Ligand Design

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Efficient Palladium-Catalyzed Alkoxycarbonylation of Bulk Industrial Olefins Using Ferrocenyl Phosphine Ligands

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Abstract: *The development of ligands plays a key role and provides important innovations in homogeneous catalysis. In this context, we report a novel class of ferrocenyl phosphines for the alkoxycarbonylation of industrially important alkenes. A basic feature of our ligands is the combination of sterically hindered and amphoteric moieties on the P atoms, which leads to improved activity and productivity for alkoxycarbonylation reactions compared to the current industrial state-of-the-art ligand 1,2-bis((di-tert-butylphosphino)methyl)benzene). Advantageously, palladium catalysts with these novel ligands also enable such transformations without additional acid under milder reaction conditions. The practicability of the optimized ligand was demonstrated by preparation on > 10 g scale and its use in palladium-catalyzed carbonylations on kilogram scale.*

The synthesis of novel ligands and the corresponding metal complexes provides the basis for basic innovations in catalysis, organic synthesis, and the industrial production of numerous fine and bulk chemicals. Illustrative examples include polymerizations, organometallic coupling reactions, hydrogenations, and metathesis. Clearly, most of the homogeneous processes developed in the chemical industry over the last decades make use of new ligands and their respective catalysts.[1] This is especially true for olefin carbonylation reactions, which are conducted on bulk scale.[2] As a representative example, methyl methacrylate, a monomer for the manufacture of resins and plastics, is produced by the Lucite α-process, which combines ethylene methoxycarbonylation and subsequent condensation with formaldehyde (Figure 1, top). This technology was patented in the late 1980s and was commercialized on multi-100.000 ton scale in 2008.[3]

Nowadays, it is generally accepted that Pd/phosphine complexes give better results than other metal complexes in alkoxycarbonylation reactions under mild conditions.[2c,4] In fact, the industrial alkoxycarbonylation catalyst is based on $Pd(OAc)_2$ and the specific ligand d^{t}bpx (**L5**; Figure 1, bottom).[3] Despite substantial work in industry and academia,[5] this ligand is unique regarding its activity and selectivity. To develop alternative efficient catalysts for such transformations in a rational manner, we thought that the improvement of rate-limiting steps of the given catalytic cycle or the prevention of catalyst deactivation reactions should be specifically addressed (see the Supporting Information, Scheme S1). To solve these problems, metal–ligand cooperativity has become a powerful tool in recent years.[6] Pioneering work on this concept was done by Drent and co-workers at Shell in the area of alkyne carbonylation.[7] Surprisingly, for the more significant olefin alkoxycarbonylation,[2c,8] this concept had not been investigated until very recently.[9]

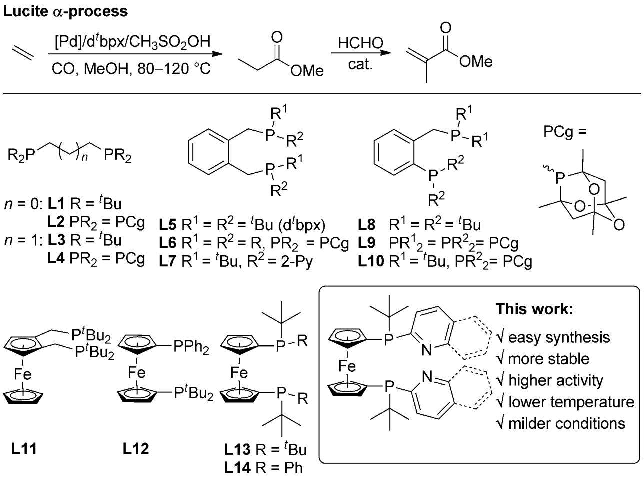

Figure 1. Representative ligands developed for the palladium-catalyzed methoxycarbonylation of ethylene.

Representative ligands developed for ethylene methoxycarbonylation are depicted in Figure 1.[9–13] While monodentate phosphines afford esters, most bidentate phosphines give high-molecular-weight polyketones. However, Drent and coworkers[7,11] as well as the Cole-Hamilton group[12] successfully demonstrated the benefits of sterically hindered and electron-rich bidentate ligands compared to the conventional PPh_3-modified Pd catalyst system. Furthermore, the bite angle of the diphosphine backbone is also crucial for the activity and chemoselectivity of the catalyst. For example, Pd catalysts based on **L1** and **L2** sluggishly gave ethylene/CO co-oligomers and polyketones, while catalysts of **L3** and **L4** led to methyl propionate with > 97 % chemoselectivity.[11] Because of the success of **L5** (d^{t}bpx), several groups in industry and academia have focused on the use and modification of **L5** in

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recent years.[5] For example, interesting analogues such as **L6**–**L10** were developed by Pringle and co-workers, and showed comparable activity.[13] Nevertheless, no significantly improved activity was realized until very recently when we introduced ligand **L7**.[9]

Owing to its stability, ready availability, and facile modification, ferrocene is an ideal choice for ligand backbones.[14] In fact, ferrocene-based ligands have been used advantageously in a range of transition-metal-catalyzed reactions,[15] including cross-couplings,[16] Heck reactions,[17] and enantioselective synthesis.[18] Additionally, these ligands have been found to be useful for several carbonylations of aryl halides.[19] However, their application in the carbonylation of alkenes has only been scarcely investigated.[20] For example, in 2004, Butler and co-workers reported the synthesis of a range of ferrocenylmethylphosphine ligands and found that **L11** showed comparable activity to **L5** in ethylene methoxycarbonylation.[21] Despite this promising activity, the tedious synthesis of **L11** impeded its further application. Herein, we report the synthesis of several novel ferrocenyl ligands and their application in the palladium-catalyzed alkoxycarbonylation of industrially important olefins (Figure 1).

Inspired by our previous work on alkoxycarbonylation,[9] we prepared novel ferrocenyl ligands that featured both sterically hindered substituents and amphoteric moieties on the P atoms (Figure 2). Following a general procedure, ferrocene was lithiated with ^{n}BuLi in heptane followed by the addition of *tert*-butyl(2-pyridyl)phosphine chloride. The crude product was easily purified by crystallization in methanol to give the pure ligand **L15**. Notably, the practicability of this method was demonstrated by the synthesis of **L15** on > 15 g scale.

Aside from **L15**, other ferrocenyl ligands with five- and six-membered heterocycles, including 2-quinolinyl, 1*H*-pyrrol-2-yl, 2-furyl, and 2-thienyl moieties, were prepared. As depicted in Figure 2, **L16**–**L21** were synthesized in yields of 46–71 % following the general method described above. In addition, ligand **L22** with *N*,*N*-dimethylanilinyl groups on the P atoms was also prepared in 60 % yield. Instead of the *tert*-butyl group, a 1-adamantyl moiety can also be successfully incorporated to give **L23** in 47 % yield. To elucidate the steric and electronic effects of substituents on the P atoms further on, ligands **L24** and **L25** with di(2-pyridyl) and di(1-methyl-2-imidazolyl) groups were synthesized. Finally, for comparing related ligands, **L26**–**L28**, which are based on different backbones, and monodentate ligand **L29** were prepared in moderate to high yields. Notably, all of these ligands were new and fully characterized. In agreement with all the spectroscopic data, the molecular structures of ligands **L15** and **L16** were also confirmed by X-ray crystallography.[25]

Furthermore, single crystals suitable for X-ray crystallography of the palladium complexes Pd(**L14**)(NMM) and Pd(**L15**)(NMM) were obtained by combining cyclopentadienyl allyl palladium with the corresponding ligands and *N*-methyl maleimide (NMM).[25] As shown in Figure 3, both complexes contain one ligand, which is coordinated to the metal center through the P atoms with pseudo-square-planar coordination geometry.

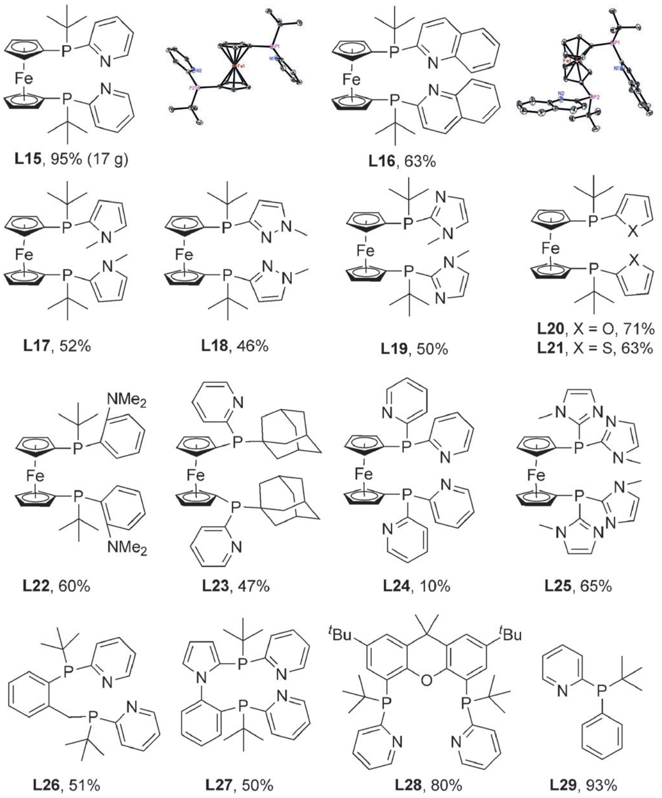


Figure 2. Synthesis of novel ligands with heterocycles on the P atoms.[25]

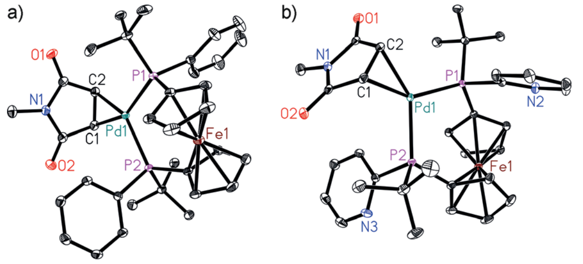
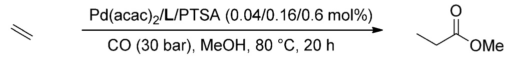


Figure 3. Molecular structures of the palladium complexes a) Pd(**L14**)(NMM)[22] and b) Pd(**L15**)(NMM).[25] Hydrogen atoms are omitted for clarity. Thermal ellipsoids set at 30% probability. The P-Pd-P bite angle of Pd(**L15**)(NMM) (103.317(11)°) is similar to that of Pd(**L14**)(NMM) (103.979(18)°). The Pd–P bond lengths of Pd(**L15**)(NMM) are 2.3305(3) and 2.3286(3) Å while those of Pd(**L14**)(NMM) are 2.3409(5) and 2.3215(5) Å, respectively.

With the novel ligands in hand, the methoxycarbonylation of ethylene was carried out under "process-related" conditions.[3a] As shown in Table 1, the industrially used ligand **L5** and its analogue **L7** gave methyl propanoate (MeP) in excellent yield after 30 and 10 min, respectively. In contrast, dppf only led to MeP in moderate yield along with alternating oligomers after 20 h.[20b] The ferrocenyl ligands **L12**–**L14** performed much better, and needed 10 h for complete conversion. Remarkably, using the new ferrocenyl ligands **L15** and **L16** resulted in MeP in quantitative yield within 10 min. When the reaction was carried out with **L17**, the desired product was afforded in 92 % yield after 20 h.

Table 1: Palladium-catalyzed methoxycarbonylation of ethylene: Investigation of various ligands.[a]



L	Yield [%][b] (t)[c]	L	Yield [%][b] (t)[c]	L	Yield [%][b] (t)[c]
L5	99 (30 min)	**L16**	99 (10 min)	**L23**	99 (10 min)
L7	99 (10 min)	**L17**	92 (20 h)	**L24**	34 (20 h)
dppf	50 (20 h)	**L18**	64 (20 h)	**L25**	3 (20 h)
L12	99 (10 h)	**L19**	72 (20 h)	**L26**	92 (20 h)
L13	99 (10 h)	**L20**	95 (20 h)	**L27**	91 (20 h)
L14	99 (10 h)	**L21**	91 (20 h)	**L28**	0 (20 h)
L15	99 (10 min)	**L22**	4 (20 h)	**L29**	14 (20 h)

[a] Reaction conditions: $Pd(acac)_2$ (6.5 mg, 0.04 mol%), bidentate (0.16 mol%) or monodentate ligand (0.32 mol%), PTSA (61 mg, 0.6 mol%), CO (30 bar), MeOH (20 mL), ethylene (1.5 g, 53.6 mmol). [b] Determined by GC analysis using isooctane as the internal standard. [c] Reaction time. acac = acetylacetonate, PTSA = *para*-toluenesulfonic acid.

Similarly, the related ligands **L18**–**L21** afforded MeP in 64–95% yield after 20 h. However, low yields or only traces of the desired product were detected when **L22**, **L24**, or **L25** were used, demonstrating the importance of both sterically hindered and basic groups on the P atoms. **L23** with a 1-adamantyl group was also demonstrated to be a highly active ligand. When **L26** or **L27** was used, the desired product was afforded in high yield after 20 h. On the other hand, xanthene-based ligand **L28** showed no activity at all. Finally, with monodentate ligand **L29**, MeP was observed in only 14% yield.

To compare the efficiency of **L5** and the ferrocenyl ligands more clearly, the methoxycarbonylation of ethylene was carried out at room temperature under otherwise identical conditions. As shown in Figure 4a, ligands **L15**, **L16**, and **L23** notably displayed unprecedented activity and afforded the desired product in quantitative yield within 3 h (activity order: **L16** > **L15** > **L23**). **L16** performed particularly well and gave almost full conversion within 1 h. Ligand **L5** showed significantly lower activity, and the yield of MeP was < 10% in this case. **L12**–**L14**, which were active at 80 °C, did not give the desired product under these milder conditions, which revealed that both sterically hindered and amphoteric groups on the P atoms are indispensable.

A general drawback of current Pd-catalyzed alkoxycarbonylation processes is the requirement for acid cocatalysts, which might lead to corrosion of the equipment. Indeed, the combination of $PdCl_2$ and our ferrocenyl ligands leads to an active catalyst system that allows for efficient ethylene methoxycarbonylation without additional co-acids. As shown in Figure 4b, **L15** performed best in terms of activity and gave MeP in almost quantitative yield within 1 h. With ligands **L16** and **L23**, the desired product was also obtained in high yield after slightly longer reaction times (5 h). To compare the activity of the corresponding catalysts, **L5** was also investigated, and MeP was detected in < 5% yield. Encouraged by these results, we next carried out the reaction under acid- and halide-free reaction conditions. Interestingly, a high yield of MeP was detected using $Pd(OAc)_2$ and **L15** as the catalyst (see Figure S1). These results suggest that the crucial Pd−H complex in the catalytic cycle can be generated efficiently under much milder conditions.

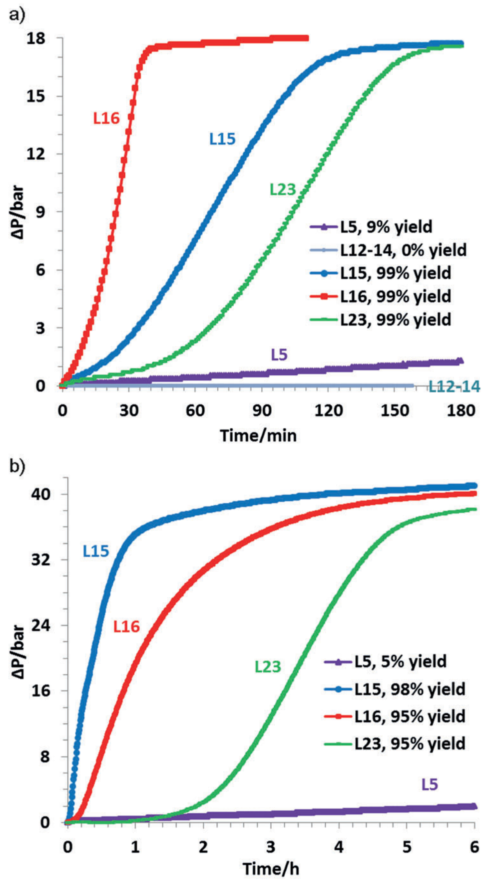


Figure 4. Palladium-catalyzed methoxycarbonylation of ethylene with various ligands a) at 23 °C and b) at 80 °C without additional acid.

Next, we applied our ferrocenyl ligands in the Pd-catalyzed methoxycarbonylation of propylene under the optimized reaction conditions (see Figure S2). As expected, with ligands **L15** and **L16**, propylene was carbonylated at 40 °C into the desired ester in quantitative yield and high *n*-selectivity within 2 h. Again, only trace amounts of the product were detected with **L5** as the ligand. In addition, with **L15**, the reaction still worked well at 23 °C and gave the desired ester in high yield after 20 h. To the best of our knowledge, this is the first example of propylene alkoxycarbonylation at such low temperatures.

C_4 olefins are mainly obtained as coproducts of naphtha cracking to produce ethylene. Hence, the Pd-catalyzed methoxycarbonylation of Raffinate-1[23] was performed with ligands **L5** and **L15** at 120 °C for 20 h. High yields of C_5 esters were obtained with **L15** within 10 h (see Figure S3). On the other hand, with **L5**, a long induction period of 10 h was observed, which was explained by inhibition by 1,3-butadiene.[24] This result demonstrates the durability of the new catalyst, which is crucial in industry when dealing with bulk chemicals with small amounts of impurities.

Finally, the effect of different alcohols was explored in the alkoxycarbonylation of ethylene. With ligand **L15**, the reaction was carried out at 80 °C in the corresponding alcohol.

As illustrated in Figure S5, primary and secondary alcohols were well tolerated, and the corresponding esters were afforded in very high yields within 30 min.

The attack of the nucleophile onto the palladium acyl complex is believed to be the rate-determining step in Pd-catalyzed alkoxycarbonylation reactions.[5] We assume that the pyridyl substituent facilitates this crucial elementary step by internal deprotonation of the alcohol and subsequent faster ester formation via hydrogen-bonded intermediates. To understand the superiority of these novel catalysts, the apparent activation energies of ethylene methoxycarbonylation with ligands **L5** and **L15** were investigated. The concentration of ethylene was calculated by the gas consumption of ethylene and CO, which was monitored on-line. The reaction rate was measured at four different temperatures, and the concentration of ethylene was plotted as a function of time (see Figure S6). The Arrhenius plot of the natural logarithm of the reaction rate versus the inverse of the absolute temperature [$\ln(v)$ vs. $1/T$] is shown in Figure 5. The apparent activation energy with the catalyst containing **L15** (50 kJ K^{-1} mol^{-1}) was much lower than that with **L5** (85 kJ K^{-1} mol^{-1}), demonstrating the rate enhancement induced by the amphoteric group.

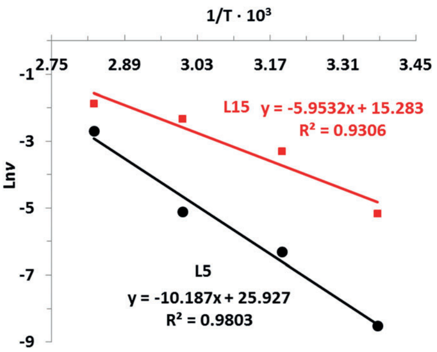


Figure 5. Arrhenius plots for ethylene methoxycarbonylation with **L5** and **L15**.

In conclusion, a novel class of ferrocenyl ligands has been developed and applied in palladium-catalyzed alkoxycarbonylation reactions of bulk industrial olefins. Several of these ligands including **L15** showed much higher activity in industrially relevant transformations than the currently applied ligand **L5**. We believe that ligand **L15** represents a new state-of-the-art ligand for ethylene alkoxycarbonylation under acid-free conditions. Moreover, **L15** is more robust against diene impurities in the carbonylation of C_4 mixtures. We are convinced that this work will not only complement the diversity of ferrocenyl ligands in organometallic chemistry but should also be an impetus for the development of efficient alkene alkoxycarbonylation reactions in academia and industry.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbonylation · ferrocenyl ligands · ligand design · olefins · palladium

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[22] For the second molecule of the asymmetric unit, bite angle: 104.039(18)°, Pd–P bond lengths: 2.3702(5), 2.3469(5) Å.

[23] Composition of Raffinate-1: 26% 1-butene, 17% 2-butene, 42% isobutylene, 0.3% 1,3-butadiene, 15% butanes.

[24] To test this hypothesis, the effect of 1,3-butadiene on the carbonylation of 1-butene with **L5** was investigated (see Figure S4). Indeed, the reaction was completely inhibited by butadiene. Notably, with **L15**, the reaction worked well in the presence of butadiene, and the ester was obtained in 94% yield. The observed lower rate at the start of the reaction was explained by slower carbonylation of butadiene.

[25] CCDC 1483940 (**L15**), 1531857 (**L16**), 1531858 (Pd(**L14**)(NMM)), and 1483939 (Pd(**L15**)(NMM)) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Communications

Ligand Design

K. Dong, R. Sang, X. Fang, R. Franke, A. Spannenberg, H. Neumann, R. Jackstell, M. Beller* ______ ■■■■–■■■■

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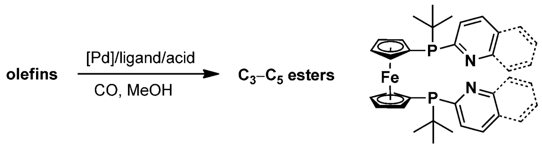

Novel ferrocenyl ligands:
√ easier to synthesize
√ more stable
√ higher activity
√ lower temperature (23 °C)
√ milder conditions

Very active: A novel class of ferrocenyl phosphine ligands for the palladium-catalyzed alkoxycarbonylation of industrially important alkenes is reported. Compared to currently applied catalysts, the resulting palladium complexes showed much higher activity under milder conditions.