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Novel method for the synthesis of enamines by palladium catalyzed amination of alkenyl bromides

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The intermolecular palladium catalyzed cross-coupling reaction between secondary amines and alkenyl bromides is described for the first time, giving rise to enamines with very high yields and regioselectivity.

Enamines are valuable intermediates in organic synthesis. They have been extensively employed as nucleophiles in Michael type additions, and also as intermediates in the synthesis of heterocycles, dienes and dienophiles in cycloaddition reactions, precursors of chiral amines upon asymmetric transformations and intermediates in natural product synthesis.[1]

The classical approach for the synthesis of enamines is the condensation of a secondary amine with a carbonyl compound, usually under mineral or Lewis acid catalysis.[2] However, this method presents several limitations, such as harsh reaction conditions, lack of regio- and chemoselectivity, and low functional group tolerance. Alternative methods for the synthesis of enamines are hydroaminations of alkynes[3] and methylenation of amides.[4]

On the other hand, in recent years, great interest has been devoted to the development of metal catalyzed cross-coupling reactions of aryl halides with amines. In particular, the parallel and concurrent efforts of the groups of Hartwig and Buchwald have led to the development of a very efficient palladium catalyzed reaction for the creation of C–N bonds from amines and aryl halides and pseudohalides (Fig. 1).[5] Over the last years, these two research groups and others have fine-tuned the catalytic system, allowing this type of transformation to be performed under very mild conditions and with a variety of coupling patterns.

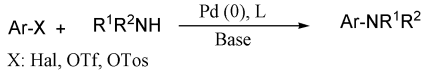


Fig. 1 Palladium catalyzed cross-coupling of amines with aryl halides.

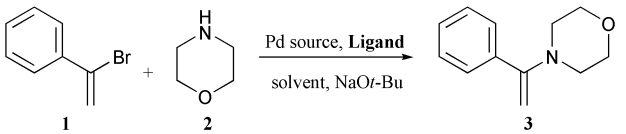
The application of the same cross-coupling reaction to alkenyl halides would furnish imines or enamines. However, this reaction has been scarcely studied. To the best of our knowledge, the palladium catalyzed intramolecular cyclization of a β-lactam and a vinyl bromide reported by Mori recently in a synthesis of carbapenems remains as the unique example of the Buchwald–Hartwig reaction involving a vinyl halide.[6]

For many years, we have been engaged in the study of the synthesis and applications of simple and cross-conjugated enamines (2-amino-1,3-butadienes). Several years ago, we disclosed the amination of terminal acetylenes catalyzed by thallium or mercury salts.[3] However, this method requires the use of toxic metal salts, and sometimes the purification of the resulting enamines is difficult. Nevertheless, the enamines resulting from the aminomercuration reaction are very versatile synthetic intermediates, for instance as dienes in cycloaddition reactions[7] and as chameleon linkers in solid-phase organic synthesis.[8] For these reasons, in an attempt to devise new strategies for the synthesis of enamines, we decided to explore the application of the Buchwald–Hartwig amination reaction to alkenyl halides.

We chose as a model system the reaction of α-bromostyrene **1** with morpholine **2** in the presence of a palladium species and examined different ligands which have been shown to generate active catalysts in the amination of aryl halides: P(*o*-Tol)$_3$,[9] (±)-BINAP,[10] DPPF,[11] DCPDAB (= 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl)[12] and P(*t*-Bu)$_3$.[13] All the reactions were carried out in toluene and using 1.5 equivalents of NaO*t*-Bu as base (Scheme 1).

Good results were obtained for most ligands, since the reaction proceeded with complete conversion and the enamine **3** was isolated as a pure material from the reaction crud (Table 1). The Pd(0)/BINAP system was also successful with different palladium sources† and with lower catalyst loading (0.5%) but failed to react at very low concentrations of catalyst (0.05%). Moreover, the reaction proceeded to completion even at 40 °C (entry 9), but furnished very little conversion at room temperature. Interestingly, no particular improvement was obtained in the rt reaction when the biphenyl derived ligand DCPDAB or the bulky electron rich P(*t*-Bu)$_3$ were used, although these systems promote the room temperature amination of aryl bromides. Therefore, given the good performance of the Pd(0)/BINAP system we decided to study the scope of the reaction of this catalytic system with other amines and alkenyl bromides (Scheme 2, Table 2).

The reactions were conducted at 90 °C in toluene and with 1% Pd unless otherwise indicated, and the results are summarized in Table 2 (Scheme 2). Excellent results were obtained for cyclic and acyclic aliphatic amines, and also for the aromatic substituted *N*-methylaniline with different substituted alkenyl bromides. In all cases the enamines **6** were isolated as pure compounds (as judged by ^{1}H and ^{13}C NMR) after dilution with



1 **2** **3**

Scheme 1 Palladium catalyzed cross-coupling of morpholine **2** with α-bromostyrene **1**.

Table 1 Formation of enamine **3** under different catalytic conditions

Entry	Pd source, %	Ligand[b]	*t*/h	*T*/°C	Conv.[a] (%)
1	$Pd_2(dba)_3$, 1%	P(*o*-Tol)$_3$	6	90	100 (78)
2	$Pd_2(dba)_3$, 1%	BINAP	6	90	100 (96)
3	$Pd(OAc)_2$, 1%	BINAP	6	90	100 (91)
4	$Pd_2(dba)_3$, 1%	DPPF	6	90	100 (69)
5	$Pd_2(dba)_3$, 1%	DCPDAB	6	90	100 (95)
6	$Pd_2(dba)_3$, 1%	P(*t*-Bu)[d]	6	90	100 (85)
7	$Pd_2(dba)_3$, 0.5%	BINAP	6	90	100 (69)
8	$Pd_2(dba)_3$, 0.05%	BINAP	6	90	< 1
9	$Pd_2(dba)_3$, 1%	BINAP	6	40	100 (89)
10	$Pd_2(dba)_3$, 1%	BINAP	6	20	22
11	$Pd_2(dba)_3$, 1%	DCPDAB	16	20	19[c]
12	$Pd_2(dba)_3$, 1%	P(*t*-Bu)[d]	6	20	2

[a] Determined by analysis of the ^{1}H NMR spectra of the reaction crud. Isolated yields are indicated in parentheses. [b] A 1:2 molar relationship of Pd:ligand was employed. [c] Reaction run in DME as solvent. [d] A 1:0.8 molar relationship of Pd:ligand was employed.

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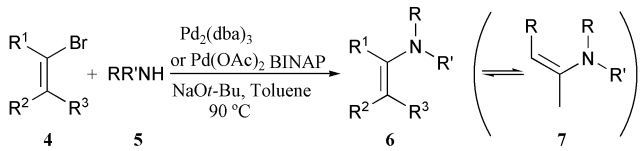
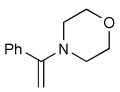
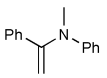
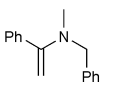
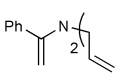
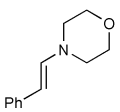
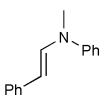
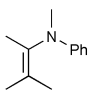
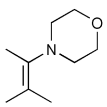
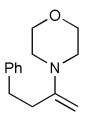
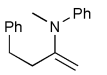


4 5 6 7

Scheme 2 Synthesis of enamines **6** by amination of alkenyl bromides **4**.

Table 2 Enamines **6** synthesized with the Pd(0)/BINAP system‡

Entry	Bromide	Amine	Pd source, %	*t*/h	Product	Yield[a] (%)
1			$Pd_2(dba)_3$, 1%	6		96 (74)
2			$Pd_2(dba)_3$, 1%	6		97 (65)
3			$Pd_2(dba)_3$, 1%	6		95
4			$Pd(OAc)_2$, 1%	12		75 (45)
5			$Pd_2(dba)_3$, 1%	6		95 (73)
6			$Pd_2(dba)_3$, 1%	6		96 (79)
7			$Pd(OAc)_2$, 1%	6		94 (81)
8			$Pd(OAc)_2$, 1%	6		91 (79)
9[b]			$Pd(OAc)_2$, 3%	0.5		86
10[c]			$Pd(OAc)_2$, 3%	1		90

[a] Based on the amount of pure material (by ^1H and ^{13}C NMR) isolated form the reaction crud. Isolated yields after high vacuum Kugelrohr distillation are indicated in parentheses. [b] Reaction run at 65 °C. [c] Reaction run at 80 °C.

hexanes and filtration through celite. This is an important feature, because due to the acid and water sensitivity of the enamine functionality, aqueous workup and conventional chromatographic techniques are not suitable for their purification.

Particularly challenging substrates are those derived from 2-bromopropene such as 2-bromo-4-phenyl-1-butene (entries 9 and 10). The product of the amination reaction of 2-bromo-4-phenyl-1-butene affords a terminal enamine **6**, which undergoes very easy isomerization to the more substituted internal enamine **7**. In fact, with the exception of some particular examples,[14] to the best of our knowledge, no general method for the preparation of these terminal enamines has been described. The regioselective synthesis of these enamines could be achieved by selecting carefully the reaction conditions. For instance, the reaction of 2-bromo-4-phenyl-1-butene with *N*-methylaniline under the standard reaction conditions (1% $Pd(OAc)_2$, BINAP, 80 °C, 6 h) gives rise to a 1 : 2 mixture of the terminal and the internal enamines. However, by reducing the reaction time to 1 h (which required the increase in the amount of catalyst to 3% in order to achieve complete conversion)§ (entry 10) the desired terminal enamine was isolated without formation of the internal isomer **7**. For the morpholine case (entry 9) the isomerization was avoided by running the reaction at lower temperature (65 °C) for 30 min and again with higher (3% Pd) catalyst loading.

In summary, we have reported the first palladium catalyzed cross-coupling reaction of amines with vinyl halides, which represents a novel method for the regioselective preparation of enamines. Studies regarding the scope and applications of this reaction, as well as a more comprehensive coverage of ligands and potential substrates, are currently being carried out in our laboratory and will be reported in due course.

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Notes and references

† The reactions with the $Pd(OAc)_2$/BINAP system were carried out by preforming the catalyst as described by Buchwald *et al*. in ref. 10.

‡ *Typical experimental procedure for the amination reaction*: A Schlenk flask under nitrogen atmosphere was charged with $Pd_2(dba)_3$ (0.005 mM, 1% Pd), (±)-BINAP (0.015 mmol), NaO*t*-Bu (1.5 mmol), 5 mL of dry toluene, 1 mmol of alkenyl bromide and 1 to 1.1 mmol of amine. The reaction was stirred at 90 °C for 6 h and then allowed to cool to room temperature. The mixture was diluted with 30 mL of dry hexanes and filtered through celite. The solvents were evaporated 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. Depending on the boiling point, the enamines can be purified by Kugelrohr distillation under high vacuum (10^{-3} Torr).

§ Longer reaction times resulted in a mixture of both enamines, for instance when the reaction was carried out with 2% Pd for 2.5 h at 80 °C a 3 : 1 mixture of terminal : internal enamines was obtained. Moreover, the terminal enamines undergo isomerization upon standing at room temperature, therefore, if they were going to be employed in a subsequent reaction, they should be used immediately after their synthesis.

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