

Palladium catalyzed amination of vinyl chlorides: a new entry to imines, enamines and 2-amino-1,3-butadienes

José Barluenga,* M. Alejandro Fernández, Fernando Aznar and Carlos Valdés

Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Oviedo, 33071, Spain. E-mail: Barluenga@uniovi.es; Fax: 34 985103450; Tel: 34 985103450

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Vinyl chlorides are employed for the first time in palladium catalyzed cross-coupling reactions with amines to furnish imines and enamines. The new methodology has been applied to the synthesis of 2-amino-1,3-butadienes, that could not be achieved from the corresponding bromides.

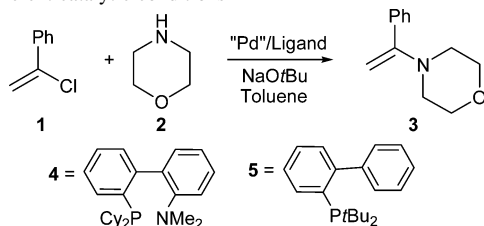
The palladium-catalyzed cross-coupling of aryl halides with amines (Buchwald–Hartwig reaction) has emerged during the last decade as a very powerful tool for the synthesis of aryl amines.¹ In contrast to the considerable effort devoted to the development of this transformation, its application to the analogous vinyl halides has been scarcely studied. We and others, have reported recently that the palladium catalyzed amination of vinyl bromides represents a very efficient method for the synthesis of imines and enamines,^{2,3} versatile intermediates in organic synthesis. To the best of our knowledge, the analogous cross-coupling reactions with vinyl chlorides remain unexplored.

Chlorides are generally poor reagents for metal catalyzed cross-couplings,⁴ however, they are usually more easily available and also more stable than the corresponding bromides and iodides. For these reasons, the incorporation of chlorides as partners in cross-coupling processes is currently an area of great interest.^{5,6} In this communication we report our preliminary results in the cross-coupling of vinyl chlorides with amines.

We chose as a model to develop proper reaction conditions the coupling of 1-chlorostyrene **1** with morpholine **2**. An array of reactions exploring the influence of different ligands and reaction conditions were carried out and a summary of the results is represented in Table 1.

The reactions were carried out in toluene, in the presence of Pd(OAc)₂ or Pd₂(dba)₃, a phosphine ligand, and NaOtBu as base.

Table 1 Cross-coupling reaction of 1-chlorostyrene **1** with morpholine **2** under different catalytic conditions



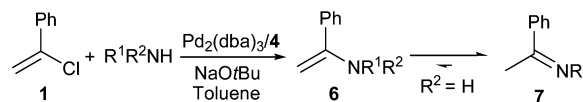
Entry	Pd source (%)	Ligand ^a	Time (h)	T (°C)	Conversion ^b (%)
1	Pd ₂ (dba) ₃ 2%	binap	6	90	80
2	Pd(OAc) ₂ 3%	binap	6	90	20
3	Pd ₂ (dba) ₃ 2%	dppf	6	90	50
4	Pd ₂ (dba) ₃ 2%	4	6	90	100 (96)
5	Pd ₂ (dba) ₃ 2%	xantphos	6	90	100 (92)
6	Pd ₂ (dba) ₃ 2%	5	6	90	50
7	Pd ₂ (dba) ₃ 1%	4	6	90	90
8	Pd ₂ (dba) ₃ 1%	xantphos	6	90	85
9	Pd ₂ (dba) ₃ 1%	4	20	rt	>5
10	Pd ₂ (dba) ₃ 1%	xantphos	20	rt	>5

^a A 1 to 2 molar relationship of Pd to ligand was employed. ^b Isolated yields are indicated in brackets.

All the ligands tested promoted the reaction to some extent at 90 °C, however, only xantphos and 2-cyclohexylphosphino-2'-dimethylaminobiphenyl **4**⁷ provided complete conversion. In fact the catalytic system Pd₂(dba)₃ (2 mol%)/**4** (4 mol%) at 90 °C resulted in the best combination for this coupling giving rise to a nearly quantitative yield of the enamine **3**. A decrease in the amount of catalyst led to a decrease in the conversion and no reaction was observed at room temperature. The optimized procedure was applied to a variety of secondary amines to furnish the corresponding enamines **6** (Scheme 1, Table 2).

Excellent conversions and yields were achieved for cyclic amines such as morpholine, *N*-methylaniline, and *N*-methylbenzylamine (entries 1–3). However, the increase of the size of the substituents diminishes dramatically the conversion of the reaction (entries 4 and 5).

The reaction proceeds also with primary amines to furnish the imines **7** after the enamine–imine tautomerism. Both aromatic and aliphatic substituted amines participated in the reaction success-



Scheme 1 Synthesis of enamines **6** and imines **7** by cross-coupling of 1-chlorostyrene with secondary and primary amines respectively.†

Table 2 Enamines **6** and imines **7** prepared†

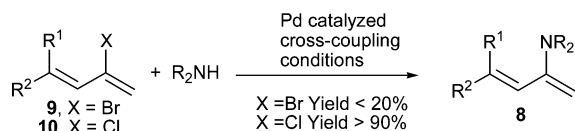
Entry	Amine	Time ^a (h)	Product	Yield ^b (%)
1	Morpholine	6	Enamine 6	96
2	<i>N</i> -Methylaniline	6	Enamine 6	94
3	<i>N</i> -Methylbenzylamine	6	Enamine 6	96
4	<i>N</i> -Ethylbenzylamine	10	Enamine 6	50 ^c
5	2-Amino-1,3-butadiene	6	Enamine 6	52 ^c
6	4-Amino-2-methoxyaniline	3	Imine 7	86
7	2-Chloro-4-aminoaniline	6	Imine 7	90
8	4-Chloro-2-aminoaniline	6	Imine 7	91
9	2-Amino-1,3-butadiene	3	Imine 7	92
10	4-Amino-2-methoxyaniline	3	Imine 7	94

^a Reaction times are not optimized. ^b Isolated yields. ^c Determined by GC.

fully. Not surprisingly, and as a result of the reduced steric requirements, the reactions with primary amines usually required shorter reaction times to reach completion. It is worth noting the higher reactivity of vinyl chlorides when compared to aryl chlorides. As showed in entries 7 and 8, the imine is the only product formed and no aryl amination product is detected. This is an interesting observation that may have applications in the design of cascade or sequential cross-coupling events.

A particularly interesting class of enamines are 2-amino-1,3-butadienes **8**. However, and in spite of their synthetic usefulness as dienes in cycloaddition processes,⁸ very few methods have been developed for their preparation.⁹ We envisioned that the palladium catalyzed cross-coupling of amines with 2-halodienes could represent a new alternative for their synthesis. The first attempts with 2-bromodiene **9**,¹⁰ afforded the coupling product with very low yields under several different reaction conditions. Apparently, decomposition of the bromodiene was taking place at a faster rate than the cross-coupling reaction itself. In fact, we also observed that 2-bromodienes decompose upon standing at room temperature after a few hours.

Nevertheless, when the reaction was carried out with 2-chlorodienes **10** under the reaction conditions showed above for vinyl chlorides, the desired 2-aminodienes **8** were obtained in nearly quantitative yield (Scheme 2, Table 3). Interestingly, the higher stability of the chloride, which usually makes their participation in



Scheme 2 Palladium catalyzed amination of 2-halo-1,3-butadienes.

Table 3 Cross-coupling reaction of 2-chlorodienes **10** with amines. Synthesis of 2-amino-1,3-butadienes **8**^{a†}

Chlorodiene	Amine	Product	Yield (%)
			94
			94
			95
			93
			95
			95

^a Reaction conditions: 1 equiv. of **8**, 1 equiv. of amine, 2 mol% of Pd₂(dba)₃, 4 mol% of **4**, 1.4 equiv. of NaOtBu, toluene 4 mL mmol⁻¹, 90 °C, 6 h.

cross-coupling reactions more difficult, seems to be critical this time for the success of the transformation!

In summary, we have described for the first time the cross-coupling reaction between amines and vinyl chlorides which represents a new entry into enamines and imines. Moreover, the additional value of the incorporation of vinyl chlorides to this process has been illustrated with the synthesis of 2-amino-1,3-butadienes, which could not be achieved with the more reactive but also more unstable bromides.

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Notes and references

† Typical experimental procedure for the amination of vinyl chlorides: A Schlenk flask under nitrogen atmosphere was charged with 2-dicyclohexylphosphino-2'-dimethylaminobiphenyl **4** (0.04 mmol, 4 mol%), Pd₂(dba)₃ (0.01 mmol, 2 mol%), sodium *tert*-butoxide (1.4 mmol) and toluene (4 mL). After 1 min the vinyl chloride (1 mmol) and the amine (1.1 mmol) were added under nitrogen and the flask was immersed in an oil bath and heated to 90 °C with stirring until the starting vinyl chloride had been completely consumed as judged by GC analysis (see Table 2 for reaction times, 6 h for aminodienes **8**). The mixture was allowed to cool to room temperature, taken up in dry hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure. The residue was redissolved in dry hexanes (15 mL), filtered again through Celite, concentrated under reduced pressure and dried under high vacuum to remove the excess of amine, to afford a residue which consisted of the essentially pure enamine, imine, or 2-amino-1,3-butadiene. Depending on the boiling point, the enamines can be purified by Kugelrohr distillation under high vacuum.

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