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Unprecedent Chemo- and Stereoselective Palladium-Catalysed Methoxycarbonylation of Norbornene

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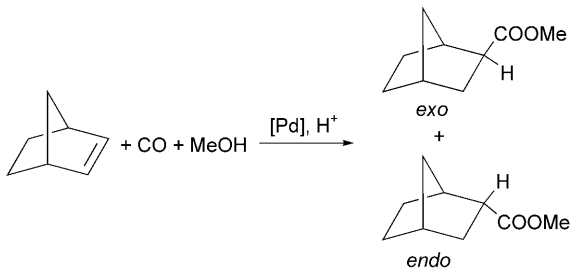
Abstract: Catalytic systems able to control chemo- and stereoselectivity have been tested in the palladium-catalysed methoxycarbonylation of norbornene. An enantioselectivity of up to 40% was obtained.

Keywords: carbonylation; chemoselectivity; norbornenes; palladium catalyst; stereoselectivity

Over the past two decades, the alkoxycarbonylation of styrene and related vinylarenes has been extensively studied as a route to obtain linear[1] and branched esters.[2] The branched esters can be hydrolysed to acids that are an important class of non-steroidal anti-inflammatory drugs.[3] Therefore together with extensive studies on styrene, often used as a model,[4] the functionalisation of substrates such as 2-vinyl-6-methoxynaphthalene,[5] 4-methoxystyrene,[2d] α-methylstyrene,[6] and acenaphthylene[7] have been the object of attention of both academic and industrial research groups. The alkoxycarbonylation of norbornene, however, has been less studied,[8,9] (Scheme 1) although its functionalisation is particularly relevant since the products present unique structural and chemical features. The functionalisation of this olefin allows the generation of three chiral carbon centres upon one C–C bond formation. Chemo-, stereo- (*exo/endo*) and enantioselectivity are important issues.[10]



Scheme 1. Methoxycarbonylation of norbornene catalysed by palladium.

As far as we know, only a few reports have appeared on this process. In 1996, Wang et al.[8] reported the first asymmetric alkoxycarbonylation of norbornene using $Pd(OAc)_2$/DDPPI/*p*-TsOH as a catalytic system claiming 72% of conversion in ester and 92% *ee* under 50 atm of CO at 120 °C. However, we were unable to reproduce these results under the given conditions, as the ether was obtained as the major product. Inoue et al.[9] carried out the alkoxycarbonylation of different olefins using as catalyst the cationic palladium complex $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ under 5 atm of CO at 100 °C for 20 h. For norbornene as substrate, the best chemoselectivity into ester obtained in this work was 74%. Therefore both examples showed that chemoselectivity to ester is a difficult issue in the case of the palladium-catalysed alkoxycarbonylation of norbornene. As well as the ether formed through the reaction of methanol, oligomers and copolymers are formed through CO/ethylene alternated insertion. This difficulty to obtain the adequate chemoselectivity can be the reason for the lack of studies in the palladium-catalysed carbonylation of norbornene.

In this communication we report the control of the chemo- and stereoselectivity in the methoxycarbonylation of norbornene catalysed by palladium complexes bearing bidentate (**1**–**5**) and monodentate (**6**, **7**) phosphine ligands (Figure 1). Diphosphine **1** has been shown to be an excellent ligand which offers exceptional activity, selectivity and stability in the Pd-catalysed methoxycarbonylation of terminal, internal alkenes,[11] styrene,[12] vinyl acetate[13] and ethene,[14] exhibiting extremely high selectivity towards the ester formation. For this reason, in our study we have chosen diphosphine **1** as a model ligand in the palladium-catalysed methoxycarbonylation of norbornene.

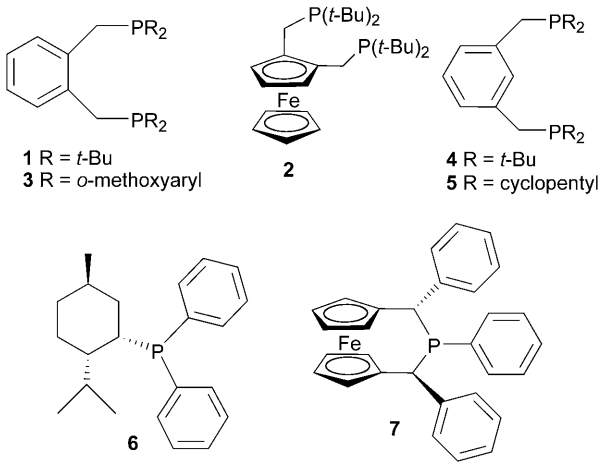


Figure 1. Bidentate and monodentate phosphine ligands used in Pd-catalysed methoxycarbonylation of norbornene.

In methoxycarbonylation the presence of acid is often required in order to favour the formation of Pd–H species.[15] One important issue is to minimise the acid to avoid the corrosion of the reaction vessel. We have explored the effect of the acid and catalytic precursors on the methoxycarbonylation of norbornene using ligand **1**. The results are summarised in Table 1. The catalytic reactions were performed using $PdCl_2$/**1** as a catalytic system under 30 bars of CO at 70 °C for 24 h. First, we performed an experiment in the absence of acid and, although 86% of conversion was obtained, the chemoselectivity was very low (22%) (entry 1). The acids *p*-TsOH, $MeSO_3H$, CF_3SO_3H, $C_2H_2O_4$ (entries 2–5) and the sulfonic acid grafted polymer SMOPEX®101 (entry 6) provided conversions ranging between 75 and 99% and selectivities to ester between 39 and 75%. In all cases, the presence of copolymers as by-products of the reaction was observed. However, when TFA was used (entry 7) the only reaction product was the desired ester in 91% conversion. Furthermore, under these conditions, total selectivity to the *exo* product was achieved. Concerning the palladium precursor, the use of $[Pd_2(dba)_3]$ as Pd(0) source in the presence of ligand **1** provided a conversion of 77% and the chemoselectivity remained high at 94% (entry 8). When $[Pd(OAc)_2]$ was used under the same conditions no conversion was observed. Using the isolated palladium complex $[PdCl_2(\mathbf{1})]$ (entry 9) under the same conditions the conversion increased to 98%, but the chemoselectivity (84%) and the stereoselectivity (66/34) decreased compared with the palladium precursor prepared *in situ* (entry 7). These results suggested that different species were formed when the *in situ* method was used. To confirm this hypothesis, HP NMR experiments were performed using both methods in the presence of 10 equivalents of TFA under 30 bar of CO using a mixture of CH_3OD/THF as solvent. The solutions were heated to 70 °C for 2 h within the spectrometer and the reactions monitored by ^{31}P NMR. When the isolated complex $PdCl_2$(**1**) was used, a single organometallic species was detected at $\delta = 35.5$ as a singlet. When the *in situ* $PdCl_2$/**1** system was investigated, the same signal was observed. The identity of the corresponding species is currently under investigation and will be reported in due course. Furthermore, during the *in situ* experiment, two new singlet signals at $\delta = 39.5$ and $\delta = 49.2$ were detected and assigned to the mono- and diprotonated ligands $(t\text{-Bu})_2P–CH_2–C_6H_4–CH_2–P(t\text{-Bu})_2H^+$ and $^+H(t\text{-Bu})_2P–CH_2–C_6H_4–CH_2–P(t\text{-Bu})_2H^+$. The identitities of these latter species were confirmed by performing the reaction of **1** in the presence of TFA at 70 °C. The difference between the catalytic results obtained with these two methods was therefore attributed to the presence of an extra equivalent of ligand **1** under *in situ* conditions. This was confirmed when the catalytic experiment was performed using the isolated complex $PdCl_2$(**1**) as precursor in the presence of 1 equivalent of ligand **1** (Table 1, entry 10) since the chemo- and stereoselectivity obtained under these conditions were found to be identical to those previously achieved using the *in situ* method. It was therefore concluded that the lower stereoselectivity obtained using the isolated complex $PdCl_2$(**1**) alone (entry 9) was due to decomposition of the ligand under the catalytic conditions.

Once the desired chemoselectivity was obtained using ligand **1**, other ligands were investigated in

Table 1. Effect of the acid and catalytic precursor on the methoxycarbonylation of norbornene using ligand **1**[a]

Entry	Catalytic Precursor	Acid	C (%)[b,c]	S (%)[b,c]	% (*exo*/*endo*)
1[d]	$PdCl_2$/**1**	–	86	22	nd
2	$PdCl_2$/**1**	*p*-TsOH	99	75	100/–
3	$PdCl_2$/**1**	$MeSO_3H$	99	39	nd
4	$PdCl_2$/**1**	CF_3SO_3H	99	54	100/–
5	$PdCl_2$/**1**	$C_2H_2O_4$	99	61	100/–
6[e]	$PdCl_2$/**1**	poly-SO_3H	75	75	nd
7	$PdCl_2$/**1**	TFA	91	100	100/–
8	$[Pd_2(dba)_3]$/**1**	TFA	77	94	nd
9	$[PdCl_2(\mathbf{1})]$	TFA	98	84	66/34
10	$[PdCl_2(\mathbf{1})]$/**1**	TFA	99	100	100/–

[a] *Reaction conditions:* Pd (0.021 mmol), L/Pd: 2, acid (0.210 mmol), norbornene (1.05 mmol), MeOH/THF (1:1), 30 bar of CO, reaction temperature: 70 °C, time: 24 h.
[b] All conversions and chemoselectivities were determined by GC and GC-MS.
[c] C = conversion; S = selectivity to ester.
[d] Without acid. nd = not determined.
[e] Poly-SO_3H = sulfonic acid grafted polyolefin SMOPEX®101.

order to compare the influence of both moieties, the backbone and the P substituents. A series of bulky diphosphines based on a ferrocenyl backbone (**2**) and a xylene backbone (**3, 4, 5**), was tested in the Pd-catalysed methoxycarbonylation of norbornene (Figure 1). The results are summarised in Table 2. When the

Table 2. Methoxycarbonylation of norbornene using bidentate phosphine ligands.[a]

Entry	Precursor	C (%)[b,c]	S (%)[b,c]	% (*exo/endo*)
1	$PdCl_2$/**1**	91	100	100/–
2	$PdCl_2$/**2**	75	100	100/–
3	$PdCl_2$/**3**	14	89	–
4	$PdCl_2$/**4**	<5	<5	–
5	$PdCl_2$/**5**	<5	<5	–

[a] *Reaction conditions:* Pd (0.021 mmol), L/Pd: 2, TFA (0.210 mmol), norbornene (1.05 mmol), MeOH/THF (1:1), 30 bars of CO, reaction temperature: 70 °C, time: 24 h.
[b] All conversions and chemoselectivities were determined by GC and GC-MS.
[c] C = conversion; S = selectivity to ester.

ligand based on a ferrocenyl backbone (**2**) is used instead of the *ortho*-xylene (**1**) and the *t*-Bu groups at the phosphorus atoms are retained, we observed that the conversion decreased to 75% while the chemoselectivity in ester and the stereoselectivity remained excellent (Table 2, entry 2 *vs.* entry 1). When the *ortho*-xylene backbone is retained but the *t*-Bu groups are replaced by *ortho*-methoxyaryl groups (**3**) the activity is drastically reduced, although the chemoselectivity remained high (entry 3)

The effect of the bite angle can be observed when comparing catalytic systems with *ortho*- and *meta*-xylene backbone and identical P susbtituents (entries 1 *vs.* 4). In the case of a larger bite angle, the activity and the chemoselectivity were very poor, $<5\%$. It was found in the literature that structurally similar ligands exhibit a remarkable chelate effect that produces very stable tridentate palladium pincer complexes.[16] Analogous complexes could be responsible here for catalyst deactivation. An identical behaviour was observed for catalytic systems with ligand **5** which contained an identical *meta*-xylene backbone and cyclopentyl P substituents (entry 5).

In summary, the best results in terms of chemo- and exoselectivity are obtained with ligands **1** and **2** which both contain *t*-Bu groups at phosphorus and form a 7-membered chelating ring with the palladium atom. Highly electron-donating and bulky diphosphine ligands are required for the successful Pd-catalysed methoxycarbonylation of norbornene.

Catalytic precursors containing monodentate phosphines and phosphetanes have been recently reported to be active in the Pd-catalysed methoxycarbonylation of styrene,[2d,17] but only a few successful examples of monophosphine ligands have achieved significant activity, regioselectivity and enantioselectivity.[2a,b] As far as we know, the Pd-catalysed methoxycarbonylation of norbornene has hardly been studied with monodentate phosphine ligands.[9] Here, we used two different monodentate phosphine ligands (Figure 1, ligands **6**, and **7**). The results are summarised in Table 3.

Table 3. Methoxycarbonylation of norbornene using monodentate phosphine ligands **6** and **7**.[a]

Entry	Precursor	L	C (%)[b,c]	S (%)[b,c]	% (*exo*)/(*ee*)[b]
1[d]	$PdCl_2$	**6**	72	100	100 (9)
2[d]	$[PdCl_2(\mathbf{6})_2]$	**6**	100	100	100 (10)
3[d]	$[Pd_2(dba)_3]$	**6**	75	17	nd
4[d]	$PdCl_2$	**7**	53	25	nd
5	$PdCl_2$	**7**	99	90	100 (40)

[a] *Reaction conditions:* Pd (0.021 mmol), L/Pd: 2, TFA (0.210 mmol), norbornene (1.05 mmol), MeOH/THF (1:1), 30 bar of CO, reaction temperature: 70 °C, time: 24 h.
[b] All conversions and selectivities were determined by GC and GC-MS.
[c] C = conversion; S = chemoselectivity to ester.
[d] Without acid. nd = not determined

It is important to note that when palladium dichloride and (*S*)-NMDPP (**6**) were used as a catalytic system without an acidic medium, 72% conversion was observed together with an excellent chemo- (100%) and exoselectivity (100%) (entry 1). These observations agree with those reported by Nozaki and co-workers[2c] in the palladium-catalysed methoxycarbonylation of styrene, where the catalytic system $PdCl_2$/**6** in the absence of acid provided esters with high conversion and selectivity. When the isolated palladium complex $[PdCl_2(\mathbf{6})_2]$ was tested under the same conditions, the conversion was greatly increased (100%) compared with the palladium precursor prepared *in situ* (72%) and the chemo- and exoselectivity remained excellent (Table 3, entry 2 *vs.* entry 1).

When $[Pd_2(dba)_3]$ was used as the Pd precursor, the chemoselectivity decreased to 17% (entry 3). It appears that the palladium dichloride plays a crucial role in the selectivity of the reaction. We have also used the (*S*,*S*)-ferrocenylphosphine **7**, a new chiral phosphine whose synthesis has been reported recently[18] and that has never been used previously in organometallic catalysis. The experiments were performed using the catalytic system $PdCl_2$/(*S*,*S*)-ferrocenylphosphine **7**. The absence of acid drastically affected both the conversion and the selectivity (entry 4). However, very good conversion, chemoselectivity and *exo*-selectivity were obtained using the

monophosphine **7** under mild acidic conditions (entry 5). With the chiral ligands **6** and **7**, *ee*s of 10% and 40% were obtained, respectively.

In summary, the first totally chemo- and stereoselective Pd-catalysed methoxycarbonylation of norbornene is reported. We have found how norbornene can be chemo- and stereoselectively functionalised by controlling the reaction conditions and using the adequate ligands. Subtle modifications of the palladium phosphine catalyst lead to significant results in activity and selectivity. The palladium system containing bulky and basic diphosphine **1** in the presence of TFA provides excellent conversions, chemoselectivities and stereoselectivities. The palladium system with monophosphine **6** is active in the absence of acid and 100% of conversion, chemo- and stereoselectivity are obtained. The promising *ee*s obtained using ligands **6** and **7** show a new route for the transformation of norbornene into useful intermediates for organic synthesis. Optimisation of these catalytic reactions is currently in progress.

Experimental Section

Typical Procedure for Methoxycarbonylation Reactions

High pressure experiments were carried out in a Berghof autoclave, and the reaction mixtures were magnetically stirred and electrically heated. In a typical experiment, a solution of the palladium precursor (0.021 mmol), TFA (0.210 mmol) and norbornene (1.05 mmol) in 5 mL of THF-MeOH mixture (1:1) were introduced into the evacuated autoclave. Carbon monoxide was introduced and the system was then heated. When thermal equilibrium was reached, stirring was initiated. After reaction, the autoclave was cooled to room temperature and depressurised. The product was filtered in a short column of celite and solvent was removed under vacuum. Conversions, chemo-, regio- and enantioselectivities were determined by GC and HPLC analyses.

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References

[1] C. Bianchini, A. Meli, W. Oberhauser, S. Parisel, O. V. Gusev, A. M. Kal'sin, N. V. Vologdin, F. M. Dolgushin, *J. Mol. Cat. A: Chem.* **2004**, *224*, 35.
[2] a) G. Cometti, G. P. Chiusoli, *J. Organomet. Chem.* **1982**, *236*, C31-C32; b) K. Nozaki, M. L. Kantam, T. Horiuchi, H. Takaya, *J. Mol. Cat A: Chem.* **1997**, *118*, 247; c) Y. Kawashima, K. Okano, K. Nozaki, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 347; d) B. K. Muñoz, C. Godard, A. Marinetti, A. Ruiz, J.-B. Buchholz, C. Claver, *Dalton Trans.* **2007**, *47*, 5524.
[3] H. Alper, M. Hamel, *J. Am. Chem. Soc.* **1990**, *112*, 2803.
[4] C. Godard, B. K. Muñoz, A. Ruiz, C. Claver, *Dalton Trans.* **2008**, 853.
[5] Y. Kawashima, K. Okano, K. Nozaki, T. Hiyama, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 347.
[6] T. Hayashi, M. Tanaka, I. Ogata, *Tetrahedron Lett.* **1978**, 3925.
[7] J. Gironés, J. Duran, A. Polo, J. Real, *Chem. Commun.* **2003**, 1776.
[8] H. Zhou, S. Lu, J. Hou, J. Chen, H. Fu, H. Wang, *Chem. Lett.* **1996**, 339.
[9] S. Oi, M. Nomura, T. Aiko, Y. Inoue, *J. Mol. Cat. A: Chem.* **1997**, *115*, 289.
[10] J, Huang, E. Bunel, A. Allgeier, J. Tedrow, T. Stors, J. Preston, T. Correl, D. Manley, T. Soukup, R. Jensen, R. Syed, G. Moniz, R. Larsen, M. Matinelli, P. J. Reider, *Tetrahedron Lett.* **2005**, *46*, 7831.
[11] C. J. Rodríguez, D. J. Foster, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2004**, 1720.
[12] H, Ooka, T. Inoue, S. Itsuno, M. Tanaka, *Chem. Commun.* **2005**, 1173.
[13] a) A. J. Rucklidge, G. J. Morris, A. M. Z. Slawin, D. J. Cole-Hamilton, *Helv. Chim. Acta* **2006**, *89*, 1783; b) A. J. Rucklidge, G. E. Morris, D. J. Cole-Hamilton, *Chem. Commun.* **2005**, 1176.
[14] W. Clegg, G. R. Eastham, M. R. J. Elsegood, R. P. Tooze, X. L. Wang, K. Whiston, *Chem. Commun.* **1999**, 1877.
[15] W. Clegg, G. R. Eastham, M. R. J. Elsegood, B. T. Heaton, J. A. Iggo, R. P. Tooze, R. Whyman, S. Zacchini, *Organometallics* **2002**, *21*, 1832.
[16] a) M. Ohff, A. Ohff, M. E. Van der Boom, D. Milstein, *J. Am. Chem. Soc.* **1997**, *119*, 11687; b) S. Gibson, D. F. Foster, G. R. Eastham, R. P. Tooze, D. J. Cole-Hamilton, *Chem. Commun.* **2001**, 779.
[17] B. K. Muñoz, A. Marinetti, A. Ruiz, S. Castillón, C. Claver, *Inorg. Chem. Commun.* **2005**, *8*, 1113.
[18] N. Fleury-Brégeot, A. Panossian, A. Chiaroni, A. Marinetti, *Eur. J. Inorg. Chem.* **2007**, 3853.

