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Phospholes as efficient ancillaries for the rhodium-catalyzed hydroformylation and hydroaminomethylation of estragole

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ABSTRACT

The hydroaminomethylation (HAM) of estragole, a bio-renewable starting material, with di-n-butylamine was studied for the first time resulting in three novel amines. The process consists of the alkene hydroformylation followed by the *in situ* reductive amination of primarily formed aldehydes. In order to control chemo- and regioselectivities, three classes of phosphorus(III) compounds were employed as ancillaries for rhodium(I) catalysts: phosphine, phosphites and phospholes. Phosphole-promoted systems have showed the best overall performance, being more selective in the hydrofomylation step than non-promoted or phosphite-promoted systems, as well as more efficient in the reductive amination step than the standard triphenylphosphine based system. It has been found that both the double bond isomerization (a concurrent reaction) and the enamine hydrogenation (the last step in the HAM process) are favored by less electron-donating ligands, with phospholes presenting an excellent compromise to ensure high chemoselectivity and reasonably fast formation of target amines.

1. Introduction

Amines are an industrially important class of chemicals because they can give access to biologically active compounds, dyes, and other fine chemicals [1,2]. The hydroaminomethylation (HAM) is the direct transformation of an alkene into a homologous amine employing abundant and easily accessible reagents: carbon monoxide, dihydrogen and a primary or a secondary amine. HAM is a cascade reaction that involves the hydroformylation step, condensation of the primarily formed aldehydes with the added amine, and hydrogenation of the resulting imines (from primary amine counterparts) or enamines (from secondary amine counterparts) to generate corresponding homologous amines. Scheme 1 shows the sequence in which a secondary amine is used as a counterpart. In the context of sustainable synthetic approaches, such a catalytic reaction in which amines are produced with a high atom economy represents an advantageous alternative to classical synthetic methods.

HAM was discovered by Reppe in 1953 [3], but only recently has gained importance in the synthesis of more complex molecules. The scope of the HAM reaction has significantly expanded with the introduction of rhodium complexes instead of the formerly used cobalt ones [4]. Although ruthenium complexes have also been used as catalysts to promote HAM [5–7], rhodium complexes are more active and selective to catalyze both the hydroformylation and the hydrogenation steps. [8,9] The use of special ligands such as diphosphines [10], diphosphites [11], xanthene-based diphosphines [12], a xanthene-based dibenzophosphole ligand [13], tetraphosphorus ligands [14–16] has allowed good selectivity control associated with high activity.

Targeting industrial application, biphasic [17–20] and heterogenized [21–23] systems that allow for the easier catalyst recycling have also been developed. Today this reaction represents a powerful synthetic tool to directly prepare fine chemicals and pharmaceuticals [11,24–29], as well as commodity chemicals [30]. The advances in this synthetically efficient process have been recently reviewed [31,32].

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Our groups are involved in the preparation of useful or potentially useful chemicals employing transition metal complex catalyzed reactions applied to natural products that can be obtained in large scale through sustainable methods [33], specially that ones involving tandem reactions under hydroformylation conditions [34–39]. We have recently reported the HAM of the monoterpenes (limonene, camphene, and beta-pinene) [40] and eugenol [41] to obtain the corresponding homologous amines, which have potential bioactivity. Herein we report the HAM of estragole (**1**) with di-n-butylamine to obtain the amines **9–11** as shown in Scheme 2. Estragole is a bio-renewable chemical that can be extracted from basil oil (90% of estragole) and other essential oils in ton-scale, as well as from crude sulfate turpentine (CST) in a thousand-ton scale [42]. Despite the potential bioactivity of the products **9–11** as, e.g., fungicides [43], it is the first time that HAM of estragole is described. Fine tuning in the electronic and steric properties of the ligand is necessary to combine higher activity and selectivity [44], thus in this work we decided to compare three class of phosphorus(III) compounds: phosphines, phosphites and phospholes (see Fig. 1). To the best of our knowledge, monophospholes have never been reported as ancillaries for the HAM reaction.

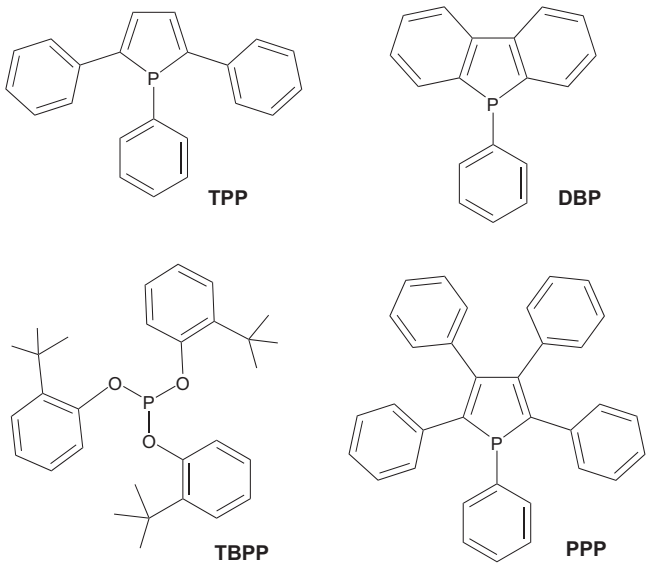


Fig. 1. Selected phosphorus ligands.

2. Experimental

2.1. General procedure

Estragole, di-n-butylamine, triphenylphosphine, triphenylphosphite were purchased from Aldrich. Tris(2-t-butylphenyl) phosphite (TBPP) [45], 1-phenydibenzophosphole (DBP) [46], 1,2,3-triphenylphosphole (TPP) [47], 1,2,3,4,5-pentaphenylphosphole (PPP) [48], $[Rh(cod)(\mu\text{-OMe})]_2$ [49], were synthesized according to literature procedures. Toluene was refluxed over sodium/benzophenone for 6 h and distilled under argon.

2.2. Catalytic runs

2.2.1. Hydroformylation

In a multiwell reactor placed in a glove box, the pre-catalyst $[Rh(cod)(\mu\text{-OMe})]_2$ (7.2×10^{-4} mmol), phosphorus ligand (7.2×10^{-3}–1.4×10^{-2} mmol), estragole (1.3 mmol) and 3 mL of toluene were introduced in each well. The reactor was then closed, removed from the glove box, purged with syngas ($CO:H_2 = 1:1$), pressurized to 20 bar and heated to 50–70 °C for 2 h under magnetic stirring. At the end of the reaction, the reactor was cooled, slowly depressurized and the reaction mixture from each well was separately analyzed by gas chromatography using dodecane as internal standard.

2.3. Hydroaminomethylation

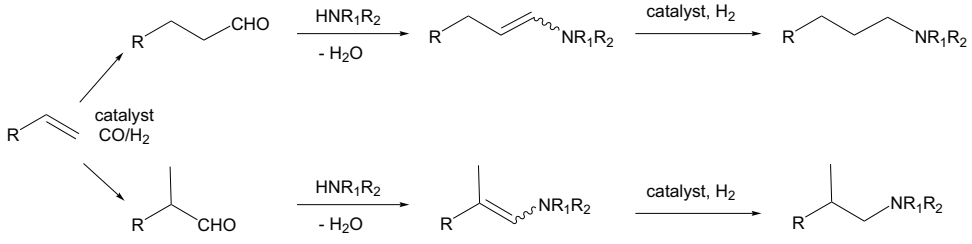
The pre-catalyst $[Rh(cod)(\mu\text{-OMe})]_2$ (5.0×10^{-3} mmol), the phosphorus ancillary (if any) and a PTFE-covered magnetic stirring bar were placed in a stainless steel bomb, which was closed and purged with three cycles of vacuum and argon. In a Schlenk tube, a solution was prepared by adding toluene (30 mL), estragole (10 mmol), di-n-butylamine (10 mmol). The solution was transferred under inert atmosphere to the bomb, which was pressurized with carbon monoxide (10 atm) and then with hydrogen (to 40 atm). The bomb was placed in a pre-heated aluminum well over magnetic stirring. Liquid samples were taken periodically through a dip tube.

2.4. Product analysis

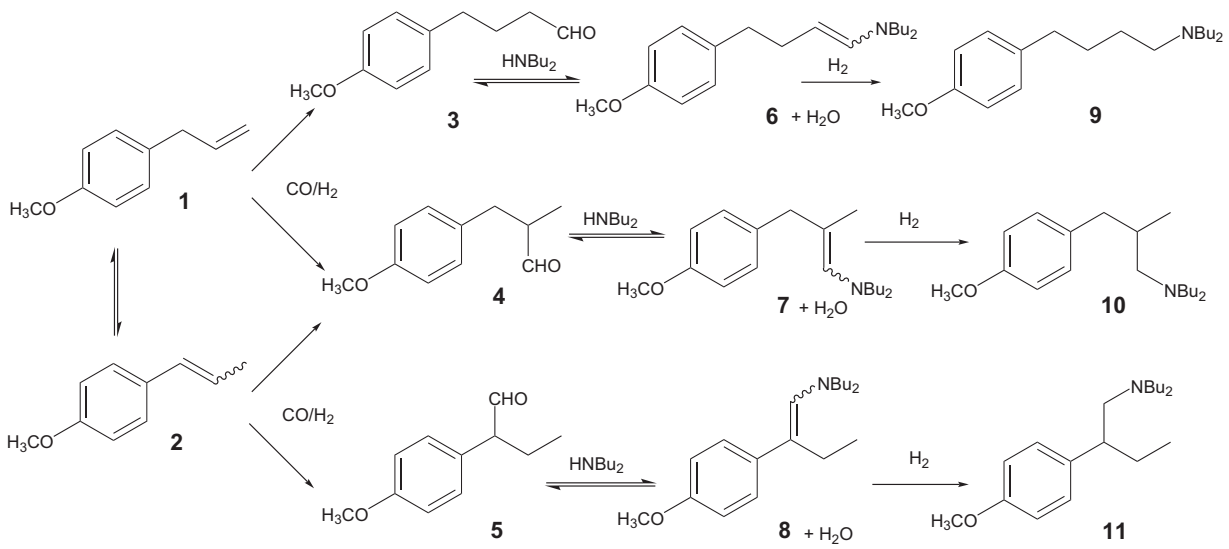
The products were quantitatively analyzed by gas chromatography (GC) using a Shimadzu GC2010 instrument equipped with a split/splitless injection port (310 °C) and flame ionization detector (280 °C), fitted with a Restek RTx-5MS capillary column (30 m × 0.25 mm × 0.25 μm) at 50 °C for 3 min, 10 °C/min up to 310 °C, kept for 10 min. Conversion and product distribution were determined by GC based on the reacted estragole employing dodecane as internal standard. Qualitative analysis was made by GC coupled with mass spectrometry in a Shimadzu GC2010/QP2010-plus instrument fitted with a Restek Rtx-5 MS capillary column (30 m × 0.25 mm × 0.25 μm), operating at 70 eV. The main HAM products were isolated by preparative thin layer chromatography in silica employing a hexane/ethyl acetate mixture (4:1) as eluent and analyzed by and ^1H, ^{13}C, DEPT-NMR (Bruker Avance DRX 200, TMS, $CDCl_3$).

2.5. Spectroscopic data

Compounds **3**, **4** and **5** have been reported in a previous publication [50].



Scheme 1. Hydroaminomethylation of olefins.



Scheme 2. Hydroaminomethylation of estragole (**1**).

9: Mass spectrometry: (*m*/*z*/rel.int.): 291/6; 248/100; 161/25; 142/88; 121/63; 100/56; 44/19. ^{13}C NMR: 14.04; 20.71; 26.25; 28.81; 29.60; 34.86; 53.70; 55.21; 113.64; 129.20; 134.63; 157.61. ^{1}H NMR: 0.91 (t, 6H, CH_3, ^{3}J = 7.0 Hz); 1.26–1.55 (m, 12H, CH_2); 2.38–2.60 (m, 6H, CH_2); 3.78 (s, 3H, CH_3); 6.82 (d, 2H, Ar:CH, ^{3}J = 8.5 Hz); 7.09 (d, 2H, Ar:CH, ^{3}J = 8.5 Hz).

10: Mass spectrometry: (*m*/*z*/rel.int.): 291/7; 142/100; 121/13; 100/67; 44/7.

^{13}C NMR: 14.13; 18.07; 20.69; 29.34; 34.13; 40.66; 54.47; 55.16; 61.44; 113.44; 129.98; 133.74; 157.56. ^{1}H NMR: 0.72–0.86 (m, 9H, CH_3); 1.18–1.28 (m, 8H, CH_2); 1.71–1.77 (m, 1H, CH); 2.11–1.07 (m, 2H, CH_2); 2.26–2.29 (m, 4H, CH_2); 2.09–2.77 (m, 2H, CH_2); 3.70 (s, 3H, CH_3); 6,74 (d, 2H, Ar:CH, ^{3}J = 8.0 Hz); 6.99 (d, 2H, Ar:CH, ^{3}J = 8.0 Hz).

11: Mass spectrometry: (*m*/*z*/rel.int.): 162/7; 148/20; 142/100; 121/13; 100/67; 44/33. ^{1}H NMR: 0.82–0.63 (m; 9H; CH_3); 1.29–1.14 (m; 10H; CH_2); 2.41–2.25 (m; 7H; CH; CH_2); 3.68 (s, 3H; CH_3); 6.74 (d, 2H, Ar:CH, ^{3}J = 8.4 Hz); 6.98 (d, 2H, Ar:CH, ^{3}J = 8.4 Hz).

3. Results and discussion

3.1. Hydroformylation of estragole

The first step of the hydroaminomethylation process is the hydroformylation reaction. Although the hydroformylation of estragole has been studied before on different experimental conditions [50,51], we have investigated the influence of different type of phosphorus ligands: triphenylphosphine, triphenylphosphite and phosphole ligands (see Fig. 1 for selected ligands) on the chemoselectivity and regioselectivity under relevant conditions for our HAM studies (Tables 1 and 2).

The reaction was performed under 20 bar of CO/H_2: 1/1 in toluene at 50 °C for 2 h in the presence of $[Rh(cod)(\mu\text{-}OMe)]_2$/L catalytic systems (L = phosphorus(III) ligand). A ligand/Rh molar ratio of 5 was chosen to minimize the contribution of non-promoted $[Rh(CO)_3H]$ species whose formation should be disfavored at the five fold ligand excess. The rhodium complexes without phosphorous ligands promote the isomerization of estragole under hydroformylation conditions.

The hydroformylation of estragole affords two main products: the linear and branched aldehydes **3** and **4**, respectively (Scheme 2). In some runs, the isomerization product **2** was produced in selectivities up to 9%; however, aldehyde **5**, which could arise from the hydroformylation of **2**, was not observed in selectivities higher than 1% under the reaction conditions employed. We run a parallel study on the hydroformylation of anethole (**2**) and found out that its rate of hydroformylation is lower than estragole and the predominant product is **5**. The concurrent hydroformylation of **2** is only relevant with π-acidic ligands (e.g. carbon monoxide and phosphites) at harsher reaction conditions or longer reaction times.

The results compiled in Table 1 are presented in the crescent order of the electron donor ability of the ligand (descendent order for ν_{CO} in the $[Ni(CO)_3L]$, L = phosphorus ligand) [52]. The ν_{CO} values for the $[Ni(CO)_3TPP]$ and $[Ni(CO)_3PPP]$ complexes have been

Table 1
Hydroformylation of estragole (**1**): ligand effect at 50 °C[a].

Entry	Ligand	Tolman's parameters		Conversion (%)	Product distribution (%)[c]				Regioselectivity
		ν_{CO} (cm^{-1})	θ°		**3**	**4**	**2**	**Others**	**3/4**
1	None	–	–	99	51	38	9	2	1.3
2	$P(OPh)_3$	2085.3[b]	128[b]	98	54	43	1	2	1.3
3	TPP	2071.9[d]	160[e]	100	76	23	0	1	3.3
4	PPP	2070.4[d]	160[e]	83	73	25	1	1	2.9
5	DBP	~2070 [f]	151[e]	60	68	30	0	2	2.3
6	PPh_3	2068.9 [b]	145[b]	58	69	28	1	2	2.5

[a] Conditions: **1** (1.3 mmol); $[Rh(cod)(\mu\text{-}OMe)]_2$ (7.2×10^{-4} mmol), ligand (7.2×10^{-3} mmol, if any); toluene (3 mL), 20 bar (CO/H_2: 1/1), 50 °C, 2 h.
[b] From ref. [52].
[c] Determined by GC employing dodecane as internal standard.
[d] From ref. [53].
[e] Measured employing the method of ref. [52] for ligands with different substituents.
[f] Estimated value from ref. [54].

Table 2
Hydroformylation of estragole (**1**): ligand concentration effect at 70 °C[a].

Entry	Ligand	P/Rh[b]	Conversion (%)	Product distribution (%)[c]				Regioselectivity
				3	**4**	**2**	**Others**	**3/4**
7	None		99	43	23	31	3	1.9
8	TPP	5	100	73	24	2	1	3.0
9		10	100	75	21	2	2	3.6
10	PPP	5	100	67	29	3	1	2.3
11		10	100	70	27	2	1	2.6
12	DBP	5	100	65	31	1	2	2.1
13		10	80	65	31	1	2	2.1
14	PPh_3	5	100	60	37	2	2	1.6
15		10	100	68	30	1	1	2.3

[a] Conditions: **1** (1.3 mmol); [Rh(cod)(μ-OMe)]$_2$ (7.2×10^{-4} mmol); toluene (3 mL), 20 bar (CO/H_2: 1/1), 70 °C, 2 h.
[b] Phosphorus/rhodium atomic ratio.
[c] Determined by GC employing dodecane as internal standard.

reported previously [53]; however, to the best of our knowledge, the ν_{CO} value for the [Ni(CO)$_3$DBP] is not available in literature. Owing to the high toxicity of the precursor [Ni(CO)$_4$], measurements for, e.g., [RhCl(CO)$_2$L] are currently reported instead. For [RhCl(CO)$_2$DBP], a ν_{CO} of 2056 cm^{-1} has been reported [54], for [RhCl(CO)$_2$TPP] – 2058 cm^{-1} [54] and for [RhCl(CO)$_2$(PPh_3)] – 2053 cm^{-1} [55], which suggests that the electron donor ability of DPB is in between of those for TPP and PPh_3. The Tolman's steric parameters for the ligands are also included in Table 1. The values for TPP, PPP, and DPB were measured by us employing the methodology described by Tolman [52] for phosphorus ligands with different substituents.

The non-promoted system converts 99% of estragole in 2 h and gives 89% of aldehydes with a regioselectivity in favor of linear aldehyde **3** (51%), as well as 9% of isomerization product **2** (entry 1). Generally speaking, for the phosphorus(III)-promoted systems (entries 2–6), the activity of the system decreases with the increase in the electron donor ability of the ligands and apparently is not influenced by their steric bulkiness. A possible explanation is that a higher electron density on the metal would favor the carbon monoxide coordination to the metal, which is detrimental for that of the substrate. On the other hand, the use of phosphorus ligands reduces the undesired double-bond isomerization (entry 1 *vs.* entries 2–6) by favoring the carbon monoxide coordination to the metal-alkyl intermediate followed by its carbonylation rather than the β-hydride elimination, which would yield the isomeric alkene (**2**).

As a general tendency, the regioselectivity seems to increase with the increase of the ligand's cone angle, which is expected since the predominant catalytically species under these reaction conditions should be [Rh(H)(CO)L$_2$], (L = phosphorus ligand) [56]. The higher is the steric hindrance at the rhodium center, the stronger is the prevalence for the formation of linear metal-alkyl intermediates. In apparent contradiction with this general tendency, the P(OPh)$_3$-promoted system presents nearly the same regioselectivity as the non-promoted system (entry 2, **3**/**4** ≈ 1.3). However, to infer the contribution of the branched alkyl intermediate not only aldehyde **4** should be taken into account, but also the alkene **2** (if formed in significant amounts) as both products arise from the branched metal-alkyl intermediate. Such calculations give the value of 1.1 for the linear to branched alkyl intermediates in the non-promoted system.

Although no direct correlation between the ν_{CO} values and regioselectivity can be deduced from the data in Table 1, the electronic properties of the ligand seem to affect the *l*/*br* ratio. Really, the regioselectivity is slightly different for the ligands with the same steric parameter (cf. entries 3 and 4). One possible explanation may be the contribution of species with less than two phosphorus ligands to the total activity and selectivity. Under the same reaction conditions, the concentration of these species may vary according to the steric and electronic properties of the ligand: it will be higher for bulkier and weaker ligands. The strength of metal–ligand bond cannot be evaluated by Tolman's electronic parameter (ν) in a straightforward manner. For example, although PPh_3 gives more electron density to the metal (smaller ν) than P(OPh)$_3$, the former easily displaces the latter from the coordination sphere of [Rh(H)(CO)(PPh_3)$_3$] not only because P(OPh)$_3$ is smaller, but also because the P-Rh bond strenght is higher due to a stronger back-bonding. This explanation may be also valid for the TPP *vs.* PPP case: due to a weaker P-Rh bond, the catalytic output of the Rh/PPP system is more influenced by the residual monoligand species (*i.e.* [Rh(H)(CO)$_2$PPP]), which are less selective for the linear aldehyde.

These hypotheses are corroborated by the experiments conducted at higher ligand concentrations and/or higher temperatures as shown in Table 2.

At 70 °C the activity of the systems is expectedly higher than at 50 °C: almost all reactions shown in Table 2 reached a complete conversion in 2 h. Comparing the systems at the same P/Rh ratio reveals that the regioselectivity for the linear product decreases with the temperature increase (*e.g.* entry 3 *vs.* entry 8; entry 5 *vs.* entry 12). It is also noteworthy that the chemoselectivity of the non-promoted system considerably decreases with the temperature increase, so that the double-bond isomerization becomes one of the major reaction pathways at 70 °C (entry 7). Products **2** and **4** together correspond to nearly 55% of the mass balance. Thus, the preferred pathway for the hydrogen migratory insertion to the double bond is the Markovnikov type reaction, which leads to the branched metal-alkyl intermediate and then to products **2** and **4**.

All promoted systems have shown a high total selectivity for the aldehydes (96–97%), with the *l*/*br* ratio increasing at higher ligand concentrations (*cf.* entries 8 and 9; 10 and 11; 14 and 15). A possible explanation is the decrease in the contribution of the residual monoligand species (*i.e.* [Rh(H)(CO)$_2$L]), which are less selective for the linear aldehyde, with the increase in the P/Rh ratio. A noticeable exception is the system with DPB (*cf.* entries 12 and 13): due to the high coordination ability of this ligand the P/Rh ratio of 5 seems to be high enough to keep almost all rhodium centers with at least two phosphorus ligands. The Rh/DBP system seems to be more sensitive to the ligand excess than the other systems as the reaction occurs much slower at P/Rh = 10 than at P/Rh = 5 (cf. entries 13 and 12) probably due to the stronger competition between the ligand and the substrate.

3.2. Hydroaminomethylation of estragole

The hydroaminomethylation (HAM) of estragole (**1**) with di-n-butylamine was carried out using the same phosphorus promoters as for hydroformylation. The bulky phosphite ligand,

Table 3
Hydroaminomethylation of estragole (**1**) with di-n-butylamine: ligand effect[a].

Entry	Ligand	Tolman's parameters		Conversion (%)	Product distribution (%)[c]					Regioselectivity(%)[c,d]		
		ν_{CO} (cm^{-1})	θ°		2	Aldehydes	Enamines	Amines	Others	α	β	γ
16	None			100	10	0	0	79	11	2	31	67
17	TBPP	2086.1[b]	175[b]	100	0	0	0	87	13	10	32	58
18	$P(OPh)_3$	2085.3[b]	128[b]	100	6	0	0	85	9	5	34	61
19	TPP	2071.9[e]	160[f]	100	1	23	0	70	6	1	28	71
20	PPP	2070.4[e]	160[f]	100	1	24	1	67	7	1	25	74
21	DBP	~2070[g]	151[f]	100	7	13	0	80	0	2	41	57
22	PPh_3	2068.9[b]	145[b]	100	3	47	1	49	0	3	41	56

[a] Conditions: **1** (10 mmol); di-n-butylamine (10 mmol); $[Rh(cod)(\mu\text{-}OMe)]_2$ (5.0×10^{-3} mmol), ligand (if any, 5.0×10^{-2} mmol) toluene (30 mL), 40 bar ($CO:H_2 = 1:3$), 80 °C, 24 h. For products, the value "zero" means not observed or less than 0.5%.
[b] From ref. [52].
[c] Determined by GC.
[d] $\alpha = (\mathbf{5}+\mathbf{8}+\mathbf{11})$; $\beta = (\mathbf{4}+\mathbf{7}+\mathbf{10})$; $\gamma = (\mathbf{3}+\mathbf{6}+\mathbf{9})$.
[e] From ref. [53].
[f] Measured employing the method of ref. [52] for ligands with different substituents.
[g] Estimated value from Ref. [54].

tris(2-t-butylphenyl)phosphite (TBPP), was added in the study to compare steric effect also in the class of phosphites.

The reaction led to three isomeric amines (**9**–**11**) as final products (Scheme 2). Depending on the reaction conditions and time, the intermediate products, aldehydes (**3**–**5**) and enamines (**6**–**8**), were observed in the reaction solution. Aldol condensation products, hydrogenation product (4-propylanisole), alcohols, and several unidentified products were also observed as minor products in some experiments and were considered together as "others" in the product distribution shown in Table 3.

In Table 3 the results for the HAM of **1** employing the ligands depicted in Fig. 1 are presented. It is well known from the literature that high ligand/Rh molar ratios are detrimental for the enamine hydrogenation step in HAM if the ligand is too electron rich. On the other hand, a too low ligand/Rh ratio would allow a significant contribution of non promoted rhodium species (*i.e.* $[Rh(CO)_3H]$). Thus, we decided to keep a ligand/Rh atomic ratio of 5, the temperature of 80 °C and a rather long reaction time (24 h) to favor the yield of amines in all HAM experiments.

The results are presented, as in Table 1, in the crescent order of the electron donor ability of the ligand (descendent order for ν_{CO}). The non-promoted system (entry 16) and the systems with phosphites (entries 17 and 18), which are the less electron-donating ligands than the others included in Table 3, are more efficient to promote the HAM as a whole, since no aldehydes or enamines are observed after 24 h. However, these systems also promote the double bond isomerization to give internal alkene **2** (ca. 10%).

For the non-promoted systems (entry 16), alkene **2** is only sparingly converted to hydroformylation products. In the presence of phosphites, especially the bulky phosphite TBPP, the conversion of **2** into the carbonylation products occurs as the products **5**, **8** and **11** (alpha products), which can only be formed from **2**, appear in considerable amounts. TBPP (entry 17) is the most efficient ligand in the series to promote the HAM of estragole with di-n-butylamine giving amines in 87% yield; however, a significant amount of side products (13%) is also observed. In the HAM sequence, water is formed as an intrinsic co-product and the employment of phosphites as ancillaries was taken with caution due to its instability in the presence of water. In a recent paper, Tricas et al. [57] have demonstrated that some phosphites, including TBPP, are quite stable in the presence of water, even under acidic conditions. Indeed, phosphites have proven to be useful in HAM reactions [11] but, if industrial application is aimed, a longer-term stability of the ligand has to be demonstrated.

The ligand PPh_3 is cheap, quite stable and efficient to promote the hydroformylation step as shown in Tables 1 and 2, but it fails in promoting efficiently the HAM. In entry 22, 47% of aldehydes remain in the reaction solution even after 24 h, indicating that the system is not efficient for the reductive amination (amine condensation + enamine hydrogenation). Fuentes et al. [44] demonstrated that the less electro-donating tris(3,4,5-trifluorophenyl)phosphine is better than PPh_3 and other stronger electron donor phosphines to promote the enamine hydrogenation step, contrasting with the fact that alkene hydrogenation is generally accelerated by electron rich ligands. Indeed, the phospholes TPP and PPP, which are less electron donating than PPh_3, (entries 19 and 20) proved to be efficient in avoiding the double bond isomerization of the substrate and are more efficient ancillaries than PPh_3 for the reductive amination, although a fair amount of aldehydes (c.a. 24%) remain in solution even after 24 h. The phosphole DBP (Entry 21) showed to promote more efficiently the reductive amination than TPP or PPP and, although some double bond isomerization of the substrate is still observed, no other side product is formed, what makes DBP a good starting point to design more efficient ancillaries for HAM.

The regioselectivity in Table 3 is reported as the sum of products derived from the aldehydes with the formyl group on the carbons α, β, and γ in relation to the aryl ring. This regioselectivity does not correlate straightforwardly with the regioselectivity of the migratory insertion of the hydride in the hydroformylation cycle. As mentioned before, the double-bond isomer **2** also results from the branched metal-alkyl intermediate. Furthermore, in the systems with phosphites, alkene **2** is also converted into the HAM products and part of the products is transformed in secondary unidentified side products. For the more electron donor phospholes and PPh_3, the contribution of the isomerization is not high, so that the regioselectivities correlate quite well with those presented in Table 2 for the runs performed at 70 °C with the P/Rh atomic ratio of 5.

Also in apparent contradiction with the steric hindrance/regioselectivity correlation is the regioselectivity of the Rh/TBPP system: the cone angle of TBPP is 175°, but the *l*/*br* ratio is comparable to the system with $P(OPh)_3$, with cone angle of 128°. In this case, it should be considered that due to a high ligand steric bulkiness, mostly monoligand species with TBPP (*i.e.* $[Rh(H)(CO)_2TBPP]$) prevail even at P/Rh = 20 [57]. Bearing only one ligand, the metal center in these species is not as steric hindered as the metal center bearing two phosphorus ligands.

To explore in more details the ligand performance, the kinetic curves for the reaction with selected ligands are presented in Fig. 2.

It is noteworthy that the hydroformylation step in the non-promoted system (Fig. 2a) is slower than that in the promoted system. The substrate conversion was complete in nearly half an hour in the presence of any phosphorous ligand, whereas 2 h were necessary with the non-promoted system. Thus, an average turnover frequency (TOF) of at least 2000 h^{-1} is reached for all

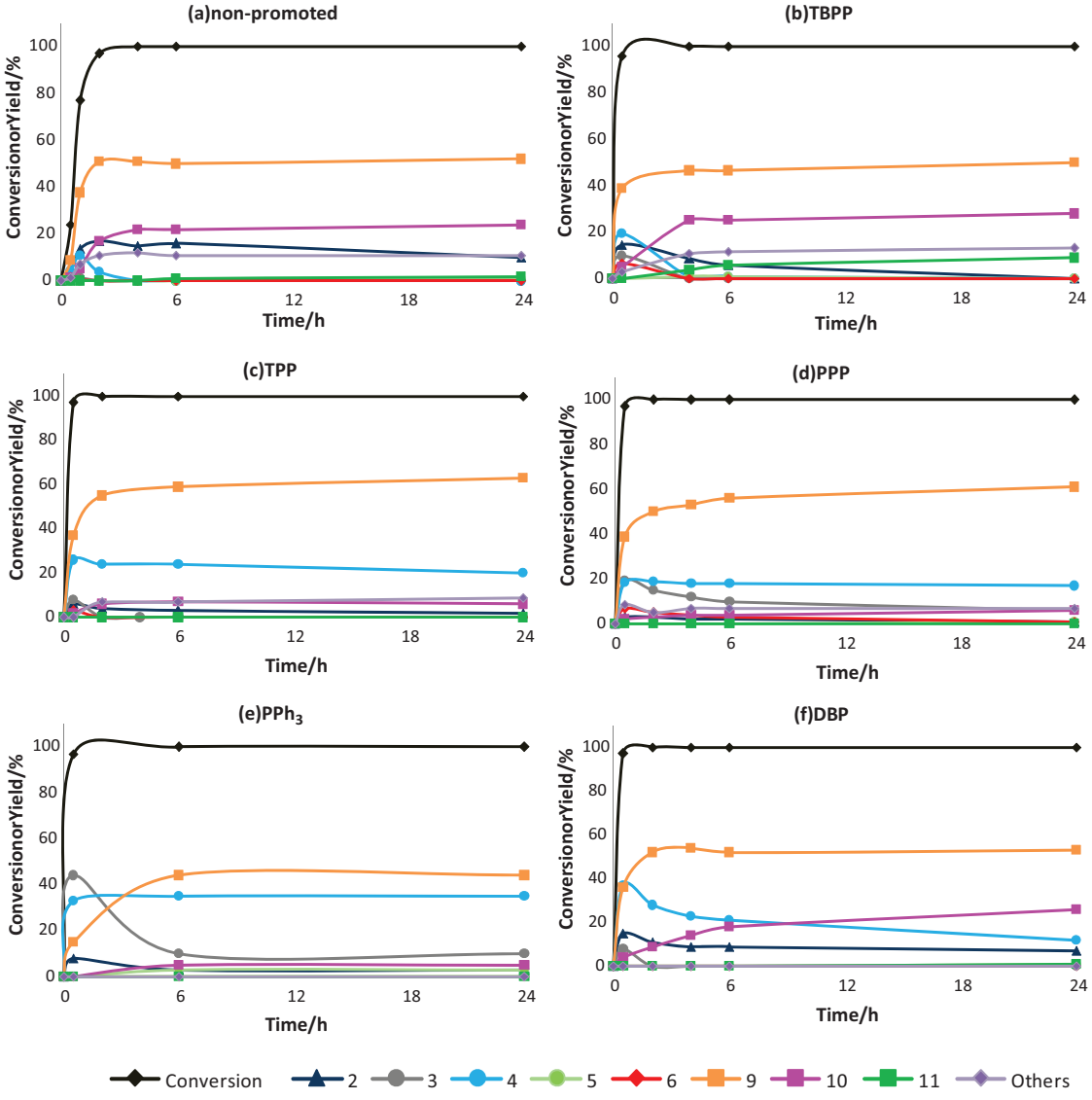


Fig. 2. Kinetic curves for the hydroaminomethylation of estragole with dibutylamine. For conditions, see Table 3.

phosphorus-promoted systems studied in this work. The phosphorus ligands give more electron density to the metal center than the carbonyl ligand and facilitate the hydrogenolysis of metal-acyl intermediates, which is considered to be the rate-determining step in the hydroformylation cycle. In addition, the phosphorus ancillaries prevent the formation of rhodium clusters that are inactive in hydroformylation, keeping more rhodium in the active form.

As concerned to the selectivity, both the non-promoted and the TBPP-promoted systems (Fig. 2b) give rise to double-bond isomerization products, but only is the latter able to convert efficiently the isomer **2** into hydroformylation products. With more basic TPP (Fig. 2c), the hydroformylation is still fast and so is the reductive amination to form amine **9**. However, the aldehyde **4** is only slowly converted into branched amine **10**. PPP has about the same cone angle as TPP, but it is slightly more electro-donating. This seems to slow down even the reductive amination of the linear aldehyde **3** as it can be noticed by its slower consumption (Fig. 2d). This effect becomes critical when the more electro-donating PPh_3 is employed as a promoter (Fig. 2e): the hydroformylation step is fast and double-bond isomerization is prevented, but the reductive amination is clearly decelerated. The use of DBP as a ligand (Fig. 2f) results in a system that is efficient to perform the reductive amination, as not only the linear aldehyde is quickly converted, but also the branched aldehyde to give the corresponding amine, although at a moderate rate.

It is worth noting that in all systems the reductive amination of branched aldehyde **4** occurs much slower than that of the linear aldehyde **3**. As expected, the branched aldehyde is more difficult to condensate with amines. Furthermore, not only the enamine condensation is more difficult, but also the hydrogenation of the branched enamine is slower. The amine condensation step is not expected to be directly influenced by the metal center, but when the product of the condensation (enamine) is hydrogenated, the equilibrium aldehyde-enamine is driven towards the products. Thus, the more efficient is the enamine hydrogenation at the metal center, the faster is the reductive amination as a whole. One possible explanation for the lower hydrogenation rate of the branched enamine is its higher steric hindrance, which makes difficult its coordination to the metal center. Nevertheless, electronic parameters may play even a more significant role: a stronger Lewis acidity on the metal center (*i.e.*, a metal center with lower electron density) would favor the reductive elimination, the last step in the enamine

hydrogenation, considered to be the rate-determining step [44]. Indeed, it seems to be the case: comparing the ligands with similar steric properties (PPh_3 *vs.* DBP, TPP *vs.* PPP), the less electro-donating is the ligand, the more efficient is the reductive amination.

The phospholes DBP, TPP and PPP are more efficient in preventing the double bond isomerization and side products formation than the phosphites TBPP and $P(OPh)_3$ and are more efficient in promoting the reductive amination than PPh_3. Furthermore, the systems with phospholes TPP and PPP are more regioselective than all the others. Thus, monophospholes or their corresponding chelating versions [13] seem to be good candidates for the improvement on state-of-art ligands for the hydroaminomethylation reaction.

4. Concluding remarks

The hydroaminomethylation (HAM) of estragole, a bio-renewable starting material available from essential oils of various plants, is reported for the first time. Di-n-butylamine was used as the amine counterpart. The corresponding amines (**9** and **10**) were obtained in high yields, with their relative amounts depending on the catalyst and the reaction conditions. The monophospholes DBP, TPP and PPP have been employed for the first time as ancillaries for the HAM and showed to be promising option because they have been more efficient in promoting the reductive amination than the classic PPh_3 ligand and resulted in less side products than the systems with phosphites.

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