Enantioselective Carbonylation

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Highly Enantioselective Hydroxycarbonylation and Alkoxycarbonylation of Alkenes using Dipalladium Complexes as Precatalysts**

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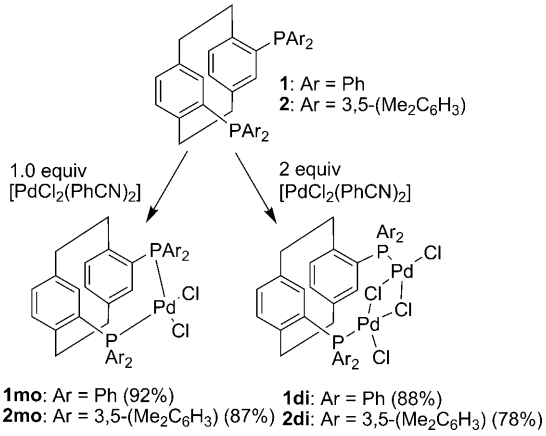
Carboxylic acids make up a significant proportion of the commercially available chiral building blocks. An optimized process that produces enantioenriched carboxylic acids from readily available, cheap chemicals without the need for resolution is highly desired. One of the more important developments in catalysis in recent years has been the development of palladium catalyzed carbonylation of ethylene into a large scale highly productive commercial process for the formation of methyl propionate.[1] An enantioselective variant of alkene carbonylation is potentially the most efficient and versatile method to make single-enantiomer carboxylic acid derivatives, and both hydroxycarbonylation[2] and methoxycarbonylation[3] have attracted attention for many years.

The majority of studies have specifically focused on methoxycarbonylation (also referred to as hydroesterification) of styrene. Important contributions to this field include some reports of very good enantioselectivity.[3] However, the reaction has not been widely used in synthesis because of the high reaction temperatures (ca. 150 °C), greater than stoichiometric amount of acid co-catalysts, and the low overall yield of the branched acid. Enantioselective hydroxycarbonylation has been very problematic indeed, and a large improvement in catalyst performance is required before it can be considered a synthetically useful process.[4]

We have undertaken studies to improve substrate scope and regiochemical control of the reaction,[2f,g,j] but our ambition has always been to realize a useful enantioselective process. For a number of years, this ambition has been thwarted by even the very best chiral diphosphine ligands giving mediocre enantioselectivities, as has been found by others; the best diphosphine reported in the literature gave only 43 % *ee*, and most ligands give near-racemic products.[4] Herein we show a highly enantioselective process that operates well below 100 °C, uses less than 1 equivalent of an acid promoter, and delivers product with up to 95 % *ee*. In addition, it makes use of a class of precatalysts, namely dimetallic halides derived from chiral bridging diphosphines, that are unexplored not only in carbonylation reactions but in any form of asymmetric catalysis.[5]

In the course of preparing a series of simple monomeric palladium complexes of the type $[PdCl_2(L)]$ (L = ligand) from the planar chiral phanephos ligands **1** and **2** (Scheme 1), we



Scheme 1. Synthesis of monomeric and dimetallic palladium complexes using the phanephos ligands **1** and **2**.

observed unexpected side-products (**1di,2di**). Additional investigation using combustion analysis and mass spectrometry suggested this side-product to be a dimetallic complex in which the chiral diphosphine bridges two palladium centers. For the well-known phanephos ligands **1** and **2**, either dipalladium (**1di,2di**) or monopalladium (**1mo,2mo**) complexes can be prepared in high yield by employing the appropriate stoichiometry.

Halide-bridged palladium dimers are well-known species in cases where each metal is bound by one monophosphine such as triphenylphosphine.[6a] However, halide-bridged dipalladium complexes in which a diphosphine also forms a bridge between the two metals are very rare,[6b–d] and this is seemingly the first example using an enantiomerically pure diphosphine.

Diphosphines are normally employed in excess in alkene carbonylation, and the successful use of diphosphines in thousands of different enantioselective reactions has relied upon them adopting a stable chelate coordination mode.

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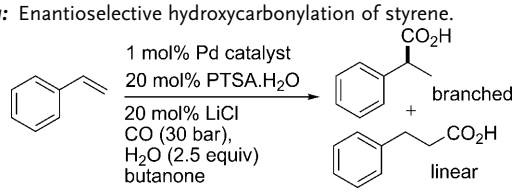
Nonetheless, the performances of the dipalladium complexes **1di** and **2di** in the hydroxycarbonylation of styrene were compared to their monomeric counterparts (Table 1). At

Table 1: Enantioselective hydroxycarbonylation of styrene.



Entry[a]	Catalyst	*T* [°C]	*t* [h]	Yield [%][b]	b/l[c]	*ee* [%][d]
1	**1di**	100	18	53	0.68	18
2	**1mo**	100	18	51	0.28	8
3	**2di**	100	17	67	0.30	18
4	**2mo**	100	17	60	0.25	16
5	**1di**	60	17	29	1.2	59
6	**1mo**	60	17	4	1.2	55
7	**2di**	60	16	58	1.0	76
8	**2mo**	60	17	14	0.73	66
9	**2di**	**50**	**42**	**71**	**1.1**	**80**
10	**2mo**	50	42	8	0.43	50
11	**1di**	50	42	35	1.1	69
12	**1mo**	50	42	4	0.75	62

[a] Reactions conditions: catalyst (1 mol%), styrene (1 mmol), water (2.5 mmol), CO (30 bar), of degassed butanone as solvent (1.5 mL), LiCl (20 mol%), and *p*-toluene sulfonic acid hydrate co-catalyst (PTSA; 20 mol%). [b] Yield of pure acid isolated after an acid/base extraction of the crude reaction mixture. [c] The branched to linear (b/l) ratio was determined by using ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral column. *R*-configured catalysts give *R*-configured product and vice versa.

temperatures above 100 °C, the products were nearly racemic, but we were encouraged by the quite reasonable reactivity. To our surprise, reducing reaction temperatures enabled the first reasonably efficient enantioselective hydroxycarbonylation. The dipalladium precatalysts reproducibly gave higher reactivity and comparable or even slightly higher enantioselectivity than their monomeric analogues. When using styrene as the substrate, the expected mixture of regioisomers was formed, but up to 81% *ee* can be realized at around 50 °C when using 20 mol% of the acid co-catalyst (Table 1 and Tables S1 and S2 in the Supporting Information). *Para-tert*-butylstyrene also underwent hydroxycarbonylation in good yield and with 85% *ee*. Markedly improved results were once again seen using the dipalladium complexes as precatalysts (Table S2 in the Supporting Information)

Our studies show that similar *ee* values can be realized in enantioselective methoxycarbonylation of styrene at a given temperature, suggesting that the new catalysts will prove useful for this class of reaction. For example, Table 2 shows the methoxycarbonylation of styrene in the presence of **1di** and **2di** by using similar reaction conditions to those used for the hydroxycarbonylation; however, methanol was used as both a reagent and solvent. The methoxycarbonylation reaction is more facile as the catalysts perform competently at 50 °C; shorter reaction times or dilution indicate that the dimers have higher activity (Table 2, entries 5–8 and Table S4

Table 2: Enantioselective methoxycarbonylation of styrene.

Entry[a]	Catalyst	*T* [°C]	*t* [h]	Ester [%][b]	b/l[c]	*ee* [%][d]
1	**1di**	50	42	>99	0.43	69
2	**1mo**	50	42	95	0.34	72
3	**2di**	50	42	>99 (66)	0.57	80
4	**2mo**	50	42	>99	0.12	80
5	**1di**	50	3	10	0.57	54
6	**1mo**	50	3	3	0.71	69
7	**2di**	50	3	17	0.86	79
8	**2mo**	50	3	18	0.69	80
9	**2di**	35	67	>99	0.88	89
10	**2di**	**25**	**42**	**71 (62)**	**0.95**	**91**

[a] Reactions conditions: catalyst (1 mol%), styrene (1 mmol), CO (30 bar), methanol (1.5 mL), LiCl (20 mol%), and *p*-toluene sulfonic acid hydrate co-catalyst (20 mol%). [b] Determined by NMR analysis using an internal standard (see the Supporting Information). Value in parentheses is the yield of the pure ester isolated after column chromatography. [c] The b/l ratio was determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral column. *R*-configured catalysts gives *R*-configured product and vice versa.

in the Supporting Information). The methoxycarbonylations still proceed well at temperatures as low as 25 °C, which allows even higher enantioselectivity to be realized (Table 2, entry 10). In the literature, alkoxycarbonylations are reported to proceed with much better enantioselectivity than hydroxycarbonylations. However, by using these dimetallic catalysts, the results in terms of enantioselectivity at a given temperature are similar to those of hydroxycarbonylation reaction, even though the activity is higher for all catalysts. This similarity is consistent with some aspects of the mechanism being common to both processes.

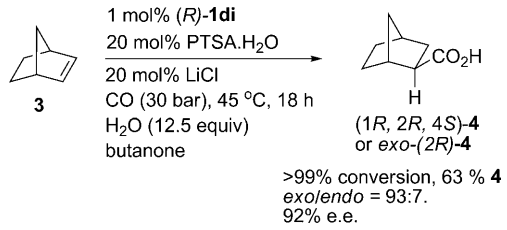
Despite operating at lower temperatures than has been generally reported in the literature, we have utilized similar catalyst loadings relative to those of previous reports (ca. 1 mol%) and the methoxycarbonylation proceeds well with just 0.09 mol% catalyst (Table S4 in the Supporting Information). This family of catalysts are possible candidates for future development for commercial application. Additional optimization of the catalyst performance or a recycling protocol would be useful improvements, and are a part of our current and future investigations. Another area of development in alkoxycarbonylation would be to define a general protocol for converting most alcohols into esters having high *ee* values. To address this issue, we have found that both *n*PrOH and *i*PrOH can be used as nucleophiles to generate the *n*-propyl and isopropyl esters, respectively, in good enantioselectivity (Table S4 in the Supporting Information). The difference in the product yield for the *n*-propyl ester when using **1mo** versus **2di** was 94%.

The regioisomeric product mixtures are almost always produced by the diphosphine catalysts and present an area for improvement in styrene carbonylation; in contrast many other alkene substrates that give more useful chiral acid products either do not present regiochemical issues or may have a different regiochemical bias in carbonylation chemistry. However, very little information is known about how different alkenes behave in hydroxy-carbonylation reactions;

our next objective was to investigate if enantioselectivity could be realized on a very different alkene substrate.

We chose to investigate hydroxycarbonyation of norbornene using the dimeric catalysts. The control of the chemoselectivity using norbornene is a challenge, and this control must be accomplished in addition to control of *exo*/*endo* selectivity and enantioselectivity. During the course of our work, the first promising results for formation of racemic methyl *exo* norbornate, as well as an asymmetric synthesis (40% *ee*) were published.[7] However, a successful hydroxycarbonylation protocol has not yet been developed.

Our early attempts with norbornene were plagued by poor chemoselectivity and the formation of low molecular weight oligomers, thus reducing the selectivity of the reaction. This problem was also found when using triphenylphosphine-based catalysts. After some optimization, the new chiral catalysts delivered high conversion, reasonable chemoselectivity (50 to 65%), high *exo/endo* selectivity, and up to 95% *ee* in the hydroxycarbonylation of norbornene (Scheme 2 and



Scheme 2. An example of one of the first successful hydroxycarbonylations of norbornene (changing to the *S*-configured catalyst delivers the (1*S*, 2*S*, 4*R*)-**4** (*exo*-(2*S*)-**4**).

Tables S5 and S6 in the Supporting Information). For this substrate, both the dipalladium catalysts and monomers give similar enantioselectivities, and in some cases better reactivity was encountered using the dipalladium catalysts. The high enantioselectivity and evidence that the substrate turns over are very promising for future studies on the applicability of this class of catalyst.

The use of a precatalyst in which the diphosphine bridges two metals is extremely rare, and an in-depth study of this catalyst and its mode of action in carbonylation reaction will be the focus of future studies. However, to completely confirm the bimetallic nature of the precatalyst, we have determined the structure of $[Pd_2Cl_2(\mu\text{-}Cl)_2(\mu\text{-xyl-phanephos})]$ using X-ray crystallography. The crystal structure is shown in Figure 1. Amongst several interesting features, the dimer possesses a shorter Pd–Pd bond [2.9136(19) Å] than has been observed in other dimeric palladium halides. The terminal chloride ligands are located gauche to each other, which is in contrast to the *syn* arrangement reported in the study of the palladium dimers of tritycene diphosphines.[6b] The $[Pd_2Cl_2(\mu\text{-}Cl)_2]$ core can be best described as possessing an unusual form of axial chirality, and the mirror image of this core (presumably formed from the opposite enantiomer of diphosphine) places the terminal chlorines in opposing directions to those shown in Figure 1.[5c] Our initial working model was that the real active catalyst would be a monomeric species that is

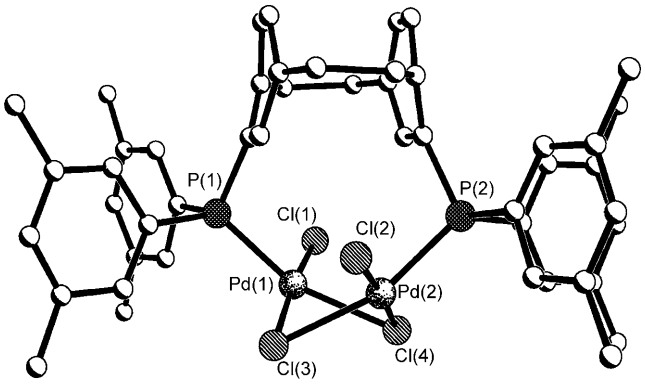


Figure 1. X-ray structure of complex **2di**.

somehow accessed more readily from the dipalladium precatalysts. If the dipalladium complexes form a monomeric catalyst, then it seems likely that some form of "PdX_2" would be released presumably in a soluble form since the reactions are homogeneous. An experiment in which the opposite enantiomer of phanephos was added to the dipalladium precatalyst was carried out, because it seemed likely that upon release of "PdX_2" the other enantiomer of phanephos would coordinate to palladium and then deliver a racemic product. The results showed almost no loss of enantioselectivity in this experiment, but a significant decrease in the yield (Table S3 in the Supporting Information). The conversion of the dimer into the active catalyst is therefore rather more complex, and an intriguing possibility that we cannot rule out thus far is that the catalytic cycle utilizes dimetallic intermediates having bridging diphosphines. Carbon monoxide, hydride, and halide ligands are all very competent bridging ligands that could facilitate this type of cycle. A halide-bridged dimetallic complex of a monophosphine has been isolated from a carbonylation experiment, but in this case was considered to be part of a nonproductive catalytic pathway.[8] However, given that the monophosphine dimer did promote the carbonylation in low yield, it is possible that monophosphine dipalladium species are not as long-lived as diphosphine dipalladium catalysts. Examination of dimetallic complexes of other chiral bridging phosphines used in other types of asymmetric catalysis may prove to be an interesting area for additional study.[5d] It is possible that distinct halide ligands within the chiral $[Pd_2Cl_2(\mu\text{-}Cl)_2]$ core could be selectively exchanged for CO and hydride ligands, thereby making migratory insertion into the alkene complex favored on one face of the complexed alkene (somewhat reminiscent of the proposed selective ligand exchanges in the Sharpless epoxidation using dimeric titanium complexes[9]). Alternatively, given that dual metal systems such as $[PdCl_2(PPh_3)_2]$ and $SnCl_2$ are enhanced carbonylation catalysts relative to a mono-metal system, and are postulated to form $Pd/SnCl_3$ species,[10] then it is possible that some form of $[PdL_xCl_y]$ is released from the dimer, but returns to act as an anionic ligand for the chiral palladium intermediates at some point in the cycle, therefore giving the rate enhancements observed. It is likely that hydrolysis/alcoholysis of the acyl species is the

rate-determining step in alkene carbonylation.[2d,h] An experiment wherein methoxycarbonylation was carried out using only 3 equivalents of methanol rather than as solvent showed the monomer to be inactive, under reaction conditions where the dimer provides 18% product. Thus, it is possible that it is the methanolysis step that is facilitated by the dimeric catalyst. Whatever the outcome of the mechanistic studies, these catalysts enable high enantioselectivity in the hydroxycarbonylation of alkenes, and the reaction is very promising for the production of chiral acids and esters using inexpensive starting materials.[11]

Experimental Section

Additional catalysis experiments, experimental procedures, and characterization data are available in the Supporting Information. The X-ray crystal structure data is available from the Cambridge Crystallographic data Centre; CCDC 783946 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The X-ray structure was determined using $Mo_{K\alpha}$ (rotating anode) at 0.71073 Å and 93 K. Formula: $C_{48}H_{50}Cl_4P_2Pd_2$; Weight 1043.42; Monoclinic crystals, Space group P2(1). Unit cell dimensions: $a = 9.437(5)$ Å, $b = 17.075(8)$ Å, $c = 13.627(7)$ Å. $\alpha = 90°$; $\beta = 100.729(9)°$; $\gamma = 90$; Volume = 2157.6(18) Å^3; Density = 1.606 Mg m^{-3}. 2 formula units per unit cell. Reflections collected = 21145 (7568 independent reflections). $R_{int} = 0.1142$. R1/wR2 $\{I > 2\sigma(I)\} = 0.0965/0.2909$. R1/wR2 (all data) = 0.1053/0.3010.

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[1] a) W. Clegg, G. R. Eastham, M. R. J. Elsegood, R. P. Tooze, X. L. Wang, K. Whiston, *Chem. Commun.* **1999**, 1877; b) C. Jimenez Rodriguez, D. F. Foster, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2004**, 1720; c) For related (also achiral) processes H. Ooka, T. Inoue, S. Itsuno, M. Tanaka, *Chem. Commun.* **2005**, 1173; d) R. I. Pugh, E. Drent, P. G. Pringle, *Chem. Commun.* **2001**, 1476.

[2] a) I. del Río, C. Claver, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **2001**, 2719; b) S. Jayasree, A. Seayad, R. V. Chaudhari, *Chem. Commun.* **2000**, 1239; c) A. Seayad, S. Jayasree, R. V. Chaudhari, *Org. Lett.* **1999**, *1*, 459; d) A. Ionescu, G. Laurenczy, O. F. Wendt, *Dalton Trans.* **2006**, 3934; e) M. S. Goedheijt, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. Van Leeuwen, *Chem. Commun.* **1998**, 2431; f) J. J. R. Frew, M. L. Clarke, U. Mayer, H. van Rensburgh R. P. Tooze, *Dalton Trans.* **2008**, 1976; g) J. J. R. Frew, M. L. Clarke, K. Damian, A. M. Z. Slawin, H. van Rensburgh R. P. Tooze, *Chem. Eur. J.* **2009**, *15*, 10504; h) D. Milstein, *J. Chem. Soc. Chem. Commun.* **1986**, 817; i) H. Neumann, A. Brennführer, M. Beller, *Adv. Synth. Catal.* **2008**, *350*, 2437; j) A. Grabulosa, J. J. R. Frew, J. A. Fuentes, A. M. Z. Slawin, M. L. Clarke, *J. Mol. Catal. A* **2010**, *330*, 18.

[3] a) E. Guiu, M. Caporali, B. Muñoz, C. Muller, M. Lutz, A. L. Spek, C. Claver, P. W. N. M. Van Leeuwen, *Organometallics* **2006**, *25*, 3102; b) C. Godard, A. Ruiz, C. Claver, *Helv. Chim. Acta* **2006**, *89*, 1610; c) I. del Río, N. Ruiz, C. Claver, *Inorg. Chem. Commun.* **2000**, *3*, 166; d) B. Muñoz, A. Marinetti, A. Ruiz, S. Castillon, C. Claver, *Inorg. Chem. Commun.* **2005**, *8*, 1113; e) S. Oi, M. Nomura, T. Aiko, Y. Inoue, *J. Mol. Catal. A* **1997**, *115*, 289; f) G. Cometti, G. P. Chiousoli, *J. Organomet. Chem.* **1982**, *236*, C31; g) B. C. Zhu, X. Z. Jiang, *Appl. Organomet. Chem.* **2006**, *20*, 277; h) D. B. G. Williams, M. L. Xhaw, M. J. Green, C. W. Holzapfel, *Angew. Chem.* **2008**, *120*, 570; *Angew. Chem. Int. Ed.* **2008**, *47*, 560.

[4] a) I. del Rio, N. Ruiz, C. Claver, L. A. van der Veen, P. W. N. M. van Leeuwen, *J. Mol. Catal. A* **2000**, *161*, 39; b) A preliminary report of an enantioselective carbonylation using binaphthyl phosphoric acid ligands appeared some time ago, but unfortunately yields were moderate and over 10% catalyst was required along with three promoters ($CuCl_2$, HCl, and oxygen). H. Alper, N. Hamel, *J. Am. Chem. Soc.* **1990**, *112*, 2803; c) Only 8–38% *ee* was realized in alkoxycarbonylations using the same system: Y. Kewu, J. Zuanzhen, *Chem. J. Internet* **2005**, *7*, 14; d) M. Dolors Miquel-Serrano, A. Aghmiz, M. Diéguez, A. M. Masdeu-Bultó, C. Claver, D. Sinou, *Tetrahedron: Asymmetry* **1999**, *10*, 4463.

[5] The nearest precedents we have found for dimeric metal halides of chiral bridging diphosphines are quite far removed: a) Achiral dimeric hydroformylation catalysts: D. A. Aubry, N. N. Bridges, K. Ezell, G. G. Stanley, *J. Am. Chem. Soc.* **2003**, *125*, 11180; b) Chiral dipalladium complexes of a special bridging triketonate ligand in asymmetric oxidation: A. K. El-Qisairi, H. A. Qaseer, P. M. Henry, *J. Organomet. Chem.* **2002**, *656*, 168; c) Copolymerization catalysts with bridging chiral nitrogen ligands: A. Scarel, J. Durand, D. Franchi, E. Zangrando, G. Mestroni, C. Carfagna, L. Mosca, R. Seraglia, G. Consiglio, B. Milani, *Chem. Eur. J.* **2005**, *11*, 6014; d) Chiral bridging ligands in hydrogenation: F. W. Patureau, S. de Boer, M. Kuil, J. Meeuwissen, P.-A. R Breuil, M. A. Siegler, A. L. Spek, A. J. Sandee, B. de Bruin, J. N. H. Reek, *J. Am. Chem. Soc.* **2009**, *131*, 6683.

[6] a) V. K. Jain, L. Jain, *Coord. Chem. Rev.* **2005**, *249*, 3075; b) O. Grossman, C. Azerraf, D. Gelman, *Organometallics* **2006**, *25*, 375; c) C. Azerraf, S. Cohen, D. Gelman, *Inorg. Chem.* **2006**, *45*, 7010; d) D. C. Smith, Jr., C. H. Lake, G. M. Gray, *Dalton Trans.* **2003**, 2950.

[7] C. Blanco, A. Ruiz, C. Godard, N. Fleury-Brégeot, A. Marinetti, C. Claver, *Adv. Synth. Catal.* **2009**, *351*, 1813.

[8] B. K. Muñoz, E. S. Garcia, C. Godard, E. Zangrando, C. Bo, A. Ruiz, C. Claver, *Eur. J. Inorg. Chem.* **2008**, 4625.

[9] M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.* **1991**, *113*, 113.

[10] J. F. Knifton, *J. Org. Chem.* **1976**, *41*, 2885.

[11] T. M. Konrad and M. L. Clarke (University of St Andrews), PCT Application 0915946.8, **2009**.

