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Systematic study on the catalytic synthesis of unsaturated 2-ketocarboxamides: palladium-catalyzed double carbonylation of 1-iodocyclohexene

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ABSTRACT

1-Iodocyclohexene, a benchmark substrate, has been double carbonylated in the presence of palladium-phosphite precatalysts. Triarylphosphites with OR substituents, able to act both as *P*-monodentate and hemilabile *P,O*-heterobidentate ligands were used in this reaction. Systematic investigations have revealed that the chemoselectivity towards cyclohexenylglyoxylamides, i.e., the products obtained in aminocarbonylation by the insertion of two carbon monoxide, is strongly influenced by the amine nucleophile, temperature and carbon monoxide pressure. The highest yields of 2-ketocarboxamides were obtained at low temperature (30 °C) and high carbon monoxide pressure (110 bar). However, the structure of the phosphite ligand has practically no effect either on catalytic activity or chemoselectivity. This fact refers to the *P*-monodentate coordination of the ligands in catalytic intermediates or that palladium nanoparticles are the catalytically active species.

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1. Introduction

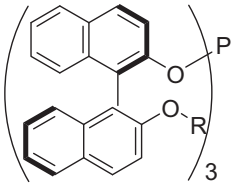
Since the early discovery of the carbonylation of aryl halides in the presence of *O*- and *N*-nucleophiles, resulting in the corresponding esters and amides, respectively,[1] hundreds of examples have shown its synthetic potential.[2–4] Various types of complicated skeletons, most of them with practical importance,[5,6] were functionalized as well. The intramolecular version of this reaction provides the corresponding cyclic derivatives, lactones and lactames, respectively.[7] The alkoxy- and aminocarbonylation of aryl halides has become an indispensable tool for the synthesis of esters as amides of unprecedented structures. The synthetic potential of palladium-catalyzed carbonylations of aromatic halides, including the first industrial applications, has been reviewed recently.[8,9]

Similar to aryl halides, iodo- and bromoalkenes of various structures readily undergo alkoxy- and aminocarbonylations resulting in α,β-unsaturated esters and carboxamides, respectively. The major difference to the corresponding aromatic substrates lies in the lack of double carbon monoxide insertion, i.e., neither the formation of 2-keto-carboxylic esters nor that of 2-ketocarboxamides were reported using this methodology. Although several types of iodoalkenes were carbonylated under the variety of conditions (solvent, ligand, carbon monoxide pressure), to the best of our knowledge, unsaturated 2-keto-carboxylic acid derivatives have not been synthesized in palladium-catalyzed alkoxy- and aminocarbonylations.[5,6]

As a part of our continuing research in this field, newly developed arylphosphites as heterobidentate P,O-ligands[10] were tested in palladium-catalysed aminocarbonylation of an iodoalkene model compound. A high-yielding double carbonylation of 1-iodocyclohexene in the presence of *N*-nucleophiles is reported.

2. Results and discussion

1-Iodocyclohexene (**1**) was aminocarbonylated in the presence of palladium catalysts formed in situ by the reaction of palladium(II) acetate and two molar equivalents of triarylphosphite (tris(2′-benzyloxy-1,1′-binaphthalene-2-yl)phosphite) (**L2**), (tris(2′-methoxy-1,1′-binaphthalene-2-yl)phosphite) (**L1**), (tris(2′-adamanthyloxy-1,1′-binaphthalene-2-yl)phosphite) (**L4**), (tris(2′-diphenylmethoxy-1,1′-binaph



L1 (R = Me)
L2 (R = Bn)
L3 (R = $CHPh_2$)
L4 (R = Ad)

Fig. 1. Binaphthyl-based triarylphosphites used in this study.

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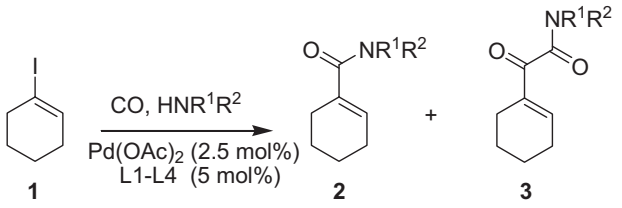
thalene-2-yl)phosphite) (**L3**) (Fig. 1). *tert*-Butylamine (**a**), aniline (**b**), methyl alaninate (**c**), morpholine (**d**) and piperidine (**e**) were used as *N*-nucleophiles (Scheme 1).



	R^1	R^2
a	H	*t*Bu
b	H	Ph
c	H	$CH(CH_3)COOMe$
d	$(CH_2)_2O(CH_2)_2$	
e	$(CH_2)_5$	

Scheme 1. Aminocarbonylation of 1-iodocyclohexene.

It is worth mentioning, that the above in situ catalyst is the phosphite analogue of the widely used palladium(0)-tertiary phosphine systems. It has been proved that palladium(II) is reduced to palladium(0) while one of the 2 equiv of ligands is oxidized.[11–13] In our case, the formation of coordinatively highly unsaturated $Pd(L)(S)_n$ (S stands for solvent (DMF)) complex is supposed while the 'second' equivalent of L is oxidized to the corresponding triaryl phosphate. Under the reaction conditions used (see below) the action of other compounds (amine, carbon monoxide) as reducing agents cannot be excluded.

Although the *tert*-butylaminocarboxamide derivative (**2a**) is the only product under standard conditions (1 bar CO, 50 °C) in the presence of palladium-**L2** catalytic system (Table 1, entry 1), 2-ketocarboxamide (**3a**) is also formed under 20–110 bar CO pressure (entries 2–7). The reaction conditions were optimized towards the formation of **3a**; the following effects are worth mentioning: (i) the decrease of the temperature favours the formation of **3a**, (ii) the increase in the CO pressure has a positive influence on the formation of **3a** in case of low temperature (30 °C) only (entries 4 and 6), (iii) at higher temperature (80 °C) the effect of the pressure on chemoselectivity is almost negligible. Consequently, the highest chemoselectivity of 67% towards 2-ketocarboxamide **3a** has been obtained at 30 °C under 110 bar CO pressure (entry 4).

Screening the amines in aminocarbonylation, an efficient synthesis of the corresponding ketoamides **3d** and **3e** was carried out with secondary amines (**d** and **e**) resulting in chemoselectivities of 67 and 71%, respectively (entries 16 and 17). Low chemoselectivity towards the double carbonylation product **3c** was observed with methyl alaninate (**c**) (entries 12 and 13). It is worth mentioning that no double carbon monoxide insertion was observed with aromatic amine (**b**) as a nucleophile. However, unexpectedly high activities for the formation of the corresponding carboxamide (**2b**) was observed (entries 8–10).

The *tert*-butylaminocarbonylation with the other ligands (**L1**, **L3** and **L4**) show similar chemoselectivities and activities as **L2** (Table 2). Ketocarboxamides (**3**) of unprecedented structure are the major products in all cases at low temperature and high carbon monoxide pressure (entries 2, 4, 7 and 10). All of these ligands provide carboxamides (**2**) exclusively in the presence of *tert*-butylamine (**a**) as the *N*-nucleophile under mild conditions (entries 1, 3 and 9). It can be stated that the OR moiety does not influence thoroughly either the reactivity or the chemoselectivity. These results suggest that the phosphite ligands (**L1**–**L4**), which are able to coordinate also in *P,O*-heterobidentate manner in catalytic precursors,[10] could bound to palladium as monodentate P-ligands (upon the activation of the iodoalkene substrate) under aminocarbonylation conditions.

Although the formation of 2-oxo-carboxamides from haloaromatics can be explained in two ways, namely, both the 'glyoxyl-route' and the 'acyl-carbamoyl-route' can be operative, detailed mechanistic studies revealed that the latter is responsible for double carbonylation.[14,15] A similar mechanism could be operative in one case of our phosphite–palladium systems containing sterically hindered heterobidentate ligands. The facile oxidative addition of in situ formed palladium(0) species resulted in an alkenyl-palladium(II) (**A**) intermediate, which is able to coordinate carbon monoxide (**B**). The acyl complex (**C**), formed in carbon monoxide insertion, is ready to coordinate the 'second' carbon monoxide as a terminal carbonyl, which undergoes a nucleophilic attack by the *N*-nucleophile (**D**). In this way, the bulky hemilabile ligands (**L1**–**L4**) favour the formation of the acyl-carbamoyl-palladium(II) ($Pd\{RC(O)\}\{C(O)NR^1R^2\}$) intermediate (**E**), which readily undergoes reductive elimination providing 2-ketocarboxamides (Scheme 2).

Table 1
Aminocarbonylation of 1-iodocyclohexene (**1**) in the presence of palladium-**L2** in situ catalysts[a]

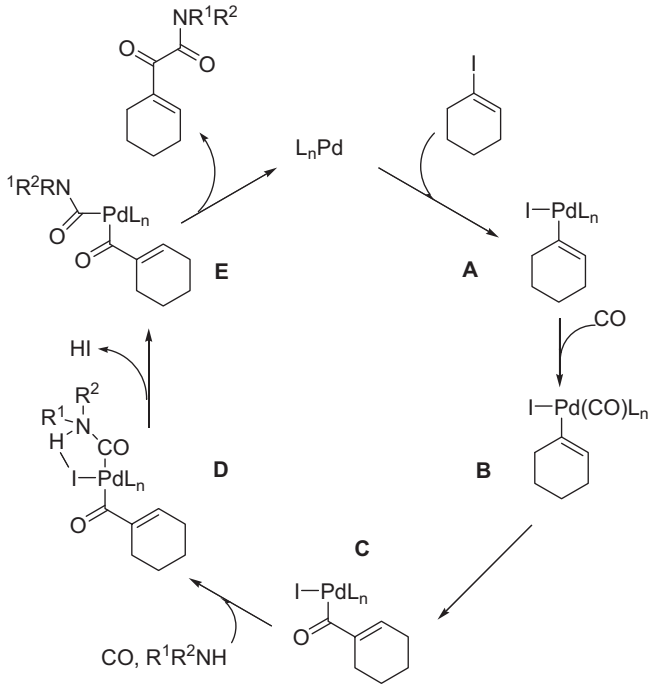
Entry	Amine	T [°C]	p(CO) [bar]	t_R [h]	Conv.[b] [%]	Turnover frequency[c] [h^{-1}]	Molar ratio of **2**/**3**
1	**a**	50	1	0.5	100	>80	100/0
2	**a**	50	40	3	100	>13	75/25
3	**a**	50	60	1	100	>40	66/34
4	**a**	30	110	2	75	15	33/67
5	**a**	30	110	6	100	>7	46/54
6	**a**	30	20	2	69	13.8	61/39
7	**a**	30	20	3	80	10.7	60/40
8	**b**[d]	50	1	1	64	25.6	100/0
9	**b**[d]	50	40	0.5	100	>80	100/0
10	**b**[d]	30	120	2	100	>20	100/0
11	**c**[e]	50	1	1	100	>40	100/0
12	**c**[e]	50	40	1	100	>40	97/3
13	**c**[e]	30	120	2	87	17.4	93/7
14	**d**[f]	50	1	1	100	>40	100/0
15	**d**[f]	30	110	2	92	18.4	34/66
16	**d**[f]	30	110	4	100	>10	33/67
17	**e**[f]	30	110	4	100	>10	29/71

[a] Reaction conditions (unless otherwise stated): 1 mmol of substrate (**1**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of ligand (**L2**); 3 mmol of **a**; 0.5 mL of triethylamine; solvent: 10 mL of DMF.
[b] Determined by GC and GC–MS (naphthalene as internal standard).
[c] (mmol of **1**)×(mmol of Pd)$^{-1}$×(reaction time)$^{-1}$.
[d] Compound **b** (2 mmol).
[e] Compound **c** (1.1 mmol) (as a hydrochloride salt).
[f] Compounds **d**, **e**(1.5 mmol).

Table 2
tert-Butylaminocarbonylation of 1-iodocyclohexene (**1**) in the presence of palladium-triarylphosphite (**L1**–**L4**) in situ catalysts[a]

Entry	Ligand	T [°C]	p(CO) [bar]	t_R [h]	Conv.[b] [%]	Turnover frequency[c] [h^{-1}]	Molar ratio of **2**/**3**
1	**L1**	50	1	1	100	>40	100/0
2	**L1**	30	110	4	100	>10	39/61
3	**L2**	50	1	0.5	100	>80	100/0
4	**L2**	30	110	2	75	15	33/67
5	**L2**	30	110	6	100	>7	46/54
6	**L3**	30	110	1	59	23.6	43/57
7	**L3**	30	110	2	71	14.2	28/72
8	**L3**	30	110	6	100	>7	43/57
9	**L4**	50	1	1	100	>40	100/0
10	**L4**	30	110	2	76	15.2	33/67
11	**L4**	30	110	6	100	>7	50/50

[a] Reaction conditions (unless otherwise stated): 1 mmol of substrate (**1**); 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of ligand (**L1**–**L4**); 3 mmol of **a**; 0.5 mL of triethylamine; solvent: 10 mL of DMF.
[b] Determined by GC and GC–MS (naphthalene as internal standard).
[c] (mmol of **1**)×(mmol of Pd)$^{-1}$×(reaction time)$^{-1}$.



Scheme 2. A simplified catalytic cycle describing the formation of 1-cyclohexenylglyoxylamides.

3. Conclusions

The double carbonylation of an iodoalkene model compound has been carried out in palladium-catalysed aminocarbonylation. Alkenyl-glyoxylamides, valuable building blocks in synthetic chemistry, have been synthesized for the first time using this methodology. Arylphosphite heterobidentate P,O-ligands possessing binaphthyl backbone were used as ligands in palladium catalysts formed in situ from palladium(II) acetate and two molar equivalents of the corresponding phosphite ligand.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1 (internal standard: naphthalene; injector temperature 250 °C; oven: starting temperature 50 °C (hold-time 11 min), heating rate 15 °C min^{-1}, final temperature 320 °C; detector temperature 180 °C; carrier gas: helium (rate: 1 mL min^{-1})). The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg.

The amine nucleophiles were purchased from Sigma–Aldrich. 1-Iodocyclohexene (**1**) was prepared according to the literature procedure[18] starting from cyclohexanone. The ligands **L1**–**L4** were prepared as described before.[10] The products of known structure (**2a**,[16,17] **2c**,[18] **2d**,[19] **2e**[20,21]), obtained by conventional synthetic methods, gave identical spectra with those given in the literature.

It is worth noting that all carboxamides (**2a**–**e**) can be isolated in nearly quantitative yields (up to 98%) being the only products under mild reaction conditions. The full characterization of the isolated new ketocarboxamides (**3a**, **3d**, **3e**) is given below (Section 4.4).

4.2. Aminocarbonylation of 1-iodocyclohexene (1) in the presence *N*-nucleophiles under high carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), phosphite ligand (**L1**–**L4**) (0.05 mmol), 1-iodocyclohexene (1 mmol), amine nucleophile (3 mmol of **a**/2 mmol of **b**/1.1 mmol of **c**/1.5 mmol of **d**) and 0.5 mL triethylamine were dissolved in DMF (10 mL) under argon in a 100 mL autoclave. The atmosphere was changed to carbon monoxide and the autoclave was pressurized to the given pressure by carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C (or 30 °C) and analyzed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (3×20 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to a crystalline material or to a waxy residue. All compounds were subjected to column chromatography (Silicagel 60 (Merck), (0.063–0.200 mm), EtOAc/$CHCl_3$ (the exact ratios are specified in characterization for each compound)).

4.3. Aminocarbonylation of 1-iodocyclohexene (1) in the presence *N*-nucleophiles under atmospheric carbon monoxide pressure

In a typical experiment $Pd(OAc)_2$, phosphite ligand (**L1**–**L4**), 1-iodocyclohexene, amine nucleophile and triethylamine were dissolved in DMF (for the quantity of the reagents See Section 4.2) under argon in a 100 mL three-necked flask equipped with a gas inlet, reflux condenser with a balloon (filled with argon) at the top. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS (internal standard: naphthalene). The mixture was then concentrated and evaporated to dryness and worked-up as described in Section 4.2.

4.4. Characterization of the products

*4.4.1. Compound **3a**[22].* ^{1}H NMR ($CDCl_3$) δ: 7.80 (br s, 1H, =CH); 6.68 (br s, 1H, NH); 2.32 (m, 2H, CH_2); 2.23 (br s, 2H, CH_2); 1.65 (m, 4H 2× CH_2); 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 189.1, 162.0, 149.7, 135.5, 51.4, 28.3, 26.7, 23.1, 21.7, 21.2. IR (KBr (cm^{-1})): 3274 (NH); 1669 (CO); 1646 (CON). MS *m*/*z* (rel int. %): 209 (12%), 194 (2%), 153 (18%), 109 (100%), 81 (46%); 57 (32%). Analysis calculated for $C_{12}H_{19}NO_2$ (209.28): C, 68.87; H, 9.15; N, 6.69; found: C, 68.72; H, 9.01; N, 6.40. R_f (2% EtOAc/$CHCl_3$) 0.48. Mp. 81–82 °C. Beige crystalline material. Yield: 0.125 g (60%).

*4.4.2. Compound **3d**.* ^{1}H NMR ($CDCl_3$) δ: 6.93 (br s, 1H, =CH); 3.64–3.74 (m, 6H, 3× CH_2); 3.30 (t, 4.8 Hz, 2H, NCH_2); 2.35 (br s, 2H, CH_2); 2.26 (br s, 2H, CH_2); 1.66 (m, 4H, 2× CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.1, 166.1, 148.9, 137.0, 66.7, 66.6, 46.3, 41.4, 26.5, 21.8, 21.4, 21.3. IR (KBr (cm^{-1})): 1654 (CO); 1644 (CON); 1626 (C=C). MS *m*/*z* (rel int. %): 223 (31%), 194 (2%), 109 (100%), 81 (49%), 70 (19%), 53 (10%). Analysis calculated for $C_{12}H_{17}NO_3$ (223.27): C, 64.55; H, 7.67; N, 6.27; found: C, 64.37; H, 7.51; N, 6.05. R_f (20% EtOAc/$CHCl_3$) 0.4. Mp. 109–110 °C. Off white crystalline material. Yield: 0.138 g (62%).

*4.4.3. Compound **3e**.* ^{1}H NMR ($CDCl_3$) δ: 6.29 (br s, 1H, =CH); 3.61 (t, 5.2 Hz, 2H, NCH_2); 3.21 (t, 5.2 Hz, 2H, NCH_2); 2.38 (m, 4H, 2× CH_2); 1.56–1.65 (m, 10H, 5× CH_2). ^{13}C NMR ($CDCl_3$) δ: 193.9, 166.1, 148.2, 136.9, 47.1, 42.0, 26.5, 26.2, 25.4, 24.4, 21.8, 21.4, 21.3. IR (KBr (cm^{-1})): 1658 (CO), 1641 (CON). MS *m*/*z* (rel int. %): 221 (28%), 192

(6%), 109 (100%), 81 (48%); 69 (46%), 53 (15%). Analysis calculated for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33; found: C, 70.40; H, 8.77; N, 6.17. R_f (10% EtOAc/$CHCl_3$) 0.48. Mp. 77–78 °C. Yellow crystalline material. Yield: 0.146 g (66%).

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