

Arylation of β -methallyl alcohol catalyzed by $\text{Pd}(\text{OAc})_2$ in combination with $\text{P}(t\text{-Bu})_3$: application to fragrance synthesis

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Abstract

$\text{Pd}(\text{OAc})_2$ in combination with $\text{P}(t\text{-Bu})_3$ catalyzes the coupling of β -methallyl alcohol with 1-bromo-3,4-(methylenedioxy)benzene (**1a**), 1-bromo-4-methoxybenzene (**1b**), or 1-bromo-4-*tert*-butylbenzene (**1c**). The reaction affords the corresponding 2-methyl-3-aryl-propanals, which are valuable floral fragrances. With **1a** or **1b** high reaction rates are obtained at 130 °C using NMP/water mixtures and an inorganic base such as Na_2CO_3 . The chemoselectivity of the reaction is almost complete, so that the process appears practically feasible. In contrast, the coupling of β -methallyl alcohol with **1c** proceeds with low reaction rates.

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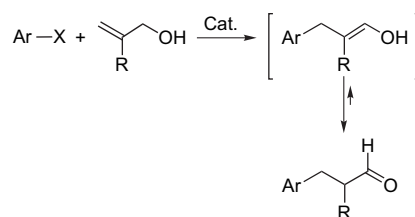
1. Introduction

The coupling of aryl halides with olefins (the Mizoroki–Heck reaction) has become one of the most important methods for the formation of carbon–carbon bonds and the reaction is widely applied both on the laboratory scale and in the fine chemical industry.^{1,2}

The continuously growing application of this reaction is connected to the availability of very efficient catalytic systems. Indeed in the last 10 years, great efforts have been made to improve the catalysis; nowadays a large variety of catalysts are at the organic chemist's disposal.^{1,3–5} Most commonly catalysis is carried out in the presence of soluble palladium species containing neutral ligands such as phosphines, heterocyclic carbenes, nitrogen, and sulfur donors.¹ Phosphorus, nitrogen, or sulfur containing palladacycles represent another class of efficient catalysts for the reaction.^{1,4} 'Ligand-free' palladium species appear particularly interesting for industrial applications owing to their high efficiency, simple preparation, and low cost.^{1,3,5} The use of non-conventional methodologies⁶ as well as the

use of water as the reaction solvent⁷ have also been recently reviewed.

Although in Mizoroki–Heck coupling the presence of a wide variety of functional groups is tolerated, the olefins mainly employed are alkenes bearing electron-withdrawing substituents such as acrylates and styrene, which are also usually used as model substrates for catalysts evaluation,¹ on the other hand, olefins bearing alcoholic functions are not commonly used as coupling reagents and their arylation has been far less investigated.⁸ As depicted in Scheme 1, the coupling of an aryl halide with a β -substituted allylic alcohol occurs according to a peculiar path since the 'expected' coupling product is an enol, which tautomerizes affording the corresponding β -arylated carbonyl derivative as the final coupling product.^{8,9}



Scheme 1.

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According to the process illustrated in Scheme 1, the arylation of β -methallyl alcohol with the appropriate aryl halide can be used to synthesize valuable compounds such as the floral fragrances Helional[®] (IFF), Lilial[®] (Givaudan), and Canthoxal[®] (IFF) (Fig. 1).

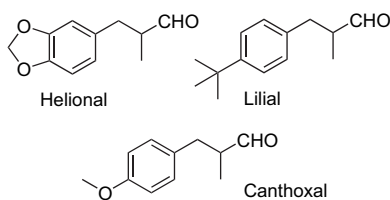
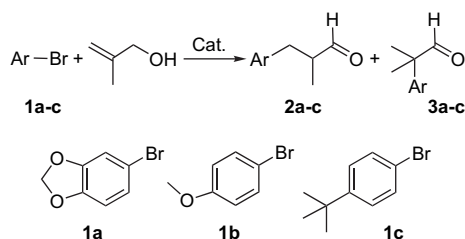


Figure 1.

The synthesis of these fragrances via coupling of the corresponding aryl iodides or bromides with β -methallyl alcohol has been patented as early as 30 years ago¹⁰ and, the Lilial synthesis, by coupling 1-*tert*-butyl-4-iodobenzene with β -methallyl alcohol, has been reinvestigated recently.¹¹ The results reported in these studies do not, however, appear promising for an industrial application owing to the relatively high catalyst loadings.

Spurred on by our continuing interest in the Heck reaction¹² and in fragrance synthesis¹³ we have revisited the coupling of β -methallyl alcohol with bromo-3,4-(methylenedioxy)-benzene (**1a**), 1-bromo-4-methoxybenzene (**1b**), or 1-bromo-4-*tert*-butylbenzene (**1c**) (Scheme 2) using some recently developed catalysts to assess the practical feasibility of a Heck reaction based approach to the synthesis of the floral fragrances shown in Figure 1. In Heck chemistry the question of 'what is the best catalyst and procedure' for a certain substrate can be unpredictable.^{1h}



Scheme 2.

2. Results and discussion

In order to delineate the best conditions for the process, we studied the reaction of 1-bromo-3,4-(methylenedioxy)benzene **1a** with β -methallyl alcohol; in fact **1a** is predicted to be a particularly challenging substrate owing to the concurrent presence of two deactivating EDG groups on the aromatic ring (Scheme 2).

Since our work was directed toward developing a practical synthesis of the sought fragrances, we have focused our attention on the use of some highly efficient catalysts that we selected on the basis of high activity, easy preparation, prompt availability of the precursors, and air stability. According to

Table 1
Influence of the nature of the catalyst on the coupling of **1a** with β -methallyl alcohol

Entry	Catalyst	Base	Conv. ^a (%)	2a ^{a,b} (%)
1	PdCl ₂ (PPh ₃) ₂	NaOAc	38	16
2	Pd(OAc) ₂ /DMG ^c	NaOAc	3	2
3	Pd ₂ (dba) ₃ /P(<i>t</i> -Bu) ₃ ^d	Cy ₂ NMe	42	34

Reaction conditions: *T*: 120 °C; *t*: 18 h; **1a**: 5 mmol; alcohol: 7 mmol; base: 14 mmol; Pd: 0.01 mmol; substrate/Pd=500:1; solvent: NMP (5 mL).

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts (<2%) of 2-benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde **3a** are formed.

^c DMG: *N,N*-dimethylglycine as promoter (DMG/Pd=20:1).

^d P(*t*-Bu)₃ added as [P(*t*-Bu)₃H]BF₄ (P/Pd=1:1 mol/mol).

this view, preliminary experiments were carried out employing, as the precatalysts, 'ligand-free' Pd(OAc)₂ stabilized with dimethylglycine¹⁴ or the system Pd₂(dba)₃/P(*t*-Bu)₃;¹⁵ the activity of these systems was compared under the same reaction conditions with that of PdCl₂(PPh₃)₂, which is the precatalyst used by Chalk.¹⁰ According to relevant data, which are presented in Table 1, it appears that **1a** is particularly deactivated, so that the reaction requires temperatures higher than 100 °C to proceed with promising rates. The selectivity of the reaction is not complete (the product distribution and yield were determined by GLC using naphthalene as the internal standard) and in all the experiments we observe the formation of variable amounts of by-products. Apart from aldehyde **3a** (Scheme 2), which is nearly always present, albeit in low amounts (<2%), the other by-products evolve by degradation of the dioxymethylene moiety. The amounts and the composition of these by-products depend on the nature of the catalyst, the solvent, the base, and the reaction conditions.

Among the catalysts tested, the Pd₂(dba)₃/P(*t*-Bu)₃ system developed by Fu¹⁵ turns out to be the most active and chemoselective. This result prompted us to investigate in more detail the use of this system, which is conveniently prepared in situ by combining Pd₂(dba)₃ (dba: dibenzylideneacetone) with 1 equiv of [(*t*-Bu)₃PH]BF₄ and Cy₂NMe;¹⁶ this latter accomplishes two functions, deprotonating the phosphonium salt to generate free P(*t*-Bu)₃ and acting as a scavenger of the hydrogen bromide, which forms during the reaction.

Experiments to optimize the reaction conditions unexpectedly reveal that the use of an inorganic base such as NaHCO₃ or Na₂CO₃ in combination with Cy₂NMe significantly increases the catalyst efficiency leading to an almost doubling of the reaction rate (compare entries 1 and 2 of Table 2). The role of the added inorganic base is likely to be ascribed to an enhanced capacity for scavenging hydrogen bromide; as a matter of fact, when a weak base such as NaOAc is used the promoting effect of the added base is strongly reduced (entry 4 of Table 2).

Pd(OAc)₂ can be used as a catalyst precursor instead of Pd₂(dba)₃ giving an equivalent catalytic system (entries 6–8 of Table 2). Indeed it has already been reported that Pd(OAc)₂ in combination with 3 equiv of P(*t*-Bu)₃ efficiently catalyzes the coupling of 4-bromoacetophenone with butyl acrylate.¹⁷

Table 2
Influence of the base on the coupling of **1a** with β -methallyl alcohol catalyzed by the Pd/P(*t*-Bu)₃ systems

Entry	Catalyst	P/Pd	Base	Conv. ^a (%)	2a ^{a,b} (%)
1	Pd ₂ (dba) ₃	1	Cy ₂ NMe	42	34
2	Pd ₂ (dba) ₃	1	Cy ₂ NMe/NaHCO ₃	93	79
3	Pd ₂ (dba) ₃	1	Cy ₂ NMe/Na ₂ CO ₃	95	80
4	Pd ₂ (dba) ₃	1	Cy ₂ NMe/NaOAc	37	28
5	Pd(OAc) ₂	1	Cy ₂ NMe	66	51
6	Pd(OAc) ₂	1	Cy ₂ NMe/NaHCO ₃	95	76
7	Pd(OAc) ₂	1	Cy ₂ NMe/Na ₂ CO ₃	98	83
8	Pd(OAc) ₂	1	Cy ₂ NMe/NaOAc	59	48
9	Pd(OAc) ₂	0	Cy ₂ NMe/NaOAc	35	18

Reaction conditions: *T*: 120 °C; *t*: 18 h; **1a**: 5 mmol; alcohol: 7 mmol; Cy₂NMe: 14 mmol; second base: 7 mmol; substrate/Pd=500:1; solvent: NMP (5 mL).

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts of aldehyde **3a** are formed.

Moreover, Pd(OAc)₂ in combination with P(*t*-Bu)₃ is an efficient catalyst for aryl bromides amination¹⁸ and Suzuki–Miyaura coupling.¹⁹

Since it is known that 'ligand-free' Pd(OAc)₂ is a good catalytic system for the Heck reaction,^{5b,5c,20} to confirm the role of the phosphine we have carried out a control experiment using Pd(OAc)₂ and Cy₂NMe in the absence of any P(*t*-Bu)₃ (entry 9 of Table 2): indeed the reaction proceeds, however, the substrate conversion is significantly lower than in the presence of P(*t*-Bu)₃.

Further experiments were carried out to evaluate the effect of the reaction temperature: the relevant data are collected in Table 3. To allow a better comparison between the results, the catalyst loading was reduced to a substrate/palladium ratio of 2000:1.

Table 3
Influence of the temperature on the coupling of **1a** with β -methallyl alcohol

Entry	<i>T</i> (°C)	Base	Conv. ^a (%)	2a ^{a,b} (%)
1	120	Cy ₂ NMe/NaHCO ₃	35	18
2	130	Cy ₂ NMe/NaHCO ₃	84	70
3	140	Cy ₂ NMe/NaHCO ₃	97	87
4	120	Cy ₂ NMe/Na ₂ CO ₃	45	30
5	130	Cy ₂ NMe/Na ₂ CO ₃	100	90

Reaction conditions: *t*: 18 h; **1a**: 5 mmol; alcohol: 7 mmol; Cy₂NMe: 14 mmol; second base: 7 mmol; Pd(OAc)₂: 0.0025 mmol; P/Pd=1:1; substrate/Pd=2000:1; solvent: NMP (5 mL).

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts (<2%) of aldehyde **3a** are formed.

An increase in the temperature has a positive effect both on the rate and the chemoselectivity of the reaction: the best results were obtained working at 130 °C in the presence of Cy₂NMe/Na₂CO₃. In keeping with this finding, all the following experiments were carried out at this temperature using selected bases.

In Table 4 are reported the data relevant to the coupling of **1a** with β -methallyl alcohol in various high boiling polar solvents.

Table 4
Coupling of **1a** with β -methallyl alcohol in different solvents

Entry	Solvent	<i>t</i> (h)	Conv. ^a (%)	2a ^{a,b} (%)
1	NMP	2	33	30
2	DMF	2	82	70
3	NMP	4	51	46
4	DMF	4	98	71
5	Cy ₂ NMe	4	70	44
6	DMSO	4	26	10

Reaction conditions: *T*: 130 °C; **1a**: 5 mmol; alcohol: 7 mmol; Cy₂NMe: 14 mmol; Na₂CO₃: 7 mmol; Pd(OAc)₂: 0.005 mmol; P/Pd=1:1; substrate/Pd=1000:1; solvent: 5 mL.

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts (<2%) aldehyde **3a** are formed.

Among the solvents tested, DMF appears distinctly the best as far as the substrate conversion is concerned; however, the chemoselectivity is relatively poor. A similar behavior is recognized also when the reaction is carried out in pure Cy₂NMe. Thus, NMP emerges as the most suitable solvent since it furnishes the highest chemoselectivities, although the reaction rate is significantly lower than in DMF.

The very high activity observed in DMF prompted us to further investigate its use in order to verify whether fine tuning of the reaction conditions could be possible.

A few experiments (Table 5) were carried with alteration of the base: as in NMP, Na₂CO₃, and NaHCO₃ behave similarly, while NaOAc gives unsatisfactory results. When only the inorganic base Na₂CO₃ was present (entry 5 of Table 5) the chemoselectivity increases significantly, but at the expense of the reaction rate.

Table 5
Influence of the base on the coupling of **1a** with β -methallyl alcohol in DMF

Entry	Base	<i>t</i> (h)	Conv. ^a (%)	2a ^{a,b} (%)
1	Cy ₂ NMe/NaOAc	2	14	8
2	Cy ₂ NMe/NaHCO ₃	2	81	67
3	Cy ₂ NMe/Na ₂ CO ₃	2	82	70
4	Cy ₂ NMe/Na ₂ CO ₃	4	98	71
5	Na ₂ CO ₃	2	15	10
6	Na ₂ CO ₃	24	100	86

Reaction conditions: *T*: 130 °C; **1a**: 5 mmol; alcohol: 7 mmol; Cy₂NMe: 14 mmol; second base: 7 mmol; Pd(OAc)₂: 0.005 mmol; P/Pd=1:1; substrate/Pd=1000:1; solvent: DMF (5 mL).

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts (<2%) of aldehyde **3a** are formed.

As mentioned before, the enhancing effect of the inorganic bases on the reaction rate is likely due to improved hydrogen bromide abstraction action; in keeping with this hypothesis, we thought it interesting to investigate if it were possible to increase the catalyst efficiency by adding some water to the reaction medium: the presence of water should increase the solubility of the inorganic base and favor removal of HBr.²¹

Indeed, we found that the addition of 10–20% (v/v) of water to NMP gives higher reaction rates and has a significant effect on catalysis (Table 6). The experiments in fact highlight a peculiar behavior: in pure NMP the presence of Cy₂NMe and

Table 6
Coupling of **1a** with β -methallyl alcohol in NMP/H₂O mixtures

Entry	Solvent (H ₂ O %)	1a /Pd	<i>t</i> (h)	Base	Conv. ^a (%)	2a ^{a,b} (%)
1	NMP	1000	4	Cy ₂ NMe/Na ₂ CO ₃	51	46
2	NMP	1000	4	Na ₂ CO ₃	25	23
3	NMP/H ₂ O (20)	1000	4	Cy ₂ NMe/Na ₂ CO ₃	59	53
4	NMP/H ₂ O (20)	1000	4	Na ₂ CO ₃	92	77
5	NMP/H ₂ O (10)	1000	4	Na ₂ CO ₃	85	70
6	NMP/H ₂ O (20) ^c	20,000	24	Cy ₂ NMe/Na ₂ CO ₃	32	23
7	NMP/H ₂ O (20) ^c	20,000	24	Na ₂ CO ₃	88	59

Reaction conditions: *T*: 130 °C; **1a**: 5 mmol; alcohol: 7 mmol; Cy₂NMe: 14 mmol; Na₂CO₃: 7 mmol; Pd(OAc)₂: 0.005 mmol; P/Pd=1:1; substrate/Pd=1000:1; solvent: 5 mL.

^a Conversions and yields were determined by GLC using naphthalene as internal standard.

^b Low amounts (<2%) of aldehyde **3a** are formed.

^c Pd: 0.00025 mmol.

Na₂CO₃ leads to a substantial increase in both the substrate conversion and the yield; instead when NMP/H₂O mixtures are employed the presence of the amine reduces the reaction rate. Unfortunately, the reaction rate enhancement, which occurs using NMP/H₂O mixtures is accompanied by some reduction in chemoselectivity. In fact, the use of higher percentages of water (data not reported in Table 6) leads to unacceptable chemoselectivities. The promotional effect of added water is also observed when the reaction is carried out using higher substrate/catalyst ratios (entries 6 and 7).

In order to verify if the process could be of industrial interest, we have carried out a set of reactions at different catalyst concentrations. The reactions were performed under the same conditions adopted in entry 4 of Table 6, the only difference being the reaction time, which was increased to 24 h (Table 7).

Table 7
Influence of the P(*t*-Bu)₃/Pd ratio on the coupling of β -methallyl alcohol with various substrates

Entry	Substrate	Sub./Pd (mol/mol)	P/Pd	Conv. ^a (%)	2a–c ^{a,b} (%)	TOF ^c (h ⁻¹)
1	1a	1000	1/1	93	68	40
2	1a	8000	1/1	83	62	280
3	1a	20,000	1/1	88	59	730
4	1a	10,000	2/1	100	90	420
5	1a	20,000	2/1	44	43	370
6	1a	50,000	2/1	19	18	390
7	1a	50,000	3/1	12	4	250
8	1b	10,000	1/1	90	88	370
9	1b	50,000	1/1	54	52	1120
10	1b	50,000	2/1	50	50	1040
11	1c	1000	1/1	33	30	10
12	1c	1000	2/1	25	23	10

Reaction conditions: *T*: 130 °C; *t*: 24 h; substrate: 5 mmol; alcohol: 7 mmol; Na₂CO₃: 7 mmol; solvent: 5 mL of NMP/H₂O (80:20).

^a Conversions and yields were determined by GLC with naphthalene as internal standard.

^b Low amounts (<2%) of aldehydes **3a–c** are formed.

^c Turnover numbers per hour.

Using a **1a**/catalyst ratio of 8000:1, a good conversion (83%) was achieved after 24 h and in comparison with the experiments listed in Table 5 only a modest decrease in chemoselectivity was noticed. This result prompted us to further increase the **1a**/

palladium ratio to 20,000:1. Quite surprisingly, even at this low catalyst loading, a 88% conversion is obtained in 24 h.

This result is intriguing because considering the turnover frequency numbers (TOFs: turnover numbers per hour, column 7 of Table 7) obtained in these experiments it appears that the catalyst activity increases as the substrate to catalyst ratio increases. This type of dependence of the catalytic activity on the substrate/catalyst ratio is not rare in Mizoroki–Heck reactions and according to the literature^{1h,5b,20} it indicates that the catalysis is due to palladium colloids.

Since the catalytic system is prepared by combining Pd(OAc)₂ and P(*t*-Bu)₃ in the 1:1 ratio, the formation of ligandless palladium nanoparticles implies the formation of some [Pd(P(*t*-Bu)₃)₂], a fairly stable palladium(0) complex.²² Since this latter complex, although inactive at room temperature, becomes very effective at high temperatures,¹⁵ the observed catalytic activity is likely due to the contemporary action of different species. Otherwise, it is possible that the formation of ligandless palladium species is due to some degradation of P(*t*-Bu)₃ so that the observed catalysis might be attributed to a combination of a monoligated 'PdP(*t*-Bu)₃' species and colloidal palladium.

In keeping with these speculations, we thought it interesting to investigate the influence of the P(*t*-Bu)₃/Pd(OAc)₂ molar ratio on the reaction.

The use of 2 equiv of phosphine per palladium (entries 4–6 of Table 7) has a significant effect on the catalysis. By comparing the data in entries 3 and 5 (both referring to experiments carried out with a substrate/catalyst ratio of 20,000:1) it appears that doubling the amount of the phosphine, the reaction rate is approximately halved; on the other hand, the chemoselectivity of the reaction increases considerably and becomes almost total. In particular, it is worth mentioning that aldehyde **3a** is not formed when the P(*t*-Bu)₃/Pd(OAc)₂ molar ratio is 2:1.

A further effect is recognized by comparing the TOFs data in column 7: when the P(*t*-Bu)₃/Pd(OAc)₂ molar ratio is 2:1 the reaction rate becomes almost insensitive to the substrate/catalyst ratio, suggesting that no colloidal palladium is involved in the catalysis. This outcome is in keeping with the work of Blackmond,²³ which, on the basis of kinetic studies, demonstrated the homogeneous nature of Heck coupling catalyzed by [Pd(P(*t*-Bu)₃)₂] at high temperature.

A further increase of the P(*t*-Bu)₃/Pd ratio to 3:1 leads to a significant decrease in the catalyst efficiency: likely the third ligand molecule in some way competes with the substrate for the coordination sphere of the metal.

In Table 7 are also reported the results for the coupling of β -methallyl alcohol with aryl bromide **1b** or **1c**. The TOFs data show that the relative reactivity order is **1b**>**1a**>>**1c**: while the higher reactivity of **1b** was expected owing to the presence of a single deactivating group on the aromatic ring, the very low reactivity of **1c** appears quite surprising, and it is probably to be ascribed to both electronic and steric factors. It is interesting to note that as found for **1a** also with **1b** and **1c** the use of only 1 equiv of P(*t*-Bu)₃ gives higher reaction rates; however, upon addition of the second ligand the reaction rate

decreases less than when the substrate is **1a**. With both **1b** and **1c** the chemoselectivity of the reaction is almost complete whatever the catalyst formulation, confirming that the low chemoselectivity obtained in the coupling of β -methallyl alcohol with **1a** is due to the peculiar nature of the latter.

3. Conclusions

The system Pd(OAc)₂/P(*t*-Bu)₃ emerges as an efficient catalytic system for the coupling of **1a** and **1b** with β -methallyl alcohol; the high reaction rates, the high chemoselectivity, and the very high turnover number obtainable make the process worthy of consideration for the practical synthesis of Helional[®] and Canthoxal[®]. While with **1b** the use of a P(*t*-Bu)₃/Pd(OAc)₂ ratio of 1:1 is well suited as it gives a higher activity accompanied by an almost exclusive chemoselectivity, with **1a** the use of 2 equiv of P(*t*-Bu)₃ per palladium atom seems preferable owing to the higher chemoselectivity, which counterbalances the decrease in the reaction rate.

4. Experimental

4.1. General

All reactions, unless otherwise stated, were carried out under an inert atmosphere (argon). *N*-Methylpyrrolidinone (NMP), *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were commercial solvents (Aldrich or Fluka), which were purified before use according to standard procedures.²⁴ 4-Bromoanisole, 1-bromo-4-*tert*-butylbenzene, 1-bromo-3,4-(methylenedioxy)benzene, and 2-methyl-2-propen-1-ol (Aldrich) were distilled before use. Tri-*tert*-butylphosphonium tetrafluoroborate (Strem), dicyclohexylmethylamine (Aldrich), and dimethylglycine (Aldrich) were used as received. Sodium acetate, sodium carbonate, and sodium hydrogencarbonate were purchased from Fluka. Palladium acetate was purchased from Engelhard Industries. PdCl₂(PPh₃)₂²⁵ and Pd₂(dba)₃²⁶ were prepared by literature methods.

The coupling products were identified by their GC–MS and ¹H and ¹³C NMR spectra. GLC analyses were performed on a Agilent 6850 gas chromatograph; GC–MS analyses were performed on a HP 5890 series II gas chromatograph interfaced to a HP 5971 quadrupole mass-detector. ¹H and ¹³C NMR spectra were registered on a Bruker Avance 300 NMR spectrometer operating at 300.11 and 75.03 MHz, respectively.

4.2. Catalytic experiments

The coupling experiments were carried out in a magnetically stirred glass reactor (50 mL) equipped with a reflux condenser with an inert gas inlet and a side arm closed with a rubber septum for the withdrawing of GLC samples. In a typical experiment (entry 3 of Table 7), under a nitrogen atmosphere, the reactor was charged with 1.00 g (5.0 mmol) of 1-bromo-3,4-(methylenedioxy)benzene, 0.50 g (7.0 mmol) of methyl-2-propen-1-ol, 0.750 g (7.0 mmol) of Na₂CO₃, 64 mg (0.5 mmol) of naphthalene as GLC internal standard, and

4.5 mL of a mixture of NMP/H₂O (4:1 v/v). Under stirring, 250 μ L of a 1 \times 10⁻³ M solution of Pd(OAc)₂ in NMP/H₂O and 250 μ L of a 1 \times 10⁻³ M solution of [HP(*t*-Bu)₃]BF₄ in NMP/H₂O were finally added. The mixture was heated under stirring at 130 °C for 24 h, then it was rapidly cooled at room temperature and the liquid phase was analyzed by GLC (HP-1 capillary column, T_i=50 °C, t_i=5 min, T_f=250 °C, rate=10 °C/min).

4.2.1. 3-(1,3-Benzodioxole-5-yl)-2-methylpropanal (**2a**) (Helional)²⁷

The reaction mixture obtained from entry 4 of Table 7 was diluted with CH₂Cl₂ and extracted with water twice. The organic layer was dried over MgSO₄, and after evaporation of the solvent the residue was purified by flash chromatography (silica gel, *n*-hexane/Et₂O 4:1). Gas chromatographic pure Helional was recovered as pale yellow liquid in 82% yield. ¹H NMR (CDCl₃): δ =9.69 (d, 1H, *J*=1.5 Hz), 6.78–6.58 (m, 3H), 5.93 (s, 2H), 2.99 (dd, 1H, *J*=5.4, 13.2 Hz), 2.57 (m, 2H), 1.08 (d, 3H, *J*=6.9 Hz); ¹³C NMR (CDCl₃): δ =204.3, 147.7, 146.1, 132.5, 121.9, 109.3, 108.2, 100.9, 48.2, 36.4, 13.2. MS (EI): *m/z* 192 [M⁺], 136, 105, 77, 51.

4.2.2. 3-(4-Methoxyphenyl)-2-methylpropanal (**2b**) (Canthoxal)²⁸

The reaction mixture (entry 9, Table 7) was treated with CH₂Cl₂ and water, then the organic layer was dried over MgSO₄, and after evaporation of the solvent the residue was purified by flash chromatography (silica, *n*-hexane/Et₂O 4:1). Gas chromatographic pure Canthoxal was recovered as pale yellow liquid in 80% yield. ¹H NMR (CDCl₃): δ =9.70 (d, 1H, *J*=1.5 Hz), 7.10–6.80 (m, 4H), 3.78 (s, 3H), 3.03 (dd, 1H, *J*=5.1, 13.0 Hz), 2.60 (m, 2H), 1.08 (d, 3H, *J*=6.9 Hz); ¹³C NMR (CDCl₃): δ =204.4, 158.2, 130.7, 129.9, 114.0, 55.1, 48.1, 35.7, 13.1. MS (EI): *m/z* 178 [M⁺], 122, 108, 77, 51.

4.2.3. 3-(4-*tert*-Butylphenyl)-2-methylpropanal (**2c**) (Lilial)²⁹

¹H NMR (CDCl₃): δ =9.76 (d, 1H, *J*=1.5 Hz), 7.60–7.00 (m, 4H), 3.10 (dd, 1H, *J*=5.2, 13.2 Hz), 2.58 (m, 2H), 1.36 (s, 9H), 1.13 (d, 3H, *J*=6.9 Hz). MS (EI): *m/z* 204 [M⁺], 148, 134, 77, 51.

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