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Efficient palladium–ferrocenylphosphine catalytic systems for allylic amination of monoterpene derivatives

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Ferrocenylphosphines added to $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ dimeric precursor produce efficient catalysts to effect the allylic amination of terpenic allylacetates. Particularly convenient are tetrakis(diphenylphosphino)ferrocene and 1,1′-bis(diphenylphosphino)ferrocene, which allow the amination of allylacetates with good to excellent selectivity, and have turnover numbers as high as 80 000, for instance, for the formation of allylaniline. Herein, we report on reactions that selectively transform geranylacetate, nerylacetate, linalylacetate and perillylacetate into the corresponding allylic amines. These preparative methods give facile access to various products of great potential industrial interest. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: allylic amination; monoterpenes; ferrocenylphosphine; palladium catalysis

INTRODUCTION

A large number of biologically active natural compounds consist of a nitrogen-containing heterocycle and occupy a leading position in medicinal therapy.[1,2] The direct synthetic procedures for amine synthesis, such as nucleophilic substitutions of organic halides by amines, cyanides or more generally by nitrogen-containing products, result in the co-production of abundant quantities of salts. In the general context of atom economy and sustainable chemistry, a base-free catalytic approach is particularly appropriate to convert plentiful starting materials such as alcohols or acetates.[3–6]

In the course of our studies on monoterpenes and their oxygenated derivatives which are of much interest in perfumery, for artificial flavoring and in the pharmaceutical industry, we previously showed a chemoselective way to produce lactones from different monoterpenic alcohols through palladium-catalyzed tandem carbonylation.[7] With a view to extend the potential use of these naturally occurring alkenes, we focused our efforts on the amination of those containing an allylic function in order to have a direct access to lactames from allylic amines, as depicted in Fig. 1, with the cyclocarbonylation of geranylamine.

Phosphorus-containing palladium complexes furnish efficient catalytic systems to allow access to unsaturated amines by allylic substitution.[8–10] It has been proved that key intermediates such as (η^3-allyl)palladium complexes are involved in amine alkylations, and that the phosphine ligands exert a profound influence on the reaction rate. Recent studies have shown that multidentate ligands, such as the tetraphosphine ligand tetrakis(diphenylphosphino)cyclopentane,[11–13] combined with palladium provide suitable systems for allylic amination with high turnover numbers (TON) and good rates. The present study is devoted to the investigation of catalytic allylic amination, in which the palladium precursor is stabilized by di-, or tetraphosphine ligands incorporating the ferrocenyl framework. To date, only a few investigations of the performances in allylic substitution of this type of polydentate ligands have been reported in the literature.[11–13] Our results

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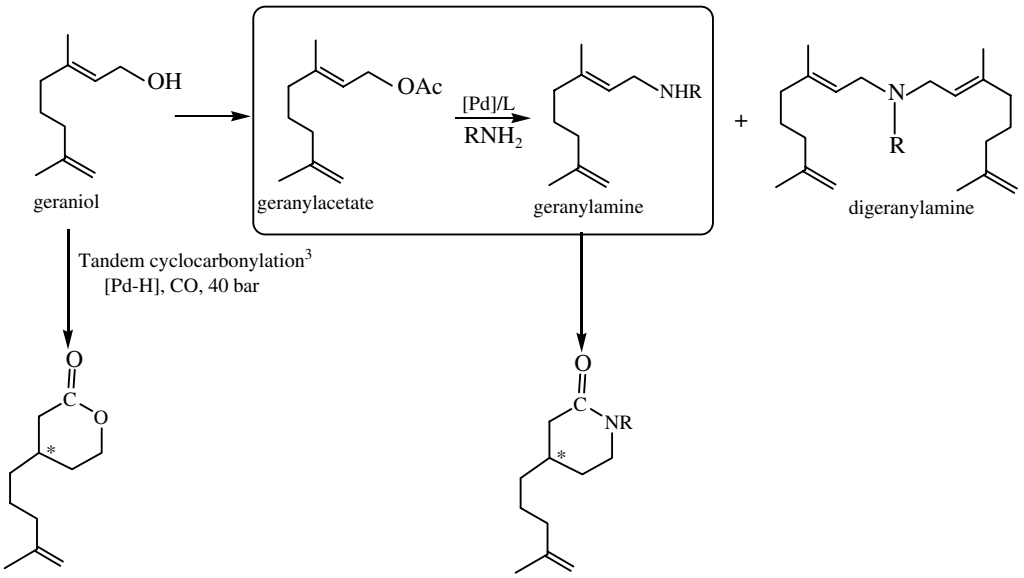

Figure 1. Synthetic routes to amine, lactone and lactame monoterpene derivatives.

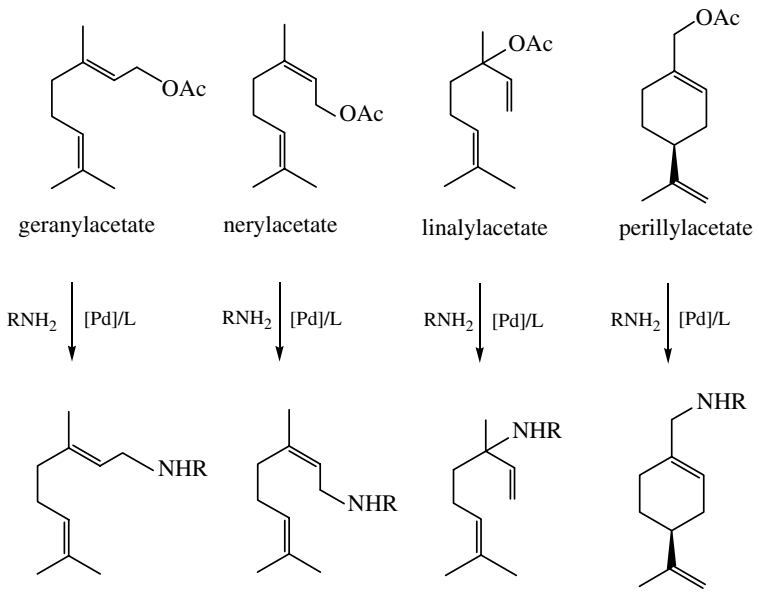

Figure 2. Monoterpenic derivatives and their corresponding amines after allylic amination reaction.

show that the 1,1′-bis(diphenylphosphino)ferrocene, and to some extent the 1,1′,2,2′-tetrakis(diphenylphosphino)-4,4′-di-*ter*-butylferrocene ligand, combined with palladium, perform the conversion of representative monoterpenic acetates (see Fig. 2) into the corresponding allylic amines with a good to excellent selectivity and high turnover numbers.

RESULTS AND DISCUSSION

To identify a suitable catalytic system for the allylic amination of the demanding substrates that are monoterpene derivatives,[14] we firstly examined the activity of the selected Pd–ligand systems for the coupling of allylacetate with aniline. The catalytic systems were generated by addition of polyphosphine ligands to the $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ dimeric complex. Considering the relevant results obtained by Doucet and Santelli when the tetraphosphine ligand tetrakis(diphenylphosphino)cyclopentane is employed,[11–13] we introduced into the palladium coordination sphere the tetradentate ligands 1,1′,2,2′-tetrakis(diphenylphosphino)-4,4′-di-*ter*-butylferrocene, **1** and 1,1′,2,2′-tetrakis(diphenylphosphino)-3,3′-4,4′,5,5′ hexamethylferrocene, **2** (depicted in Fig. 3).

In **1** and **2**, each cyclopentadienyl ring holds a pair of chelating -PPh_2, and two *tert*-butyl or six methyl substituents are present on the cyclopentadienyl rings of the ferrocenyl

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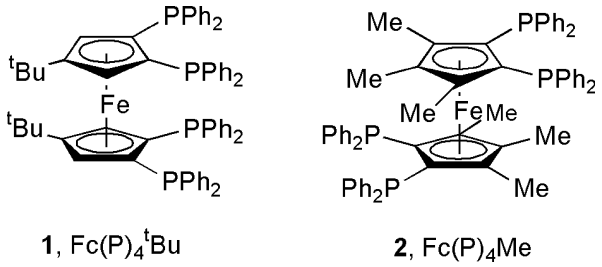

Figure 3. Ferrocenyl tetraphosphines $Fc(P)_4{}^tBu$, **1**, and $Fc(P)_4Me$, **2**.

backbone. These two original tetradentate metalloligands have been described, and have been shown by Hierso and coworkers to be remarkable auxiliary ligands, highly active in palladium-catalyzed C–C cross-coupling and Heck reactions.[15–17] In addition, one of our concerns, related to atom economy and sustainable chemistry, is to optimize the reaction conditions in the absence of inorganic bases as co-reagents, and to use the highest substrate to catalyst ratio (S : C) possible. To prevent the formation of diallylicderivatives, we introduced two equivalents of aniline to allylic acetate.

Study of the performances of Pd–1 and Pd–2 in the amination of allylacetate

From the reaction of allylacetate with aniline, a complete conversion in *N*-allylaniline was obtained, employing either the Pd–**1** or the Pd–**2** system in a molar ratio of substrate to catalyst S : C = 100 [see Fig. 4(a)].

However, as soon as the amount of catalyst was reduced, some dramatic differences in the reaction rate and in the conversion yields were noted. For instance, at S : C = 500 the conversion was almost complete after 18 h in the presence of ligand **1**, whereas only 60% conversion was obtained in the mean time from the system incorporating ligand **2** [Fig. 4(a)]. The system Pd–**1** still presents a good catalytic activity for higher dilutions; indeed when a ratio S : C = 10 000 was employed, an ongoing conversion was still observed after 40 h, with a selectivity in *N*-allylaniline maintained at 97% [Fig. 4(b)]. Thus for 0.01 mol% of $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ (0.02 mol% of Pd) and 2 equivalents of **1** ([**1**] : Pd = 1) the turnover number reached 3100 per metal atom, i.e. a high value for a primary amine. In reference 11 a TON of 2800 in 20 h at room temperature is reported employing the very active tetraphosphine Tedicyp in allylacetate coupling to phenylethylamine; conversely, employing the Pd–**2** system at a ratio S : C = 10 000, the conversion was lowered to only 5% after 40 h. At such low concentration, the stability of the catalytic system Pd–**1** appeared superior. Such a difference in the performances is presumably not due to the relative basicity of the two phosphine ligands; the electron-donicity of three methyl groups on each cyclopentadienyl or of one *tert*-butyl substituent is not expected to be so decisive. A more significant difference lies in the structural properties of the two ligands. As previously indicated concerning ligand **1**,[15,16]

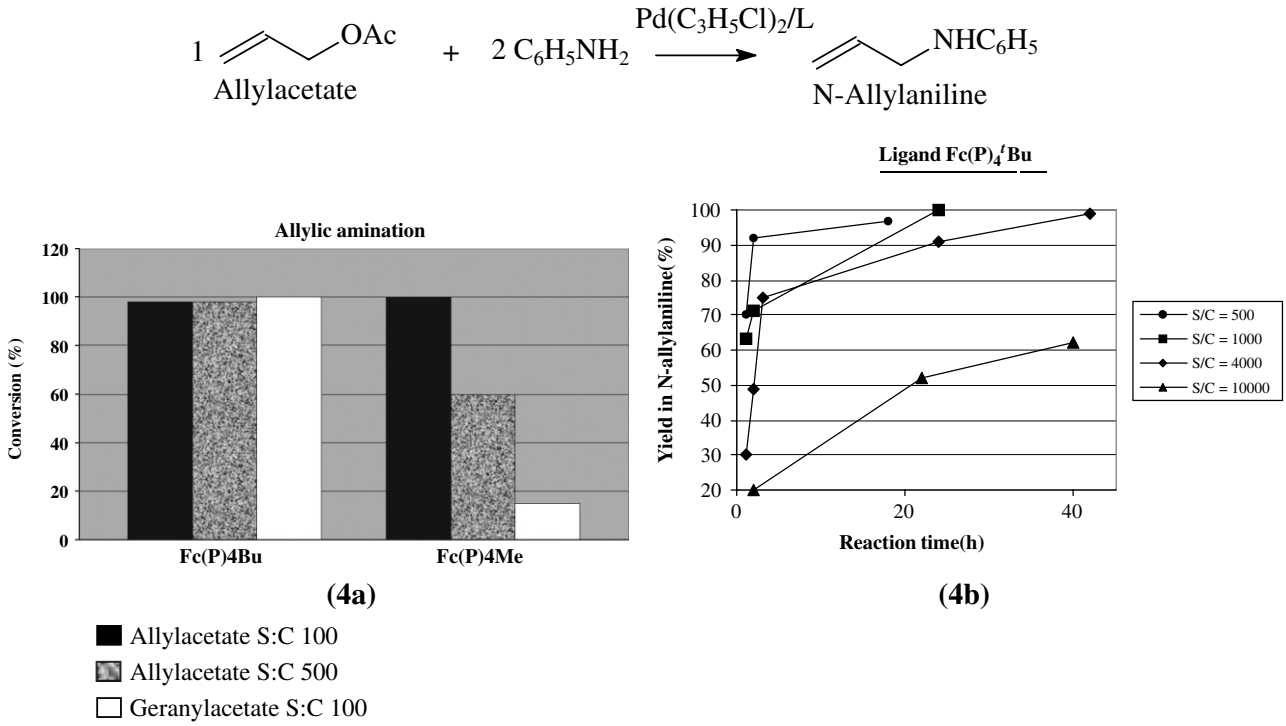

Figure 4. (a) Conversion in allylaniline and geranylaniline in the presence of ferrocenyl tetraphosphine $Fc(P)_4{}^tBu$ and $Fc(P)_4Me$. (b) Conversion in allylaniline from different ratio S : C in the presence of $Fc(P)_4{}^tBu$.

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the steric hindrance of the two *tert*-butyl groups maintains a restricted rotation of the cyclopentadienyl rings in a cisoid blocked conformation, for which the four phosphorus atoms point towards the same direction (see Fig. 3). Thus, ligand **1**, contrary to **2** (where the homoannular phosphorus pairs face opposite directions due to the unrestricted rotation of the Cp rings), might provide three or four of its phosphorus atoms to coordinate palladium.[16] The ligand **1** conformation, which is conserved in solution above 90 °C, would ensure a high coordination number to the metal center, the stability of the catalytic system at low concentration being increased on a longer period of time.

Performances of Pd–1 in amination of monoterpene acetates

The relative reactivity of the palladium–catalytic systems generated from **1** and **2** was somewhat confirmed by the results of the amination of geranylacetate with aniline [Fig. 4(a)]. Geranylacetate is quantitatively converted into geranylaniline at 40 °C employing Pd–**1** at S : C = 100 (78% selectivity in 16 h, see Table 1, entry 1). In presence of Pd–**2** the conversion yield is poor (12% in 16 h and 42% in 4 days, the selectivity decreasing below 60% due to an isomerization process). Some other amines, as well as the allylic monoterpenes neryl-, perillyl- and linalylacetate, were tested. In addition to aniline (N_1), the primary amines benzyl- and butylamine (N_2 and N_3 respectively) and the cyclic secondary amine, morpholine (N_4), were introduced. Since the conversion of geranylacetate using the system Pd–**2** gave deceptive results, we focused our attention on ligand **1**, and Table 1 is exclusively concerned with the Pd–**1** system.

Upon reaction under ambient conditions of geranylacetate with benzylamine and butylamine, no reaction occurred (entry 2). To fully convert the substrate, a temperature of 80 °C for 12 h was necessary (entry 3). In the case of the coupling from morpholine N_4 to geranylacetate (entry 4) interesting performances were achieved: at a ratio S : C = 500, 95% conversion was obtained in 7 h with a 95% selectivity into geranylmorpholine (5% of nerylmorpholine was formed due to an isomerisation process). At lower loadings of catalyst the conversion was poor, whatever the temperature (2% conversion at S : C = 10 000 in 20 h, entries 5 and 6). The harsh conditions required depending on the nature of the primary amine (N_1 is more easily converted than N_2 and N_3) is certainly related to the catalytic cycle. As both a nucleophilic attack of the amine on a palladium–allyl intermediary species and elimination of acetic acid in the medium are involved, the reactivity of the incoming amine could much depend on a subtle difference between its nucleophilic character and its basicity.

The amination of nerylacetate employing morpholine at ambient temperature (at S : C = 500), resulted in a 94% conversion yield in 18 h, for which 66% of nerylmorpholine is obtained (entry 7). In addition, a competing isomerization process led to the formation of 17% of geranylmorpholine and 17% of linalylmorpholine. Starting from linalylacetate (S : C = 1 000, entry 8) the same amination proceeds at room temperature more rapidly since the substrate is fully converted within 30 min, however with a rather poor selectivity. The distribution of isomeric products includes only 11% of linalylmorpholine for 47% of geranylmorpholine and 42% of nerylmorpholine. Using a ratio S : C = 10 000, the rate of the reaction significantly decreased (entries 9 and 10, 70% conversion after 23 h). A total conversion was obtained in 48 h, the distribution of isomers observed previously being conserved along the reaction. Obviously, after the formation of the palladium-allyl intermediary species, the nucleophilic attack of the amine on the allylic carbon C_3 is sterically and electronically disfavored in comparison to the attack on the

Table 1. Results of allylic amination reaction catalyzed by the Pd-**1** system

Entry	Substrate	Amine	S : C	*T* (°C)	*T* (h)	Conversion (%)	Selectivity[a] (%)
1	Geranylacetate	N_1	100	40	16	100	78
2		N_2	100	RT	12	—	—
		N_3	100	RT	12	—	—
3		N_2	100	80	12	100	100
		N_3	100	80	12	100	100
4		N_4	500	40	7	95	95[b]
5		N_4	10 000	40	20	2	100
6				80	20	2	100
7	Nerylacetate	N_4	500	RT	18	94	66 (17, 17)[c]
8	Linalylacetate	N_4	1 000	RT	0,5	100	11 (47, 42)[d]
9		N_4	10 000	RT	23	70	5 (38, 27)[d]
10		N_4	10 000	RT	48	100	9 (47, 44)[d]
11	Perillylacetate	N_1	100	40	45	100	73[b]

Catalytic conditions : catalyst $[Pd(ally)Cl]_2$–FcP_4tBu (1 : 2), toluene, acetate : amine (1 : 2 equiv.). [a] Yields in brackets concern the isomeric product ratio. [b] Unidentified secondary products were formed. [c] Geranyl- and linalylmorpholine were formed, respectively. [d] Geranyl- and nerylmorpholine were formed, respectively.

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allylic carbon C_1 due to the presence of the methyl group on C_3.

The amination of perillylacetate, a cyclic allylic monoterpene, required longer reaction times for a full conversion (45 h at 40 °C, at S : C = 100, entry 11) but gave a much better selectivity of 73%. A competitive migration of the endocyclic double bond is probably at the origin of the slight decrease in selectivity.

To conclude on this part, the palladium–tetraphosphine ligand system Pd–**1** at 5×10^{-1} to 10^{-2} mol% low loadings allow conversion in high yields, and mostly good selectivity, of allylacetates into the corresponding allylic amines. Monoterpene acetate derivatives have been used with success for the first time in these reactions, opening the way for further exploration of terperne functionalization. Our study shows that aniline (N_1) and morpholine (N_4) appear as the less demanding amine substrates for these allylic substitutions.

Pd–1,1′-bis(diphenylphosphino)ferrocene system in amination of monoterpene acetates

We were interested in comparing the catalytic activity of ligands **1** and **2** to the related bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene **3** (dppf), a commercial ligand of easy access. Table 2 displays salient results obtained with dppf, **3**, for the amination of allylacetate with aniline (entries 12–20).

These experiments have been conducted to check the performances and the limitations of dppf as auxiliary ligand in allylic substitution. The reaction can be conveniently performed under ambient conditions, and shows very good selectivity. For a S : C ratio of 100 the conversion into the corresponding allylaniline is complete in 1 h (total selectivity, entry 12). The reaction rate decreases in the absence of solvent (yield 98% in 6 h, selectivity 91%, entry 13) or in water (yield 84% in 60 h, selectivity 79%, entry 14); this is presumably due to mass transfer limitations. The substrate to catalyst ratio can be substantially increased (entries 15–20). At ratio S : C = 500, 1000, 5000, 10 000 and even 100 000, high conversions are reached in 2–70 h. Complete conversions with yields of expected product above 90% are obtained at $500 \leq S:C \leq 10\,000$ (entries 15–18). In the highly diluted experiment carried out at S : C = 100 000, a conversion of 84% is obtained (the selectivity in the expected allylaniline being 95%) in 70 h (entry 20), resulting in an impressive TON of 80 000 and a turnover frequency of 1150 h^{-1}. In the absence of solvent the coupling gives a 78% conversion with a 89% selectivity in 120 h (yield of *N*-allylaniline 69%, entry 19).

As satisfactory results were obtained with allylacetate as model substrate, we further explored the amination of geranylacetate. At room temperature geranylacetate reacts with aniline to yield 82% of geranylaniline in 25 h (98% selectivity, entry 21); raising the temperature to 40 °C allows transformation of 98% of the starting material in 1 h with a 96% selectivity in geranylaniline (entry 22). When the S : C ratio is increased to 500 the overall rate decreases (a conversion of only 36% was obtained in 2 h, entry 23); however, heating at 80 °C gives a total conversion in 5 h with a good selectivity of 90% (entry 24). For a ratio S : C = 1000,

Table 2. Results of allylic amination reaction catalyzed by the Pd-**3** system

Entry	Substrate	Amine	S : C	*T* (°C)	*T* (h)	Conversion (%)	Selectivity[a] (%)
12	Allylacetate	N_1	100	RT	1	100	100
13		N_1[b]	100	RT	6	98	91 (89)[b]
14		N_1[c]	100	RT	60	84	79 (66)[c]
15		N_1	500	RT	2	98	97 (95)
16		N_1	1 000	RT	3	100	96
17		N_1	5 000	RT	20	100	95
18		N_1	10 000	RT	36	98	94 (92)
19		N_1[b]	10 000	RT	120	78	89 (69)[b]
20		N_1	100 000	RT	70	84	95 (80)
21	Geranylacetate	N_1	100	RT	25	82	98 (80)
22			100	40	1	98	96 (94)
23		N_1	500	40	2	36	75 (27)
24			500	80	5	100	90
25		N_1	1 000	80	17	99	94 (93)
26		N_2	100	40	17	57	40 (22)
27		N_4	100	40	0.5	100	95
28			1 000	80	0.5	100	95
29	Nerylacetate	N_1	100	RT	25	80	98 (78)
30	Perillylacetate	N_3	100	RT	25	58	95 (55)

Catalytic conditions: catalyst $[Pd(ally)Cl]_2$–dppf (1 : 2), toluene, acetate : amine (1 : 2 equiv.). [a] Yields in brackets are the overall conversion in expected product. [b] Solvent-less conditions. [c] In water solvent.

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still at 80 °C, the yield can be maintained at 99% (selectivity 93% in 17 h, entry 25).

With the view to evaluating the limitations of the Pd–**3** catalytic system, we conducted the amination of geranylacetate with benzylamine. At a ratio S:C = 100 the reaction appears difficult, since at 40 °C, only 57% conversion is obtained in 17 h with a 40% selectivity (23% of desired product, entry 26). In contrast, the catalytic system affords excellent performances for geranylacetate amination employing morpholine (entries 27 and 28); indeed the conversion is total within 30 min at 40 °C (S:C = 100) or at 80 °C (S:C = 1 000) with a high selectivity of 95%. These results are consistent with those obtained from the catalytic system Pd–**1**, for which the cyclic morpholine was easier to couple than the primary amines benzylamine and butylamine.

Finally, the amination of nerylacetate with aniline at ratio S:C = 100, affords a 80% conversion (with a 98% selectivity) in 25 h (entry 29), while perillylacetate is transformed into perillylbutylamine in a fairly good yield (58%) under similar conditions (with 95% of selectivity, entry 30).

CONCLUSION

An efficient methodology for the preparation of monoterpenic allylamines from catalytic systems combining a Pd(II) precursor and a ferrocenylphosphine ligand has been described. This preparative method, carried out under mild conditions of temperature, with low catalyst loadings and in the absence of inorganic base, satisfies the requirement of sustainable chemistry and atom economy. Moreover, it opens the way to a variety of valuable compounds since substrates such as allylacetate, geranylacetate, nerylacetate, perillylacetate and linylacetate have been successfully coupled with primary and secondary amines such as aniline, morpholine, benzylamine and butylamine. The investigation under convenient conditions showed that both dppf and the tetraphosphine **1** can be advantageously employed, owing to their robustness along reactions during several hours. In the contrary, the tetraphosphine **2** does not reach the performances observed from **1**, presumably due to structural properties. Finally, in the described reactions the commercially available dppf look attractive since high selectivity are observed together with excellent conversion yields.

EXPERIMENTAL

All manipulations were carried out under a nitrogen atmosphere. All the chemical products were purchased from commercial sources, except for the complex $[Pd(\mu\text{-}Cl)(\eta^3\text{-}C_3H_5)]_2$ and the tetraphosphine ligands, which were synthesized accordingly to methods previously reported.[18–20] All monoterpene acetates were prepared by classical esterification of corresponding allylic alcohol derivatives with acetic anhydride in pyridine.

General procedure

In a typical experiment, the mixture of acetate and amine (1 : 2 equiv.) in solution was added under nitrogen atmosphere to the solution containing the catalyst previously prepared by addition of 1 equivalent of palladium source and the ligand. The mixture was stirred at adequate temperature and follow up by GC analysis. After cooling, the reaction mixture was poured into aqueous 10% HCl solution and the organic products then extracted with ether. The organic layer was washed with a solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated. Column chromatography purification (silica gel, *n*-hexane–EtOAc, 5 : 1) afforded the pure product which was characterized by IR, ^1H and ^{13}C NMR. Yields (%) were calculated based on GC analysis with external standards.

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