy hypersurface when adding the amine to the benzyne via a two-step zwitterionic mechanism that separates the addition of the amine and the hydrogen transfer to the aryl.

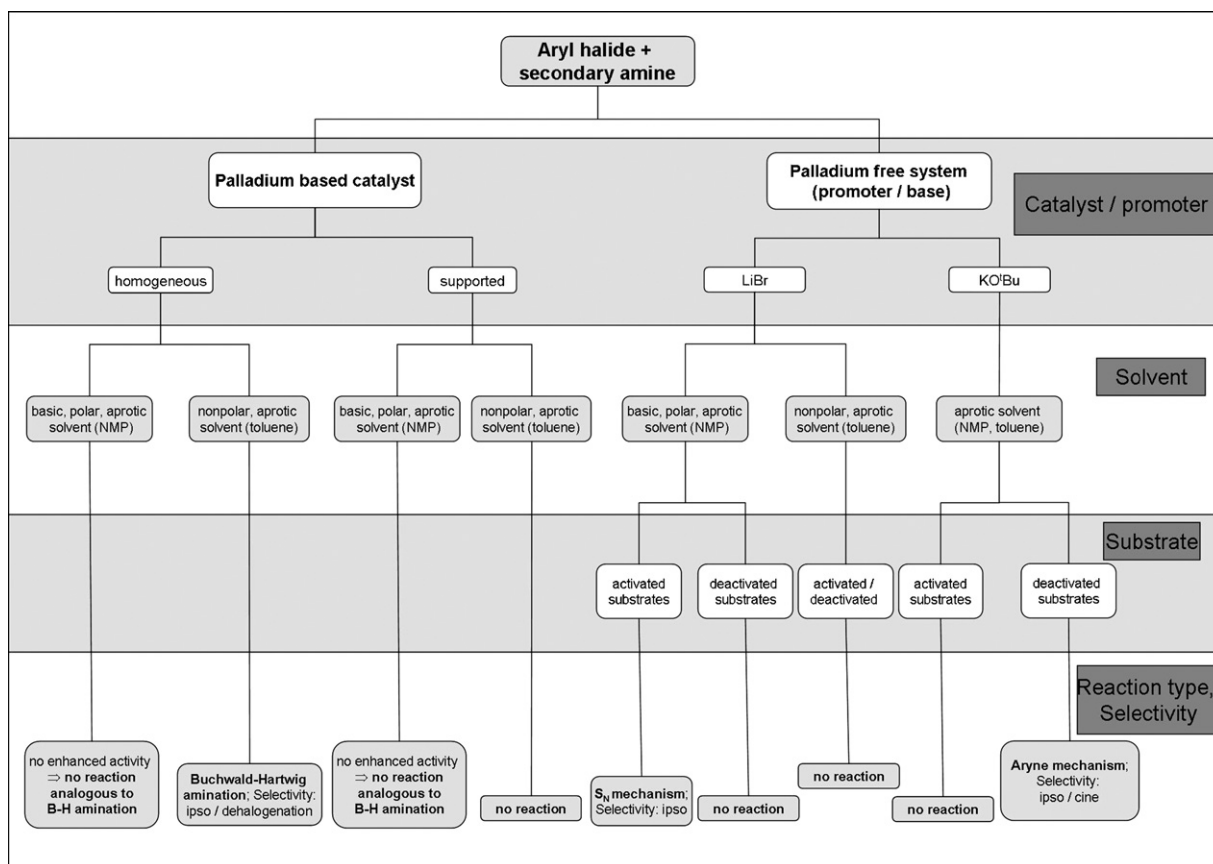
As can be seen from Scheme 6, there are no huge energetic differences for both substituents R (OMe or Me) in the calculated reaction barriers or the thermodynamical data of the zwitterions or the aminated products. Therefore, the aryne mechanism should be

unselective as expected. But with respect to the experimental data, this is only true for R = OMe. For R = Me the selective addition of the amine to the *meta* position of the toluene (*cine* substitution with respect to the leaving group) cannot be explained via the textbook benzyne mechanism.

A nucleophilic aromatic substitution via an addition–elimination mechanism can be ruled out because the main product is not the *ipso*-substituted isomer. Therefore a rearrangement has to occur before, after, or during the dechlorination. This rearrangement might involve even C–H activation at the benzylic position due to the basic conditions in order to increase the size of the π -conjugation system, which should not be possible at the anisole compound. Scheme 7 shows a postulation of such a mechanism as one possible explanation. Also a radical mechanism in combination with



Scheme 7. Possible rearrangement mechanism to explain the surprising regioselectivity at the amination of 4-chlorotoluene (based on possible C–H abstractions according to pK_a values).



Scheme 8. Flowchart comparing and summarizing relevant parameters (catalysts, promoters, and solvents) and reaction types (mechanisms) for alternative approaches to amination reactions of different substrates investigated in the present paper.

the aryne mechanism as observed by Bunnett and Kim [53–55] might be feasible. More investigations on these mechanisms are necessary and in progress.

3.3. Survey of the different reaction pathways

Scheme 8 presents a flowchart summarizing the most important findings of this study and shall help the reader to get the general idea of different reaction pathways for amination reactions under specific reaction conditions (catalyst, promoters, and solvent). Aryl halides can be converted in presence of palladium-based catalysts as well as under transition metal free conditions. The right choice of reaction conditions is crucial. Depending on the chosen parameters, amination proceeds via different reaction pathways, which lead to different product selectivity.

In presence of palladium, substrates show different reactivity depending on the nature of the Pd catalyst (homogeneous or heterogeneous). Choice of the solvent can also affect the system. Supported Pd catalysts do not promote amination reactions under standard conditions (nonpolar, aprotic solvents, like toluene) for homogeneous catalysts. This might be explained by the fact that no highly active, soluble Pd species can be generated by dissolution from solid catalysts in toluene.

If the amination reaction is performed in polar, basic solvents, like NMP, the reaction obviously occurs via transition metal free pathways, regardless of addition of noble metal based catalysts. Presumably, activation of aryl halides in amination reactions is not possible on Pd surfaces. This is in accordance with observations made for Heck reactions in presence of heterogeneous catalysts [48].

Beside conventional Pd-catalyzed coupling reactions, direct amination (transition metal free) is feasible using different promoters. Lithium bromide was found to promote nucleophilic substitution reactions (S_N; leading selectively to *ipso*-substituted aryl amines) of activated aryl halides in NMP, e.g. by additional activation of 4-chloroacetophenone in presence of Li⁺ ions (see **Scheme 3**). As expected, this type of reaction could not be observed for non- or deactivated substrates (like chlorobenzene, 4-chloroanisole or 4-chlorotoluene) or in toluene solution (limited solubility of LiBr).

Use of strong inorganic bases, like potassium *tert*-butoxide, in stoichiometric amounts permits transition metal free amination of deactivated substrates. Under these reaction conditions, formation of aryne intermediates has been observed in various solvents [29]. Arynes are highly reactive towards nucleophilic amines, which results in formation of aryl amines. Resulting products can be either *ipso*- or *cine*-substituted aryl amines, because nucleophilic attacks of the amine can happen at both of the carbon atoms of the triple bond (see **Scheme 5**).

4. Conclusions

We presented an application of supported Pd and Cu catalysts for amination reactions of aryl chlorides. These heterogeneous catalysts are air stable, easy to separate from the product and active in low concentrations (0.1 mol%). The resulting reaction system is simple; no organic ligands are required to stabilize the noble metal and addition of a base can be renounced due to the basic properties of the solvent and the excess amine.

As an alternative to noble metal-catalyzed aminations we have presented two new transition metal free protocols. We have shown

that specific reaction conditions are required for reactions of activated and deactivated aryl halides respectively. Direct amination of activated aryl chlorides and fluorides is possible by nucleophilic substitution. The promoting effect of LiBr in reactions of 4-haloacetophenones can be explained by an additional activation of the C–X bond by mesomeric structures. In contrast to that, conversion of deactivated aryl chlorides occurs obviously via an aryne mechanism. In this case, presence of a strong base (KO^tBu) is required to form an aryne intermediate which is reactive towards the amine.

Depending on the aromatic substitution pattern, surprisingly high selectivities occur during the metal-free amination protocol. The underlying mechanism is not yet clear. We presented three different pathways for the preparation of tertiary amines. Due to the different reaction mechanisms, the right choice of reaction conditions is crucial for realization of the different routes.

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