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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-chloroacetohphenone 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 substitutents at the aromatic ring on selectivity in metal free aminations found in this work.

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 $[P(o\text{-}C_6H_4Me)_3]_2PdCl_2$ 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 $Pd_2(dba)_3$/BINAP intimately admixed with KF-alumina for the amination of aryl bromides [22]. Recently, Kiil and co-workers presented the use of FibreCat™ catalysts (i.e. $Pd(OAc)_2$ 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 $[Pd(NH_3)_4]^{2+}$/NaY (1 wt% Pd), $[Cu(NH_3)_4]^{2+}$/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 ($\Delta_{rel} = \pm 5\%$).

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,