CHEMICAL REVIEWS

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Review

Magic of Alpha: The Chemistry of a Remarkable Bidentate Phosphine, 1,2-Bis(di-*tert*-butylphosphinomethyl)benzene

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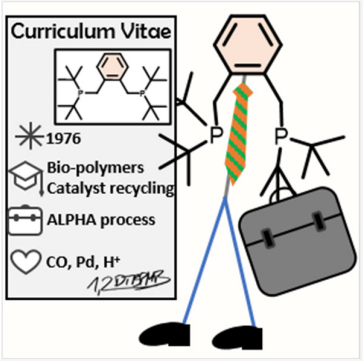
ABSTRACT: The bidentate phosphine ligand 1,2-bis(di-*tert*-butylphosphinomethyl)-benzene (1,2-DTBPMB) has been reported over the years as being one of, if not *the*, best ligands for achieving the alkoxycarbonylation of various unsaturated compounds. Bonded to palladium, the ligand provides the basis for the first step in the commercial (Alpha) production of methyl methacrylate as well as very high selectivity to linear esters and acids from terminal or internal double bonds. The present review is an overview covering the literature dealing with the 1,2-DTBPMB ligand: from its first reference, its catalysis, including the alkoxycarbonylation reaction and its mechanism, its isomerization abilities including the highly selective isomerizing methoxycarbonylation, other reactions such as cross-coupling, recycling approaches, and the development of improved, modified ligands, in which some *tert*-butyl ligands are replaced by 2-pyridyl moieties and which show exceptional rates for carbonylation reactions at low temperatures.



CONTENTS

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Chem. Rev. 2021, 121, 6610–6653

1. INTRODUCTION

The Alpha process is a two-step process developed by Lucite International (now part of Mitsubishi Chemicals) to produce methyl methacrylate at 370 000 tonnes per year in Singapore and Saudi Arabia.[1,2] The success of the Alpha process, which involves the methoxycarbonylation of ethene to methyl propanoate, can be attributed to the amazing properties of the diphosphine ligand, 1,2-bis(di-*tert*-butylphosphinomethyl)-benzene (1,2-DTBPMB), in the palladium-catalyzed reaction. No other ligand was efficient in this process. In this review, we discuss the many exceptional applications of this magical ligand and some of the reasons for its success.

1.1. Motivation

Since 1,2-DTBPMB was initially mentioned in 1976, its use as a potent bidentate phosphine ligand has been reported for different transition-metal-catalyzed transformations. The most prominent examples constitute palladium-catalyzed carbonylation reactions of alkenes, particularly of ethene, as for example in the production of methyl propanoate in Lucite's Alpha process toward the production of methyl methacrylate. However, motivated by that success story, 1,2-DTBPMB has also been tested in many different transformations beyond methoxycarbonylation of ethene. In this review, we summarize the many transformations and developments around the application of 1,2-DTBPMB as a versatile ligand. This review aims at a comprehensive picture of the application of 1,2-DTBPMB in all different catalytic reactions that have been reported until now. It is divided into alkoxycarbonylation reactions of alkenes, among them also isomerizing transformations of internally unsaturated substrates and biobased substrates, and other carbonylations, including CO-free carbonylations and recycling approaches. In addition, non-carbonylative reactions are discussed, and finally, improved 1,2-DTBPMB-derived ligands as novel modifications will be discussed, leading to a new generation of this ligand class. A special emphasis will be on mechanistic elucidations. A timeline for the key developments in the history of DTBPMB is given in Figure 1.

1.2. Chemical Structure and Properties

The diphosphine 1,2-bis(di-*tert*-butylphosphinomethyl)-benzene (abbreviated as 1,2-DTBPMB, Figure 2) was first reported in 1976 by Moulton and Shaw, stabilizing the first reported *cis*-dihydride of platinum(II) owing to its bulky end groups.[3] In 1992, Crascall and Spencer showed that the degree of interaction with the metal center depends on the bite angle and the steric hindrance of the substituents on the diphosphine using the example of 1,2-DTBPMB and others.[4]

The structure of the ligand 1,2-DTBPMB consists of a diphosphine with a xylene backbone (Figure 2). The two *tert*-butyl groups on each phosphorus have been proven to provide one of the keys to its success in catalysis (see section 3.3).

The chemical and physical data of 1,2-DTBPMB are summarized in Table 1.

1.3. Synthesis and Transition-Metal Complexes

According to the very first synthesis in 1976 by Shaw, 1,2-DTBPMB was "*made by treating o-BrCH$_2$C$_6$H$_4$CH$_2$Br with PH^{t}Bu$_2$, and subsequent treatment with a base*"[3] with no subsequent information. Thereby, its first use was in the formation of a platinum complex.[3] In 1996, Tooze et al. mentioned the synthesis of the same ligand starting from a dihalide and a secondary phosphine via a phosphonium salt for subsequent complexation with palladium (Figure 3).[11]

A similar procedure was carried out by Scherer and co-workers in 2011 for subsequent nickel complexation,[5] resulting in a low yield of 5−10%. However, starting from PH^{t}Bu$_2$ is problematic since it is toxic, highly reactive, and flammable. Furthermore, the complex separation of an unidentified byproduct is necessary, which drastically reduces the yield.[12]

A very detailed procedure was developed in 1999 by Eastham, Thorpe, and Tooze[12] and improved in 2002[13] using commercially available compounds. We will only introduce the general principle of the synthesis (Figure 4). The reader is referred to the corresponding patents for a detailed description. Magnesium powder is activated and stirred with traces of iodine. The magnesium iodide is removed through filtration, and the residual metal is suspended in THF. α,α'-Dichloro-*o*-xylene is added, providing a diGrignard product in 94% yield. α,α'-Dichloro-*o*-xylene is preferred over α,α'-dibromo-*o*-xylene, the latter yielding only 15% of the desired diGrignard product. The diGrignard product is subsequently filtered and introduced dropwise into a THF solution containing 2 equiv of excess di-*tert*-butylchlorophosphine and refluxed for 8 h. The reaction provides 1,2-bis(di-*tert*-butylphosphinomethyl)benzene in 55% yield based on the diGrignard intermediate. This procedure was improved by increasing the ratio of phosphine:diGrignard to 8:1, giving a yield of 62%,[13] corresponding to an overall yield of 58%.

A more common and improved method, patented in 2002,[14] starts from *o*-xylene, as a readily available substrate (Figure 5). Sodium *tert*-butoxide, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and *o*-xylene are first dissolved in heptane. *n*-Butyllithium is slowly added, and after reaction, an orange precipitate is formed which is filtered off and washed with pentane. In the second step, di-*tert*-butylchlorophosphine is added to the suspension of the sodium salt in pentane. The reaction is quenched with water affording two layers, and the ligand is obtained from the upper pentane layer with a yield of 84.6%.[14]

Nowadays 1,2-DTBPMB is commercially available from several suppliers, so that its synthesis on the laboratory scale is usually not necessary. Due to its sensitivity to air, it is usually stored and used under an inert atmosphere.

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Chem. Rev. 2021, 121, 6610−6653

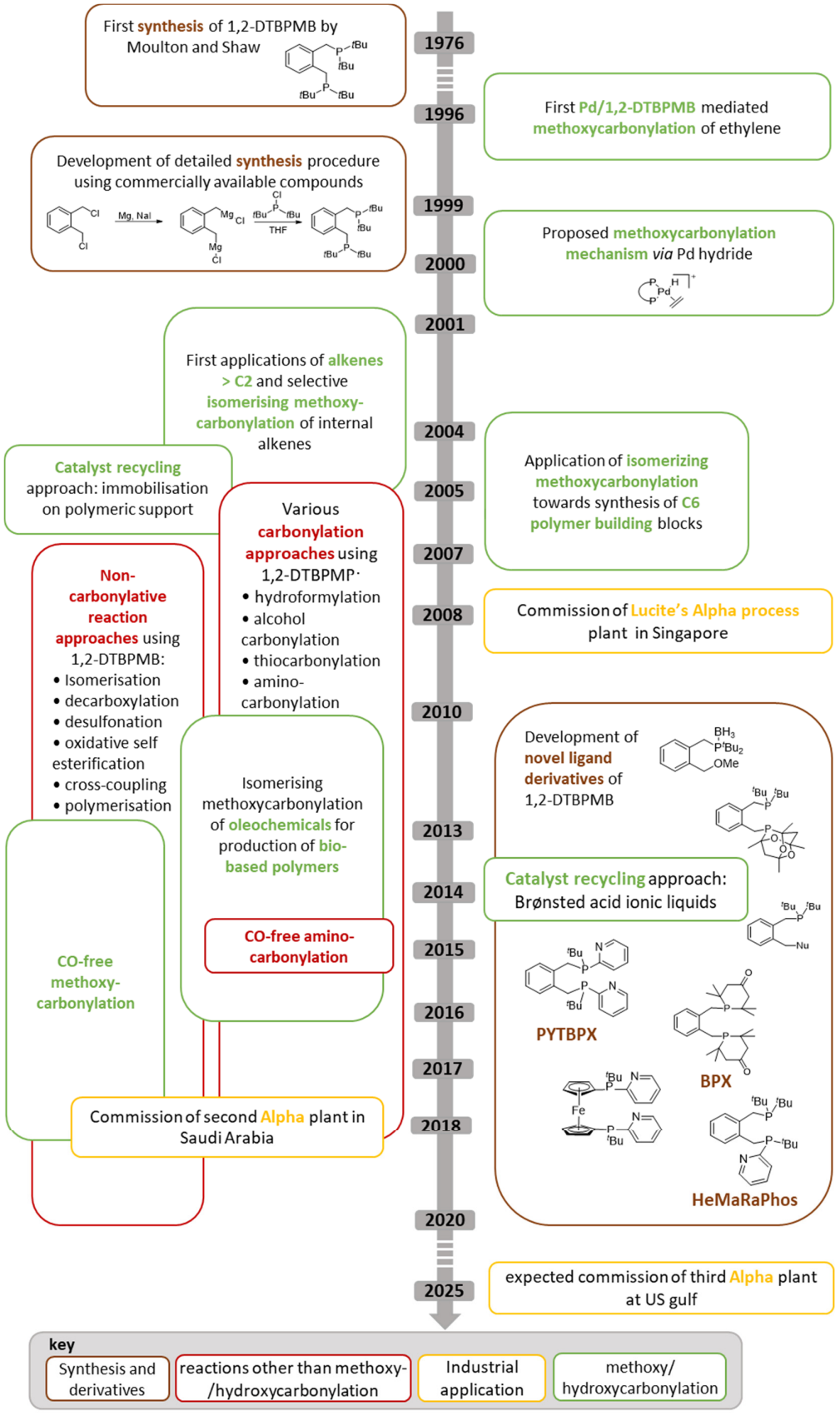

Figure 1. Milestones in the development and application of 1,2-DTBPMB.

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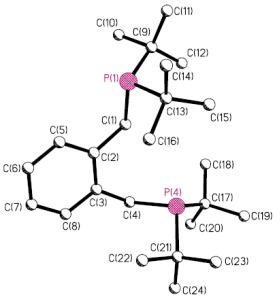
Chem. Rev. 2021, 121, 6610−6653

Table 1. Properties of 1,2-DTBPMB[a]

Physical data	
Melting point	59 – 62 °C [6]
pK (of di- and mono-protonated ligand)	pK_1 = 1.12, pK_2 = 0.56 [7]
Analytical data	
$^{31}P\{^1H\}$ NMR (20 °C, $CDCl_3$)	δ (161 MHz) = 28.5 ppm [8]
^1H NMR (20 °C, $CDCl_3$, 400 MHz)	δ = 1.14 (d, $^2J_{HP}$ = 10.8 Hz, 36H), 3.04 (d, $^2J_{HP}$ = 2.8 Hz, 4H, CH_2), 7.05 – 7.07 (m, 2H, $CH_{arom.}$), 7.52 – 7.55 (m, 2H, $CH_{arom.}$) ppm. [8]
$^{13}C\{^1H\}$ NMR (20 °C, $CDCl_3$, 100 MHz)	δ = 26.4 (dd, $^1J_{CP}$ = 24.0 Hz, $^4J_{CP}$ = 4.7 Hz, CH_2), 29.9 (d, $^1J_{CP}$ = 13.1 Hz, CCH_3), 31.9 (d, $^1J_{CP}$ = 22.5, CCH_3), 125.2 (d, $^4J_{CP}$ = 1.8 Hz, CH_{meta}), 138.7 (dd, $^3J_{CP}$ = 15.1 Hz), 138.7 (dd, $^2J_{CP}$ = 9.4 Hz, $^3J_{CP}$ = 2.6 Hz, C_{ipso}) ppm.[8]
Crystal structure	M = 394.53, triclinic, space group $P\bar{1}$, a = 9.9447(19), b = 11.839(2), c = 11.991(2) Å; α = 117.625(6), β = 92.392(9), γ = 99.186(8)°, U = 1224.0(4) Å^3, Z = 2, D_c = 1.070 Mgm^{-3}, μ = 0.184 mm^{-1}, F(000) = 436. Of 6891 measured data, 4039 were unique (R_{int} = 0.0199) and 3675 observed (I >2σ(I)]) to give R_1 = 0.0404 and wR_2 = 0.1045, GOF = 1.040.[5] 
Other structural data	
Bite angle	104°[9] [Pt-complex]; 99.3°[10] [Pd-complex]
Cone angle	276°[9] [Pt-complex]
Names	
CAS	121954-50-5
Related to *o*-xylene backbone	α,α'-bis(di-*tert*-butylphosphino)-*o*-xylene (DTBPX, Bupox)
Related to benzene backbone	1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB, DTPB)

[a]The structure is reproduced with permission from ref 5. Copyright 2010 Royal Society of Chemistry.

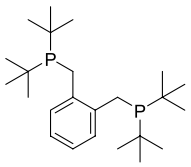


Figure 2. Chemical structure of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene.

2. CARBONYLATION REACTIONS WITH 1,2-DTBPMB

2.1. Types of Carbonylation Reaction

Carbonylation reactions lead to the formation of a carbonyl group in a carbon chain through the introduction of carbon monoxide. One of the first reactions of this kind ever reported was the "oxo synthesis" or hydroformylation, discovered by Roelen in 1938.[15] Hydroformylation consists of the formation of aldehydes by the reaction of syngas (mixture of carbon monoxide and hydrogen) with an alkene through a catalytic process.

In carbonylation reactions, the functions that are formed (aldehydes, polyketones, esters, carboxylic acids, amides, lactones, etc.) are of great value as organic products and intermediates.[16] Additionally, carbonylation reactions of unsaturated double bonds are 100% atom economic, making them very attractive from both an ecological as well as an economic point of view. Carbonylation reactions of unsymmetrical alkenes generate regioselectivity with the formation of either linear or branched products. Enantioselectivity is also possible with the formation of chiral molecules. Examples of the most encountered carbonylation reactions are outlined in Table 2.

At the same time as Roelen discovered hydroformylation, Reppe discovered the hydroxycarbonylation and alkoxycarbonylation reactions of acetylene, ethylene, and further olefins.[24,25] The reaction of ethylene with carbon monoxide and water (or an alcohol) was shown to produce carboxylic acid and its esters using nickel catalysts. Reppe claimed the formation of cyclopropanones through the addition of CO to the double bond, before ring opening toward α-methyl or linear carboxylic acids/esters occurs.[24] The original harsh conditions led to the desired products but promoted the production of undesired side products. Milder conditions were achieved through the use of cobalt catalysts.[26] The first palladium catalysts developed by Tsuji et al. in the 1960s proved to be active at much lower temperature (about 100 °C) than cobalt catalysts.[27−29] The introduction of monodentate phosphine ligands, such as triphenylphosphine, first described by Sen in the palladium system,[30] later patented by Drent in the 1980s,[31] led to a major advance in the field of alkoxycarbonylation. Also, the application of diphosphine ligands in the rhodium-catalyzed hydroformylation of 1-hexene to increase the linearity of product[32] moved the potential of 1,2-DTBPMB in catalysis to its starting blocks.

2.2. Alkoxy- and Hydroxycarbonylation of 1-Alkenes

Palladium complexes of 1,2-DTBPMB were first shown to be efficient catalysts for the alkoxycarbonylation of ethene, a process that has been commercialized. In this section, we report the first historical developments on ethene alkoxycarbonylation, mechanistic elucidations, and the transfer to longer-chain alkenes and vinyl compounds.

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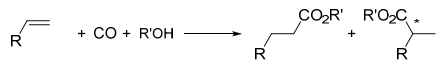
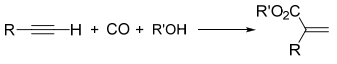
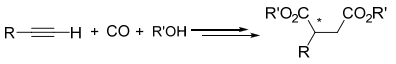
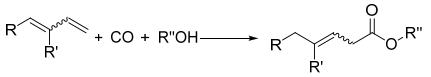
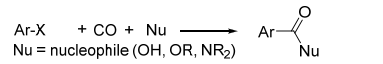
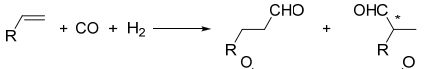
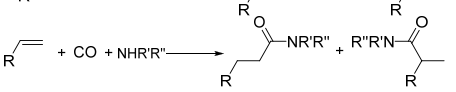
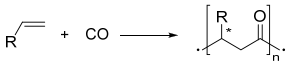
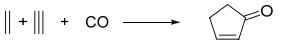
Chem. Rev. 2021, 121, 6610−6653

Table 2. Most Encountered Catalyzed Carbonylation Reactions[a]

Reaction	References	Function built	Scheme
Alkoxy-carbonylation of alkenes	section 2 and 3	Saturated ester	
Alkyne carbonylation	section 3.2.5	Unsaturated ester	
Alkyne carbonylation	section 3.2.5	Diester	
Diene carbonylation	section 3.2.1.2 and 3.2.4	β,γ-unsaturated ester	
Carbonylative cross-coupling of Aryl halides	Section 4.2	Aryl ester	
Hydroformylation	[15,17−19] section 4.3	Aldehyde	
Amino-carbonylation	section 4.1 and 5.2	Amide	
Copolymerization	[20]	Polyketone	
Pauson-Khand reaction	[21,22]	Cyclopentenone	
Alcohol Carbonylation	[23] section 4.4	Carboxylic acid	

[a]References relate to pioneering works or comprehensive reviews.

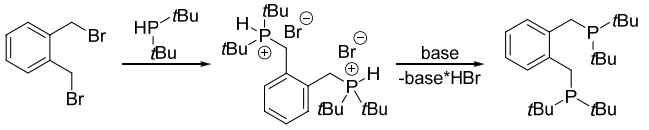


Figure 3. First reported general procedure for the synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene via phosphonium salt.[3,11]

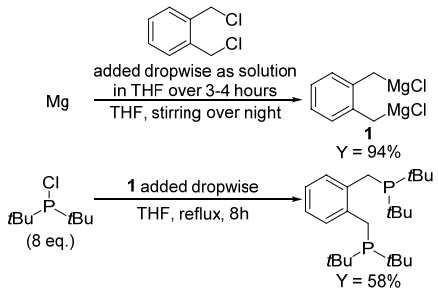


Figure 4. First reported detailed procedure for the synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene. Magnesium is activated with iodine in THF solution.[13]

2.2.1. Ethene. *2.2.1.1. History.* To the best of our knowledge, no catalytic studies had been reported before the work of Tooze and co-workers on the methoxycarbonylation of ethene using 1,2-DTBPMB for the production of methyl propanoate in 1996,[11,33] which was rapidly followed by numerous patents from several authors.[34] The Pd/1,2-DTBPMB complex was treated with a sulfonic acid, such as methanesulfonic acid (MSA), to form the active catalytic complex.[11,33] In contrast to former palladium systems, where

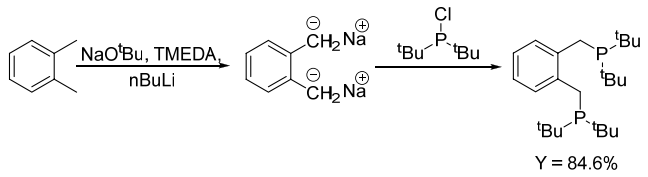


Figure 5. Procedure for the synthesis of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene starting from *o*-xylene.[14]

high reaction rates were accompanied by fast catalyst deactivation, the bidentate phosphine ligand 1,2-DTBPMB remarkably stabilizes the catalyst at high conversion and selectivity for the methoxycarbonylation of ethene (see section 6 for details on the stability of 1,2-DTBPMB).[9]

In 1999, Tooze and co-workers claimed that the ligand, once complexed to palladium, shows very high activity toward the methoxycarbonylation of ethene with a turnover frequency of 12 000 h^{-1}. Additionally, the selectivity of the catalyst is as high as 99.9% so that almost no byproducts are formed.[29] The catalyst is highly stable and can undergo >1 million turnovers before needing to be replaced. The obtained methyl propanoate was suggested to be a possible intermediate for the synthesis of methyl methacrylate. Indeed, the catalytic system patented by Lucite is nowadays used in the "Alpha Process" for the production of methyl propanoate, leading to the synthesis of methyl methacrylate[1] (see section 2.2.1.2 for more details). A system describing the continuous process for the methoxycarbonylation of ethene was patented in 2011 by Eastham and Tindale,[35] and a system comprising zwitterions added to the reaction mixture for enhancing the performance of the reaction was recently patented by Riisager and

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Chem. Rev. 2021, 121, 6610−6653

colleagues. The zwitterions are butylsulfonyl compounds with the cationic headgroup selected from pyridinium, methylimidazolium, triethylammonium, or triphenylphosphonium.[36] The field of hydro-/methoxycarbonylation of ethene to propanoic acid or methyl propanoate using 1,2-DTBPMB-based systems and variations of the ligand was recently discussed by Pringle and co-workers.[9,37,38]

2.2.1.2. Alpha Process. The Alpha Process, developed by Lucite International, relies on two reactions: the homogeneously catalyzed production of methyl propanoate via methoxycarbonylation, followed by heterogeneously catalyzed aldol condensation of the latter with formaldehyde to produce methyl methacrylate (Figure 6),[1] which is finally polymerized to poly(methyl methacrylate), mainly known for its use as Plexiglas/Perspex/Lucite.

Initial work to develop new technology for the manufacture of MMA began in ICI Acrylics in the early 1990s.[39] Starting from a clean sheet, a small team of chemists and engineers identified several different routes, which on paper at least looked to be feasible replacements for existing technology. All of the potential new routes were evaluated against three principal targets as follows: First it was desirable to have a lower cost of production versus existing technology to enable better competition versus other producers and therefore increased profits. There was also an ambition to drive down the cost of PMMA to enable it to better compete against other plastics such as polystyrene and polyacrylates. Second, a lower environmental footprint versus existing technology, and third, enhanced flexibility to locate production plants globally versus existing technology. At the time this project began, virtually all of the world's MMA was produced by two technologies, ACH and C4 (Figure 6).[40−43]

In the ACH technology, acetone is reacted with HCN to produce acetone cyanohydrin (ACH), which in turn is hydrolyzed by sulfuric acid to form a sulfate ester of methacrylamide. Reaction of this with methanol produces MMA and ammonium bisulfate.[41−43] Historically, the ammonium bisulfate was disposed of in oceans and rivers or in deep well processing. This is no longer permitted, and the solutions to this issue add additional cost to the ACH technology. The primary solution is to recover the waste acid as sulfuric acid by investing in what is referred to as sulfuric acid recovery (SAR) technology.[44] New routes involving sulfuric acid in the hydrolysis have also been developed.[40]

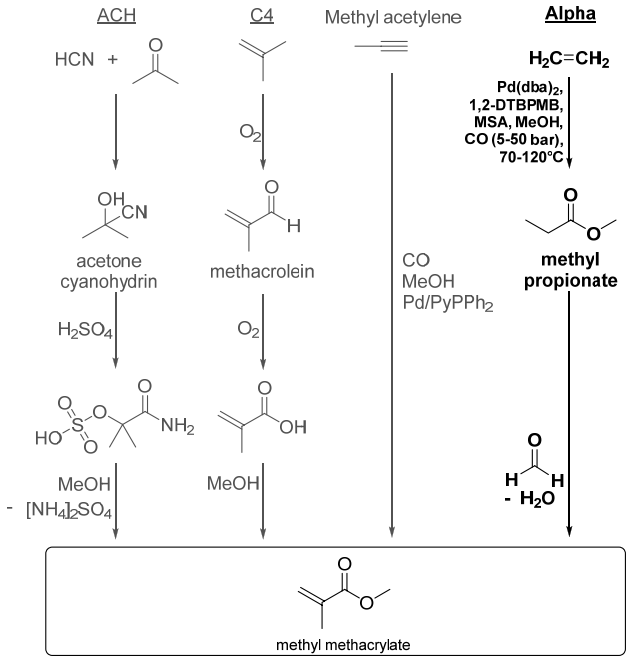

Figure 6. Lucite's alpha process, methoxycarbonylation of ethene to methyl propionate, and conversion to methyl methacrylate as an alternative to ACH, methylacetylene, and C4 routes.

In the C4 process, isobutylene (2-methyl propene) is oxidized to methacrolein (2-methylpropenal) and then further oxidized to methacrylic acid (MAA, 2-methylpropenoic acid) before esterification to MMA using methanol.[45] In the ACH process, cost of production can vary widely as the majority of acetone comes from the cumene process which coproduces acetone and phenol from benzene and propene. Hence, acetone supply and therefore cost are linked to demand for phenol and ultimately propene prices.[45] Approximately 25% of acetone produced globally goes into the MMA market.[46] From an environmental perspective, HCN and ACH are extremely toxic, and MMA plants employing ACH technology are some of the most highly regulated in the chemical industry.[1] While ICI, which became Lucite International and subsequently Mitsubishi Chemical, practiced ACH technology from the 1930s, it was considered desirable not to use these toxic chemicals. Furthermore, the vast majority of HCN used in ACH technology comes from colocation with acrylonitrile (3-cyanopropene) manufacture where HCN is a byproduct.[42] This limits the flexibility of location of ACH plants to those sites with an acrylonitrile facility. The alternative is on-site production of HCN from natural gas and ammonia.

The C4 process requires 2-methylpropene as a reagent. This is a byproduct of ethene crackers but has a very similar boiling point to 1-butene, which is also present, so they are usually separated by the formation of methyl(2-methylpropyl)ether (MTBE) or 2-methylpropan-2-ol (*t*-butanol). In some countries, high demand for MTBE as a gasoline additive reduces the amount of 2-methylpropene available for MMA formation, while in others, especially the US, concerns about MTBE toxicity in ground waters have led to bans. These various issues make the C4 process less attractive.[45]

In principle, methoxycarbonylation of propyne (methylacetylene route, Figure 6), which has been demonstrated by Drent and co-workers to give high selectivity to MMA in only one step under mild conditions when using 2-pyridyldiphenylphosphine ($PyPPh_2$) complexes of palladium, would be the ideal process for making MMA.[47] However, the quantities of propyne produced by conventional crackers are insufficient for commercial operation of this technology given the scale of modern day MMA plants. Modern age MMA plants were recently brought online, and those in the pipeline are 250 ktonne[2] and 400 ktonne,[48] respectively. A secondary issue is the fact that propadiene, an isomer of propyne, acts as a catalyst poison. Isomerization and purification of the propyne must be carried out to low ppm propadiene levels,[49] which adds cost to the process.

The ligand 1,2-DTBPMB plays an exclusive role in the first step of the process, which is carried out at a temperature of 70−120 °C and at a CO pressure of 5−50 bar, as patented by Tooze and co-workers in 1996.[9] Since 2008, the Pd/1,2-DTBPMB system has allowed the production, after the second step of the reaction, of methyl methacrylate in the Alpha 1 process plant on Jurong Island, Singapore, with a capacity of

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Chem. Rev. 2021, 121, 6610−6653

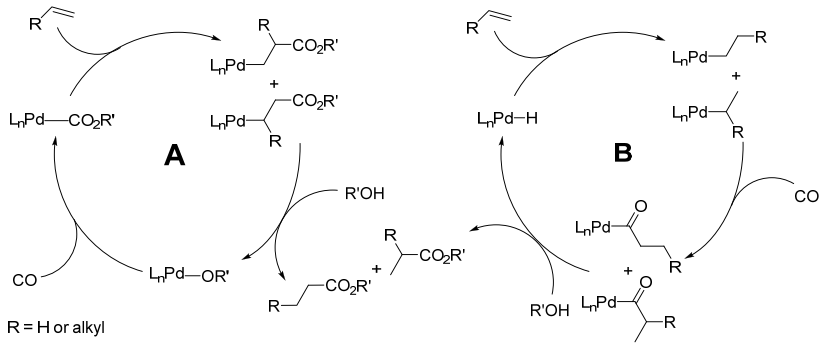

Figure 7. Two proposed general catalytic cycles for alkoxycarbonylation of ethene and alkenes, respectively. (A) Carbomethoxy mechanism. (B) Hydride mechanism. Adapted with permission from ref 51. Copyright 1991 Elsevier.

120,000 tons a year of methyl methacrylate. This novel route is competitive with the conventional acetone cyanohydrin (ACH) and isobutene (C4) process but much less environmentally damaging.

After commission of the plant, Saudi Methacrylates (SAMAC), a joint venture between Lucite's parent company Mitsubishi Chemical (MCC) and Saudi petrochemical, commissioned a second plant of 250 000 tons of methyl methacrylate a year capacity in 2018.[2] Finally, as recently announced, Mitsubishi Chemical aims to build a production facility for MMA production on the US Gulf coast also using the Alpha technology. The plant is expected to be operational in 2025 with a capacity of 350 000 tons.[48]

In comparison to the conventional ACH process, the Alpha process using 1,2-DTBPMB as a ligand is beneficial in terms of avoidance of hazardous chemicals and waste, which result in lower costs for safety restrictions as well as reduced social and ecological risks. The capital cost is 30−40%[1] lower than for an ACH or C4 plant. Apart from using highly toxic HCN, the ACH process generates 1.15 tonnes of ammonium bisulfate per tonne of MMA (*E* factor = 1.15, atom efficiency = 46.5%). In contrast, the waste from the Alpha process (*E* factor = 0, atom = 85% economy, with water as the byproduct) is minimal, consisting of an aqueous stream, which needs little purification and a minor stream containing heavy esters which can be incinerated, producing heat that is used in the process.[1] Additionally, the substrates in the Alpha process are lower priced and widely available, even from biomass. The C4 process, based on oxidation of isobutene, is only used in the Far East, while potential Alpha plants can be located all over the world due to feedstock availability,[1] as shown by Lucite International/Mitsubishi Chemical. In summary, application of 1,2-DTBPMB contributes to sustainable methyl methacrylate production. It is an example where a new process is not only greener but also less expensive to operate.

2.2.1.3. Mechanistic Studies of Ethene Alkoxycarbonylation. Before 1,2-DTBPMB was investigated in the mechanism of alkoxycarbonylation, mechanistic studies were carried out by Toniolo and Cavinato in 1990 on several new (at the time) phosphine/palladium systems. The authors suggested that two mechanisms were possible for the alkoxycarbonylation reaction of ethene and alkenes in general (see sections 2.2.2 and 2.2.3).[50] Other studies, including the copolymerization of alkenes with carbon monoxide, confirmed both mechanisms to occur.[51−55] The two suggested mechanistic paths (see Figure 7) involve either a carboalkoxy-palladium species or a hydridopalladium species. In the first (carbomethoxy) mechanism (**A**, left), a palladium-bound carbomethoxy group migrates onto coordinated alkene, ethene, or other. The ester is released through alcoholysis, while the active catalyst is regenerated by coordination of carbon monoxide. The second (hydride) mechanism (**B**, right) involves the migration of a hydrido ligand from palladium to coordinated alkene, followed by a second migration of the formed alkyl group onto coordinated carbon monoxide. Alcoholysis releases the ester and regenerates the active catalytic species. In both mechanisms, the rate-determining step is the nucleophilic attack of the alcohol.

Originally, it had been suggested that the methoxycarbonylation of ethene leads to methyl propanoate when using monodentate phosphine ligands and to copolymers (formed by sequential addition of CO and alkene into the growing chain) when using bidentate ligands.[55−57] However, this simple ligand/product relationship does not hold. Knight, Doherty, and co-workers have shown that catalyst systems based on *cis*- and *trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane are selective for copolymerization of ethene with carbon monoxide as expected for bidentate ligands.[58] However, catalyst systems based on *exo*,*endo*-2,3-bis(diphenylphosphinomethyl)-norbornane are selective for producing methyl propanoate, while Pd−catalyst complexes formed from *endo*,*endo*-2,3-bis(diphenylphosphinomethyl)norbornane are selective for making the copolymer, with a productivity similar to that of *trans*-1,2- bis(diphenylphosphinomethyl)cyclohexane. The authors assume the large natural bite angle of the *exo*,*endo*-Pd−complex to result in chemoselectivity toward methyl propanoate since bidentate phosphines tend to open at larger natural bite angles. Consequently, they assume the *exo*,*endo*-species to function as a monodentate phosphine, while the *endo*,*endo*-species acts as a bidentate ligand with a slightly smaller natural bite angle of the corresponding Pd complex.

In 1996, Drent and Budzelaar suggested that the carbomethoxy cycle is dominant if oxidants are present in catalyst systems that comprise aryldiphosphines.[55] This was explained using the fact that palladium−hydride species oxidize in the presence of oxidant in methanol, yielding the palladium−methoxy complexes.[55] In 2000, Tooze and co-workers found evidence that actually the hydride mechanism was occurring during the methoxycarbonylation of ethene while using palladium−triphenylphosphine complexes.[59]

Further investigations have been done for a better understanding of the mechanism of the alkoxycabonylation while specifically using the 1,2-DTBPMB ligand. Thus, in 2000, Heaton and co-workers were the first to isolate all

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Chem. Rev. 2021, 121, 6610−6653

intermediates involved in the methoxycarbonylation of ethene.[60] The authors found that, contrary to what was previously suggested, the palladium−hydride species was stable in the presence of oxygen at temperatures as high as 80 °C or in the presence of an excess of benzoquinone. No evidence of the palladium−methoxy complex was found. These studies gave strong support to the hypothesis that the methoxycarbonylation of ethene follows the hydride catalytic cycle (cycle **B** in Figure 7). Two years later, Cole-Hamilton and co-workers gave further evidence in support of the hydride mechanism by carrying out labeling experiments in MeOD and under CO-rich (continuous feeding of 11.5 bar of CO:ethene 1:1, paddle stirrer 1000 rpm) and CO-starvation conditions (initially 10 bar CO:ethene 1:1, magnetic stirring).[61] MSA (<0.1 mol % relative to MeOD) was undeuterated. Under conditions of CO starvation, several isotopomers containing 0−5 D atoms were obtained with the composition not changing significantly throughout the reaction. The large amounts of d^0-methyl propanoate formed at the beginning of the reaction can only be explained if the hydride mechanism operates. d^0-Methyl propanoate forms if migration of D from palladium onto ethene and exchange between free and bound ethene are reversible, as shown on the left-hand lower section of Figure 8.

The carbomethoxy mechanism is unable to explain the formation of the large amount of d^0-methyl propanoate at low reaction times because the termination step transfers deuterium from MeOD to end up in the formed methyl propanoate (Figure 9).

The authors further conclude that, under these conditions, the relative rates of the individual steps in the cycle are H migration > ethene exchange > Pd−H/D exchange > CO coordination.

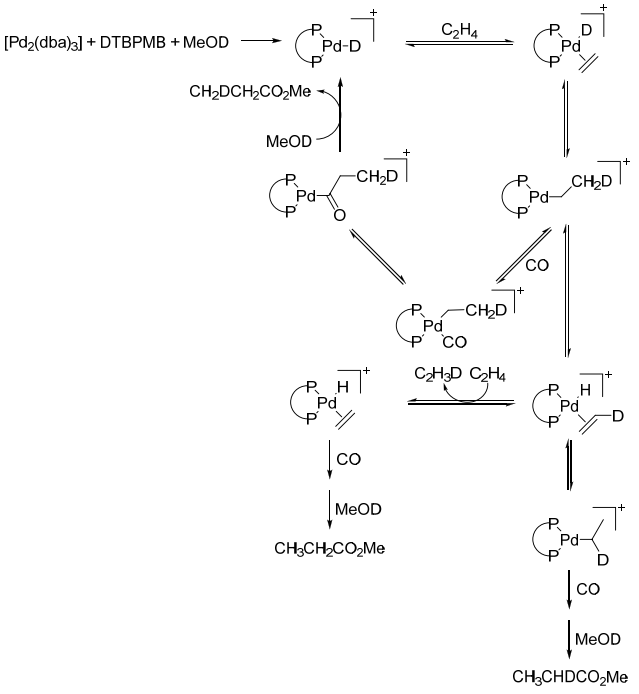

Figure 8. Proposed hydride mechanism for the formation of H/D-methyl propanoate from CO, ethene, and MeOD catalyzed by the Pd/1,2-DTBPMB system. P—P = 1,2-DTBPMB. Reproduced with permission from ref 62. Copyright 2002 Royal Society of Chemistry.

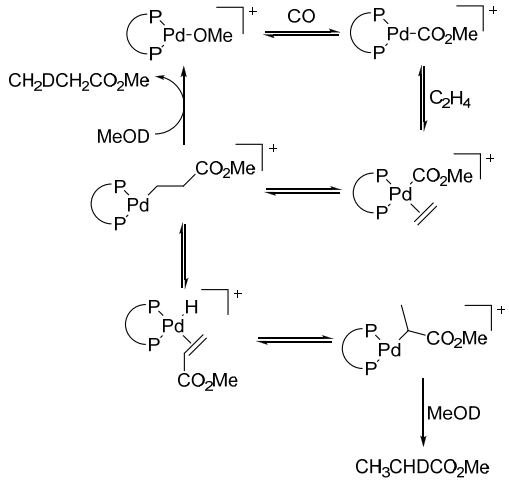

Figure 9. Proposed carbomethoxy mechanism for the formation of variously deuterated methyl propanoate from CO, ethene, and MeOD catalyzed by the Pd/1,2-DTBPMB system. P—P = 1,2-DTBPMB. Reproduced with permission from ref 62. Copyright 2002 Royal Society of Chemistry.

Quite different labeling patterns are observed under conditions where mass transport of CO into the solution is not limiting. In this case, only two isotopomers of methyl propanoate, $CH_2DCH_2CO_2Me$ and CH_3CHDCO_2Me, are formed. These products, which are formed by the main cycle and the mechanism shown at the bottom right in Figure 8, show that the relative rate order for the individual steps is H migration > CO coordination ≫ ethene loss > H/D exchange. The authors also conclude that the rate-determining step of the overall catalytic reaction occurs after the formation of the ethyl group.

In both mechanisms, the authors suggest that the vacant sites on palladium might be stabilized by coordination of $MeSO_3^-$ (as they use methanesulfonic acid), CO, methyl propanoate, or even the solvent. At the same time, the role of the solvent and of methanesulfonic acid was studied and explained by Heaton and co-workers.[63] They proposed that methanol fulfils two key roles in addition to being a reagent. First, methanol is involved in the formation of the key intermediate for the methoxycarbonylation of ethene:$[Pd(1,2\text{-}dtbpmb)H(MeOH)]^+$. Second, methanol stabilizes the hydride species. Indeed, when the hydride species is in THF, the reaction yields dihydrogen, while this is not observed in methanol. However, the stability of the hydride is surprising and may be explained by the role of methanesulfonic acid. The use of $MeSO_3H$ instead of CF_3SO_3H (TfOH) enhances the stability of the hydride so that it is stable in solution at 80 °C for several hours.

The final step of the alkoxycarbonylation reaction is reaction of methanol with the palladium acyl complex formed in the hydride cycle to give methyl propanoate and regenerate the cationic hydridopalladium complex. In 2003, Van Leeuwen and co-workers studied the methanolysis of a wide variety of ethanoylpalladium complexes containing bidentate ligands with a variety of bite angles including $[Pd(C(O)CH_3)(O_2CCF_3)(1,2\text{-}DTBPMB)]$ synthesized in situ from $[Pd(C(O)CH_3)Cl(1,2\text{-}DTBPMB)]$ and silver trifluoroacetate.[64] Of all the ligands studied, 1,2-DTBPMB gave the highest rate of alcoholysis of a model acyl complex (so fast that it could not be measured even at −90 °C). Heaton and co-workers were

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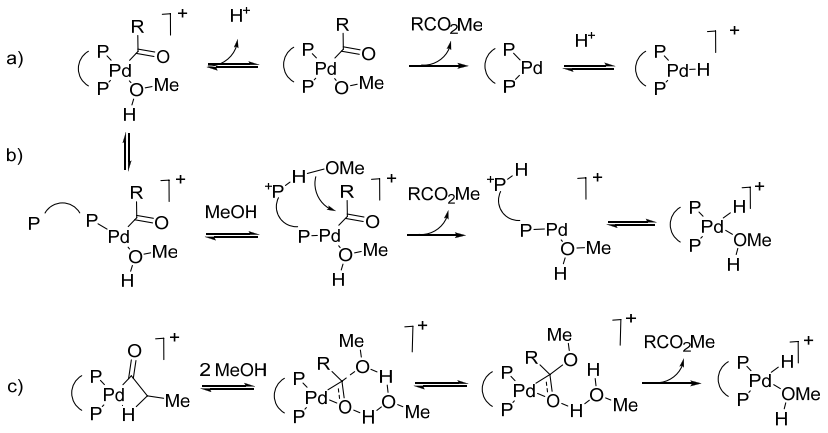

Figure 10. Possible mechanisms for the final step in the formation of methyl propanoate during the methoxycarbonylation of ethene catalyzed by Pd complexes of 1,2-DTBPMB. (a) Modified from ref 64. (b) Alternative mechanism. (c) Modified from ref 66.

also unable to measure the rate of methanolysis when using variable-temperature NMR experiments on the reaction between $[Pd(C_2H_5)(DTBPMB)]^+$, which contains an ethyl group with a β-agostic H atom, and CO. This reaction was too fast to follow by NMR spectroscopy even at low temperature. They did however isolate and fully characterize $[Pd(C(O)C_2H_5)(THF)(1,2\text{-}DTBPMB)]^+$,[65] which is fluxional so that the P atoms interchange on the NMR time scale. Two possible mechanisms were proposed, one involving a twist through a tetrahedral Pd intermediate and the other involving reversible dissociation of THF to a trigonal three-coordinate palladium complex. Since the Pd−P bond *trans* to the acyl ligand in the analogous $[Pd(C(O)C_2H_5)Cl(1,2\text{-}DTBPMB)]$, which has been crystallographically characterized, is one of the longest known, it is probable that the related Pd−P bond in $[Pd(C(O)C_2H_5)(THF)(1,2\text{-}DTBPMB)]^+$ will also be long and weak. It is then possible that an alternative mechanism for the fluxionality might involve decomplexation of the more weakly coordinated P atom of the bidentate ligand to form a trigonal planar complex followed by P recoordination of *trans*-THF (first two steps in Mechanism b) (Figure 10).

It is often assumed that the methanolysis step in the catalytic cycle is rate determining, and indeed the rate-determining step must come after the formation of the ethyl group; therefore, it must be ethyl migration onto CO or methanolysis.[62] Van Leeuwen and co-workers argue that for complexes containing 1,2-DTBPMB the rate of methanolysis is so fast that it may not be the step with the highest activation energy but that competition between CO, methanol, and anion for the vacant site in $[Pd(C(O)C_2H_5)X(1,2\text{-}DTBPMB)]^+$ (X = MeOH, CO, or $MeSO_3^-$) may mean that only very small amounts of the complex required for the irreversible formation of methyl propanoate (X = MeOH) may be present, so the absolute rate of this step is lower than that of the preceding ones in the cycle.[64]

The reason that methanolysis is so much faster when 1,2-DTBPMB is the ligand than for any other palladium phosphine complexes is less clear. It is probable that external nucleophilic attack of methanol directly into the acyl group does not occur because that would be faster for less electron-rich complexes. Van Leeuwen and co-workers conclude that the detailed mechanism of this step involves coordination of methanol followed by deprotonation and reductive elimination of the ester, probably by internal nucleophilic attack of methoxide onto the acyl carbon atom as shown in Mechanism (a), Figure 10.[64] The expected[67] high rate of reductive elimination of methyl propanoate, which has been calculated to have almost zero activation energy when 1,2-DTBPMB is the ligand,[68] is attributed to steric pressure of the *tert*-butyl groups and the sweet spot in the bite angle of 103−104°.[64] However, what seems less likely in this mechanism is the ready deprotonation of coordinated methanol from a complex that is very electron rich in an acidic solution with no obvious bases present. This step would be favored by a much lower electron density on the metal. Indeed, recent calculations have shown that this deprotonation is uphill by >230 kJ mol^{-1} if methanol is the base, and this reduces to 122 kJ mol^{-1}, which is probably still inaccessible, if the base is a cluster of nine methanol molecules, as a model for the continuum.[66] Again, a very low steady state concentration of the methoxy complex might perhaps explain the low absolute rate of the overall methanolysis step.

This problem with the methanol deprotonation step in Mechanism (a) in Figure 10 together with the presence of the very long Pd−P bond *trans* to acyl lead us to speculate that this phosphorus atom might decomplex. This would be possible given the larger (seven-membered) ring, leading to lower chelate stabilization, and would have two important effects. First, it would dramatically reduce the electron density on the complex, making it much more susceptible to nucleophilic attack, and second it would release a free phosphine, which will be fully protonated by methanol,[69] thus releasing a methoxide ion as a much better nucleophile than methanol itself. Protonation of the free phosphine and nucleophilic attack of methanol on the acyl complex are more likely to be a concerted process (Figure 10b). Following this step, which liberates methyl propanoate, P−H addition would regenerate the hydrido complex with the bidentate phosphine. P−H addition to zerovalent complexes of Pd containing 1,2-DTBPMB has also been shown to occur readily,[69] and the rigid backbone will favor oxidative addition to the same Pd atom rather than forming palladium-containing oligomers. Calculations on simpler systems showed that phosphine loss would greatly facilitate methanolysis.[70] Calculations on the methoxycarbonylation of 1-hexene suggest that the Pd−P elongates during the methanolysis step,[71] which could also lead to a reduction of the electron density on Pd, but that cleavage and protonation might lead to Pd precipitation, which is sometimes observed. The intramolecular attack of methanol

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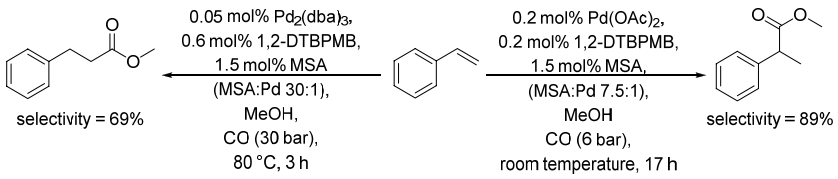

Figure 11. Control of regioselectivity in the Pd/1,2-DTBPMB-mediated methoxycarbonylation of styrene.[5,81] Adapted with permission from ref 81. Copyright 2005 Royal Society of Chemistry.

onto the acyl carbon atom then occurs by a concerted process forming the Pd−H and C−OMe bonds simultaneously.[71] It has been shown that Pd black can be brought back into the cycle by reaction with $[1,2\text{-DTBPMBH}_2]^{2+}$.[72]

Very recently, Bühl and co-workers have proposed another alternative mechanism on the basis of theoretical calculations.[66] Here, the acyl ligand is η^2-bound to palladium as shown in mechanism (c) in Figure 10. Hydrogen bonding of a chain of two or more (two shown) methanol molecules to the O atom of the acyl group delivers the OMe of the remote methanol to the acyl carbon atom through a six-membered transition state, thus effecting the nucleophilic attack. Loss of methyl propanoate and protonation reform the hydridopalladium complex. Activation barriers for this pathway can be as low as 75 kJ mol^{-1}, giving an estimated turnover frequency under the reaction conditions of between 155 h^{-1} (two methanol molecules in the transition state) and 256 000 h^{-1} (three methanol molecules in the transition state) compared with 12 000 h^{-1} observed experimentally.[33] Similar calculations replacing the *tert*-butyl in 1,2-DTBPMB by methyl show a calculated drop in rate by nine orders of magnitude, confirming the importance of steric congestion in this system. Free energies of activation have not been reported for ethene methoxycarbonylation but for methyl oleate, where the rate-determining step is again methanolysis of the acyl complex, which will have very similar electronic and steric properties to those of the propanoyl complex, Walther et al. have reported a value of 75 kJ mol^{-1},[71] identical to that calculated for the mechanism proposed for ethene methoxycarbonylation by Bühl and co-workers.[66]

All these studies have been made with palladium complexes. However, in 2014, Wass, Pringle, and co-workers carefully examined the platinum/1,2-DTBPMB system and the mechanistic paths involved during the methoxycarbonylation of ethene.[73] Generally, a reversible binding of CO to the platinum(II) intermediates is observed, resulting in a carbonyl hydride complex that is less reactive toward methoxycarbonylation of ethene. In contrast, palladium(II) exhibits a lower affinity for CO and therefore higher reactivity.[73,74]

2.2.2. 1-Alkenes > C_2. *2.2.2.1. Linear Terminal Alkenes.* In addition to methoxycarbonylation of ethene, longer-chain alkenes were examined. In preliminary studies using aromatic tertiary phosphine ligands, such as outlined in 1974 by Hara, Ohno, and Tsuji et al., regioselectivity toward the linear product was below 50%,[75] offering potential for improvement through a modified catalytic system.

After 1,2-DTBPMB had been shown to have a positive influence on catalyst activity and stability,[11,33] it was also applied in methoxycarbonylation of longer-chain 1-alkenes.

In 2001, Drent and Jager desired to increase the selectivity to the linear ester and widened the variety of substrates in methoxycarbonylation. They investigated alkenes from 4 to 14 carbon atoms, which can be substituted with alkyl, aryl groups, or groups containing hetero atoms. *Inter alia*, they used propene, butene, pentene, hexene, octene, methyl pentenoate, and pentenenitrile as substrates in a study of several diphosphine ligands. The best results were obtained using 1,2-DTBPMB. Carrying out the methoxycarbonylation of 1-octene in a mixture of anisole:methanol 2:1 as solvent, full conversion to the ester with high selectivity to the linear species (97%) was observed.[76] However, this system did not show any real improvement in comparison to the one without anisole and still used relatively harsh conditions (T > 100 °C, p > 60 bar).

In 2004, progress in terms of milder conditions was shown by Cole-Hamilton and co-workers for the methoxycarbonylation of 1-octene with 97.8% conversion and 99% linear selectivity under very mild conditions (1 bar of CO and 20 °C) in a reaction time of 3 h.[77,78] Similarly, excellent selectivity is obtained from 1-hexene and 1-dodecene, although 1-dodecene is converted moderately (75%). Some processes for similar reactions using the same catalytic system were patented by Eastham in 2004, confirming that high linear selectivity is achieved especially under milder conditions (pressure below 30 bar, temperature below 50 °C).[78] However, catalyst precipitation was observed and could be avoided through the addition of ester product, such as methyl nonanoate when 1-octene was the substrate.[79] In section 6, we will further discuss countermeasures for deactivation and recycling approaches.

2.2.2.2. Styrene and Vinyl Acetate. Vinyl compounds are also of high interest in methoxycarbonylation, as conversion of styrene and generally vinyl aromatics in carbonylations can lead to pharmaceuticals or agrochemicals. Especially, branched arylpropionic acids and esters find application in pharmaceuticals and fine chemicals, while linear, nonaryl esters are preferred as high value products on a larger scale for the chemical industry.[80] Interestingly, in 2005, Ooka and Tanaka reported the use of 1,2-DTBPMB in the methoxycarbonylation of styrenes resulting in high selectivity (89%) toward the branched product under relatively mild conditions (room temperature, 6 bar of CO, methanesulfonic acid:P:Pd 7.5:2:1, Figure 11).[81] In contrast, Cole-Hamilton and co-workers found 69% selectivity toward the linear product (Figure 11) under harsher conditions (80 °C, 30 bar CO, methanesulfonic acid:P:Pd 30:12:1).[5]

Beller and co-workers assumed that the branched benzyl complex is more stable than the linear complex since it is stabilized by π-benzylic interaction of the phenyl group with palladium. On the other hand, the steric hindrance of the *tert*-butyl groups would hinder formation of the branched product,[82] as is observed for other nonaromatic alkenes. We conclude that the effect of π-stabilization is stronger than the effect of steric hindrance, indicating some limitation of 1,2-DTBPMB toward its linear selectivity.

Referring to the reported mechanisms on alkoxycarbonylation, the insertion of styrene into a metal−acyl bond leads to

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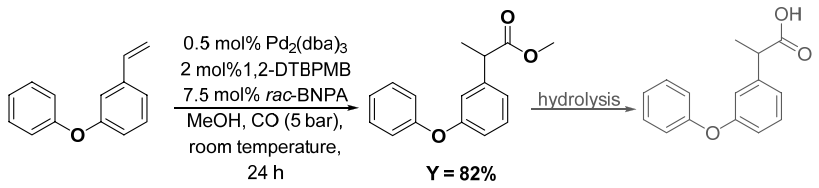

Figure 12. Methoxycarbonylation of 1-phenoxy-3-vinylphenol as an intermediate step in the synthesis of racemic fenoprofen. Adapted with permission from ref 86. Copyright 2019 Royal Society of Chemistry.

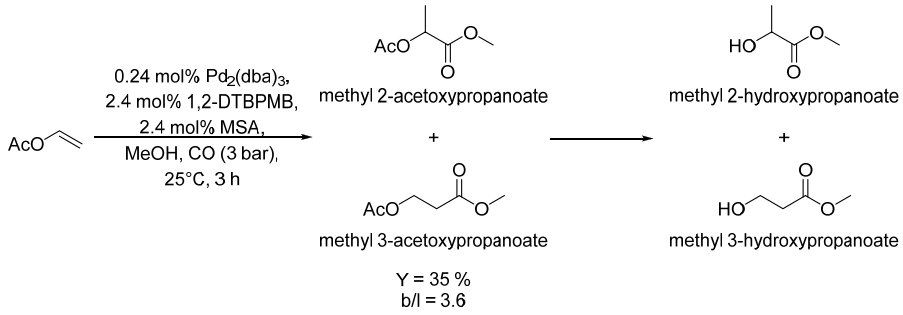

Figure 13. Methoxycarbonylation of vinyl acetate as an intermediate step in the production of methyl lactate. Adapted with permission from ref 69. Copyright 2006 John Wiley and Sons.

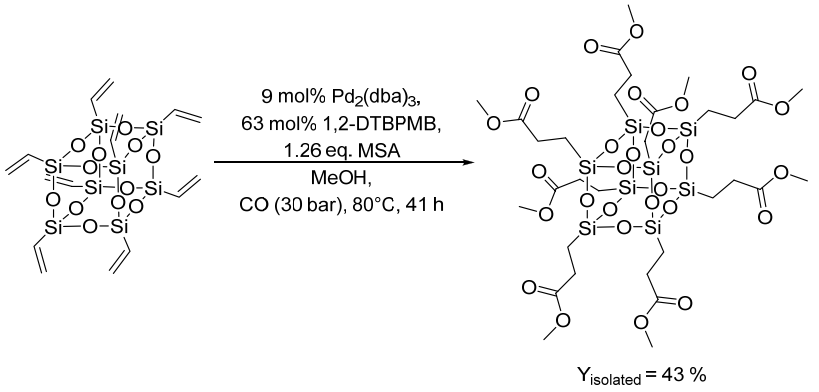

Figure 14. Preparation of OMPO via methoxycarbonylation reaction. Adapted with permission from ref 88. Copyright 2006 Elsevier.

mainly branched products, while insertion into hydrides leads to linear products.[83] Generally, very bulky phosphine ligands result in high selectivity toward the branched product in styrene methoxycarbonylation,[84] confirming our assumption above. While regioselectivity can be controlled through reaction conditions and phosphine ligand structure, enantioselectivity cannot be controlled by using the achiral ligand 1,2-DTBPMB. To control both enantioselectivity and regioselectivity, other systems such as dinuclear palladium complexes combined with chiral ligands such as phanephos[85] are superior. However, asymmetric catalysis is not a part of this review.

Branched selective methoxycarbonylation of 1-phenoxy-3-vinylphenol catalyzed by Pd/DTBPMB in the presence of racemic 1,1′-bi-2-naphthol-phosphoric acid (*rac*-BNPA) (82% branched yield, 12% linear) has been used as part of a synthesis of racemic fenoprofen, a nonsteroid anti-inflammatory drug. The five-step synthesis from cardanol proceeds in 47.5% overall yield (Figure 12).[86]

The methoxycarbonylation of vinyl acetate using 1,2-DTBPMB was reported by Cole-Hamilton in 2005, with up to 78% selectivity to the branched product, methyl 2-(acetyloxy)propanoate. The product is a potential source of lactic acid and its esters (Figure 13), which are potential alternative solvents of low volatility and high biodegradability. Although the main synthetic path to lactic acid is the fermentation of glucose, vinyl acetate is a cheap, highly available feedstock.[87]

As well as being involved in the carbonylation process, it appeared that the ligand played a role as a stabilizer toward vinyl acetate, preventing its degradation to methyl acetate due to transesterification with methanol catalyzed by methanesulfonic acid, as described by Cole-Hamilton and co-workers in 2006.[69] In most methoxycarbonylation reactions involving the Pd/1,2-DTBPMB system, a large excess of acid is employed, but in this case the reactions were carried out using an excess of 1,2-DTBPMB over acid. NMR studies showed that all the acid was present in the form of the diphosphonium salt, $[C_6H_4(CH_2PHtBu_2)_2]^{2+}$. This quaternary phoshonium salt is able to oxidatively add P−H across the palladium center to generate the catalytically active hydrido complex but is not sufficiently acidic to catalyze the methanolysis of vinyl acetate. In order to try to improve the branched selectivity, which is desired in this case, Cole-Hamilton and co-workers screened a range of diphosphine ligands with slightly reduced steric

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Chem. Rev. 2021, 121, 6610−6653

demand and electron-donating capacity by successively replacing the *tert*-butyl groups on 1,2-DTBPMB by isopropyl groups, but the most bulky ligand tested, 1,2-DTBPMB, resulted in the best activity and branched selectivity.[69] Higher branched selectivity was obtained with higher ligand loadings and lower temperature, the latter at the expense of activity. Catalysts employing ligands in which the *o*-xylene-derived backbone was replaced by those derived from 1,2- or 2,3-dimethylnathphthalene performed very similarly to those containing 1,2-DTBPMB.[69]

In 2005, Ooka, Tanaka, and co-workers reported the methoxycarbonylation of vinyl acetate using a polymeric sulfonic acid instead of methanesulfonic acid under CO (60 bar) at 60 °C.[81] Some side reactions occur, so the selectivity to esters is 74% (branched selectivity 72%). The sulfonate group was attached to a polymeric resin, with an optimal ratio SO_3H/Pd = 4.5. This heterogenized catalyst is capable of being recycled at least three times after evaporation of volatile residues without any loss in stability. The same system shows a high efficiency for the methoxycarbonylation of styrene, again with a high selectivity (88%) to the branched product.[81]

2.2.2.3. Polyhedral Oligomeric Silsesquioxanes. In 2006, Morris, Cole-Hamilton, and co-workers reported the methoxycarbonylation reaction for making 1,3,5,7,9,11,13,15-octakis-[methyl 2-propanoateooctasiloxane] (OMPO, Figure 14) as a representative for polyhedral oligomeric silsesquioxanes (POSS), which are applied in nanocomposites and high performance polymer materials. The functionalization of silsesquioxanes with ester or acid groups opens potential for further functionalization to novel molecules. 1,2-DTBPMB was chosen as a ligand since it was known to be highly selective toward terminal functionalization.[88] The methoxycarbonylation offers an alternative to hydrosilylation[89] to prepare such a methyl-ester-functionalized silsesquioxane.

2.2.3. Cyclic Alkenes. *2.2.3.1. Norbornene.* Norbornene is a highly interesting substrate for functionalization by, e.g., methoxycarbonylation since three chiral carbon centers are formed upon formation of one new C−C bond. Regioselectivity is not an issue due to the symmetry of the substrate, but enantioselectivity and *endo*-/*exo*-selectivity are important.[90] The product offers potential application in the fragrance industry.[91] Methoxycarbonylation of norbornene was first reported in 1996 by Zhou et al. using the nonchelate diphosphine ligand 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis-(diphenylphosphino)-L-iditol (DDPPI, Figure 15).[92]

They claimed a conversion of 72% with 92% enantiomeric excess[92] which was not reproducible afterward.[93] With a different catalyst system based on achiral [Pd-$(MeCN)_2(PPh_3)_2$][BF_4], Inoue and co-workers obtained 74% racemic ester.[94] Although the high terminal selectivity obtained with Pd/1.2-DTBPMB is not required for norbornene methoxycarbonylation, in 2009, Ruiz, Claver, Godard, and co-workers demonstrated the suitability of this system so that 91% ester yield and >99% selectivity toward the thermodynamically more stable *exo*-ester were achieved at

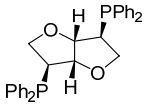

Figure 15. 1,4:3,6-Dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-L-iditol (DDPPI) as nonchelating diphosphine.[92]

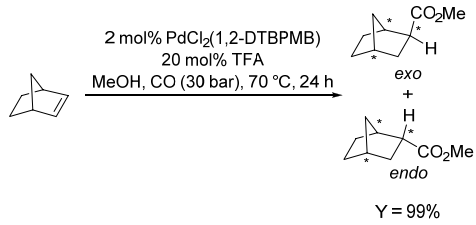

Figure 16. Methoxycarbonylation of norbornene.[91,93] Adapted with permission from ref 93. Copyright 2009 John Wiley and Sons.

70 °C (Figure 16).[93] The ester yield was increased to 99% by *ex situ* generation of the Pd/1,2-DTBPMB complex by the same authors in 2012.[91] At room temperature, the same *exo*-selectivity is obtained, but conversion is much lower. In contrast, application of the synthesized ligand ((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)diphenylphosphane results in quantitative yield and selectivity, although enantiomeric excess is hard to increase above 10% by modifying ligands only.

In summary, this example reflects the broad substrate tolerance in Pd/1,2-DTBPMB-mediated methoxycarbonylation. Although enantioselectivity is a challenge that cannot be addressed with the achiral ligand, quantitative conversion, chemoselectivity, and excellent *exo*-selectivity are achieved.

3. ISOMERIZING CARBONYLATIONS

The Pd/1,2-DTBPMB system was successfully implemented for alkoxycarbonylation of terminal alkenes. However, using internal alkenes, branched esters are not observed. Due to the ligand's outstanding ability to promote double-bond migration, terminal esters are the predominant products from internal alkenes through preliminary isomerization. Therefore, the tandem reaction of isomerization and subsequent alkoxycarbonylation opens up a wide range of applications.

3.1. Nonfunctionalized Internal Alkenes

3.1.1. 2-Butene. As already mentioned in section 2.2.2.1, in 2001, Drent and Jager investigated longer-chain alkenes in the Pd/1,2-DTBPMB-mediated methoxycarbonylation.[76] Conversion of internal alkenes such as 2-butene also results in high regioselectivity toward linear ester products. Methyl pentanoate is obtained from 2-butene with 97% selectivity at nearly full conversion. The initial reaction rate is higher using 30 bar instead of 60 bar of CO, resulting in the same conversion and selectivity (Figure 17).

Applying 60 bar of CO, methyl-3-pentenoate was quantitatively converted by obtaining the linear diester, dimethyladipate, with 96% selectivity. The branched diesters 2-methyl dimethylglutarate and 2-ethyl dimethylsuccinate are obtained in traces only. Compared to the ligands 1,3-bis[di-*tert*-butylphospino]propane and 1,3-*P*,*P*′-di(2-phospha-1,3,5,7-tetramethyl-6,9-10-trioxatricyclo[3.3.1.1{3,7}]-decyl)propane,

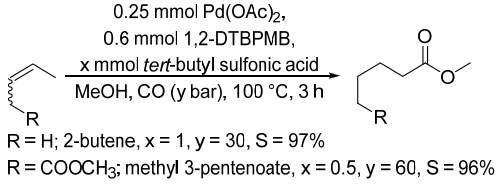

Figure 17. Methoxycarbonylation of 2-butene/methyl 3-pentenoate, indicating the isomerization activity of 1,2-DTBPMB.[76]

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Chem. Rev. 2021, 121, 6610−6653

the best result in terms of product linearity was obtained using 1,2-DTBPMB,[76] indicating its excellent isomerization activity.

3.1.2. Internal Octenes. The potential of isomerization was further investigated applying several internal octenes. In 2004, Cole-Hamilton and co-workers found that even under very mild conditions (room temperature, bubbling 1 atm of CO, 3 h) methyl nonanoate is obtained with 99% selectivity from 2-octene.[77] By raising the temperature to 80 °C and pressurizing the system to 30 bar of CO, conversion is increased from 30% to 96%, confirming first the alkene isomerization ability of Pd/1,2-DTBPMB and second its higher activity toward terminal alkene conversion to linear products than internal alkene conversion to branched products. When the reaction time is prolonged to 16 h, also 3-octene and 4-octene were converted quantitatively, obtaining 94% product linearity.

Although combining isomerization with other reactions catalyzed by homogeneous catalysts using a single (e.g., hydroformylation,[95] hyperbranched polymerization[96]) or two catalysts (e.g., metathesis)[97] is known, the very high terminal selectivity as well as the applicability to functionalized substrates of this isomerizing methoxycarbonylation make it highly attractive.

3.1.3. Methyl-Branched Pentenes. To further investigate the versatility of 1,2-DTBPMB-mediated isomerization, Cole-Hamilton and co-workers applied several methyl-branched pentenes in the methoxycarbonylation, resulting in outstanding selectivity toward the linear products, independent of the position of the double bond.[77] Interestingly, isomerization of 2-methyl-1-pentene is influenced by the availability of CO: if bubbled through the reaction mixture, methyl 3-methylhexanoate is the main product, but if passed over the stirred mixture, isomerization and, as a result, methyl 5-methylhexanoate are formed (Figure 18). In conclusion, the rate of isomerization can be higher than that of carbonylation when the system is starved of CO.

3.2. Synthesis of α,ω-Bifunctional Compounds

Linear, bifunctional molecules are of high industrial relevance, for example, in the production of polyesters or polyamides. Such compounds can potentially be formed by ω-functionalization of unsaturated α-functionalized molecules or by difunctionalization of dienes or alkynes. Obviously, if an internal double bond is present, isomerization is indispensable for ω-functionalization.

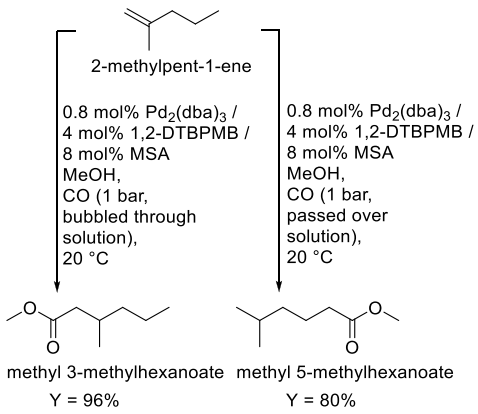

Figure 18. Dependence of Pd/1,2-DTBPMB-mediated isomerization on CO availability.[77]

In the context of the first reported application of 1,2-DTBPMB in the methoxycarbonylation of internal alkenes, Drent and Jager also applied alkenes bearing further functionalities in 2001. In their patent, they mentioned the use of dienes, trienes, and also substituted alkenes containing halides, sulfur, phosphorus, oxygen, and nitrogen, demonstrating the use of methyl 3-pentenoate to produce dimethyl 1,6-hexandioate (dimethyl adipate) as an example[76] and pointing to a wider scope for 1,2-DTBPMB-mediated carbonylations and therefore a wider field of applications. In the case of internally unsaturated α-functionalized molecules as starting materials, oleochemicals are of special interest. α,ω-Bifunctional compounds offer versatile applications to polymerization for the synthesis of polyesters and polyamides but also in specialty chemicals.[98] Therefore, the isomerization ability of 1,2-DTBPMB is highly attractive regarding the usability of (functionalized) internal alkenes in the tandem isomerization/carbonylation for production of high value chemicals.

3.2.1. Methoxy- and Hydroxycarbonylation of Unsaturated Esters. *3.2.1.1. Methoxycarbonylation of Acrylates for the Production of Acrylate Esters.* In 2005, Eastham, Cole-Hamilton, and co-workers reported the methoxycarbonylation of methyl acrylate to dimethyl succinate using Pd/1,2-DTBPMB and methanesulfonic acid, showing the tolerance for the ester functionality in the substrate (Figure 19).[98] However, competing Michael addition occurs under these reaction conditions, lowering the yield in comparison to methyl methacrylate as a substrate.

3.2.1.2. Synthesis of C6 Polymer Building Blocks: Adipic Acid and ε-Caprolactam from C5 Carboxylic Acids/Esters. The carbonylation of unsaturated C5 carboxylic acids/esters is potentially a key step toward the formation of adipic acid derivatives and ε-caprolactam, which are involved in the synthesis of polymers, especially nylon and several others. Therefore, sustainable and efficient industrial processes for the synthesis of these C6 polymer building blocks are required.

The classical and cheap production of adipic acid involves "ketone-alcohol oil" (KA oil), a mixture of petrochemically based cyclohexanone and cyclohexanol which is oxidized with nitric acid. Due to low selectivity, this process is run at low conversion of 4−8% so that distillation of cyclohexane for recycling is required. In the second step, the KA oil is oxidized with nitric acid, which is meanwhile reduced to NO_x and nitrous oxide (N_2O).[99] If not released as emissions, NO_x can be catalytically destroyed at high cost.[100] If nitrogen-containing impurities appear in the product, extensive purification is necessary.[101]

Regarding ε-caprolactam, its production is also mainly based on cyclohexanone. The latter is converted to the corresponding oxime, which is finally treated with sulfuric acid to induce Beckmann rearrangement so that ε-caprolactam is obtained. In this process, huge quantities of ammonium sulfate are formed as a byproduct.[102,103] To reduce the harmful greenhouse effect

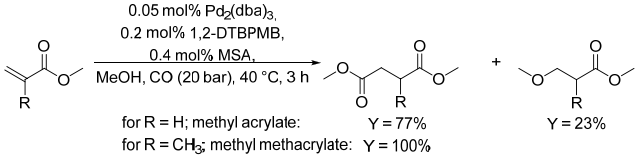

Figure 19. Methoxycarbonylation of methyl acrylate. Adapted with permission from ref 98. Copyright 2004 Royal Society of Chemistry.

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Chem. Rev. 2021, 121, 6610−6653

of adipic acid production and avoid waste in ε-caprolactam production, alternative highly selective routes, at least partially starting from renewable resources, are needed.

The alternative ways, which will be discussed in this section, have the challenge of at least one isomerization step in common, pointing to the key role of 1,2-DTBPMB in the production of C6 polymer building blocks.

The methoxycarbonylation of unsaturated esters with high selectivity toward the linear α,ω-diesters was first reported by Drent and Jager in converting methyl 3-pentenoate to dimethyl 1,6-hexanedoate (dimethyl adipate) with an α,ω-selectivity of 96% in the presence of anisole at 60 bar and 100 °C (Figure 17).[76]

In addition to their work on methoxycarbonylation of terminal unsaturated esters, Eastham, Cole-Hamilton, and co-workers claimed quantitative conversion for internal unsaturated pentenoic acids and their esters with high selectivity toward dimethyl adipate (Figure 20) in 2005.[98] The Pd/1,2-DTBPMB system is capable of isomerizing the double bond even out of conjugation to the terminal position, before being selectively carbonylated. Remarkably, pentenoic acid as substrate results in the same ester product, showing that esterification takes place under these methoxycarbonylation conditions without any constraint, and there is no need for a separate esterification of the unsaturated acid prior to methoxycarbonylation to obtain the same diester as from an unsaturated ester substrate. With this work, the basis for alternative synthesis routes of C6 polymer building blocks such as adipic acid, its derivatives, and ε-caprolactam (Figure 21) was built.

In addition to the high selectivity toward dimethyl adipate starting from pentenoic acid (esters) compared to the conventional KA route, the pathway is turned toward sustainability since pentenoic acids are producible from biobased γ-valerolactone. The latter originates from levulinic acid[100] and hydroxymethyl furfural, respectively. The lactone is heterogeneously catalytically ring-opened, yielding pentenoic acid, comprising all regioisomers.[104] Subsequently, pentenoic acid is hydroxycarbonylated using Pd/1,2-DTBPMB in the presence of an acid as shown by Drent, Van Ginkel, and Jager in 2004,[105] followed by several patents.[101,104] Alternatively, as shown above, pentenoic acid can be methoxycarbonylated to dimethyl adipate.[98]

Additionally, pentenoic acid isomers and their derivatives are accessible through addition of hydrogen cyanide to butadiene[106,107] and subsequent hydrolysis in the presence of a catalyst. Another way would be Pd/1,2-DTBPMB-mediated hydroxycarbonylation of butadiene, first reported by Drent and Jager in 2004.[108] Obviously, hydroxycarbonylation of butadiene and subsequent hydroxycarbonylation of the pentenoic acid intermediate, as reported in 2006 by Drent, Jager, and co-workers,[109] are advantageous since the same Pd/1,2-DTBPMB catalyst system is used omitting intermediate purification.

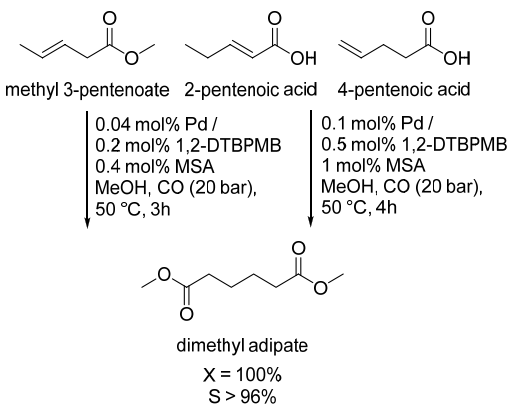

Figure 20. Methoxycarbonylation and isomerization/esterification for the synthesis of dimethyl adipate.[98]

In the hydroxycarbonylation of pentenoic acid, methanesulfonic acid is mostly chosen as an additive. However, in 2004, Drent and Jager have also shown that if the main substrate isomer is 3-pentenoic acid this same acid can also function as the acidic catalyst promoter. As a result, there is no need for a further acidic additive, still resulting in a conversion higher than 90%.[105] The *n*/*iso* ratio is above 70 if the preformed Pd/1,2-DTBPMB complex is applied.[110] In 2007, Eastham and Tindale claimed that in the hydroxycarbonylation reaction an excess of the ligand over the metal is advantageous, as the ligand may play the role of a base to buffer the acid level and prevent the degradation of the substrate.[111] A similar effect was described by Cole-Hamilton in 2005 (see section 2.2.2.2) in the methoxycarbonylation of vinyl acetate.[87] Finally, adipic acid precipitates or crystallizes, and the catalyst containing filtrate can be recycled after removal of side products, as shown by Drent et al. in 2006. The amount of residual palladium in the product is 0.0001 to 1 ppmw.[101] Several other catalyst systems based on Co[112] or Rh[113] had been investigated earlier in the 1970s/80s resulting in lower selectivity and requiring harsher conditions, respectively. In conclusion, the described Pd/1,2-DTBPMB-mediated hydroxycarbonylation is superior to conventional adipic acid production in terms of sustainability due to optional use of renewable resources and sufficient recyclability of the catalyst.

Similar to hydroxycarbonylation, also methoxycarbonylation of butadiene is feasible for the syntheses of C6 polymer building blocks (Figure 21). The product, methyl 3-pentenoate, can undergo 1,2-DTBPMB-mediated tandem isomerization/methoxycarbonylation to yield dimethyl adipate. After hydrolysis of the diester, adipic acid is obtained efficiently, as reported by De Vries and co-workers in 2012.[100,114] The direct dimethoxycarbonylation of 1,3-butadiene was patented by Drent and Jager in 2000, using several diphosphine ligands such as 1,2-*P*,*P*′-bis(9-phosphabicyclononyl)ethane. However, selectivity toward the desired linear dimethyl adipate is insufficient (59%).[115]

Furthermore, the synthesis of 5-cyanovaleric acid, as a precursor for ε-caprolactam, is feasible via methoxycarbonylation of pentenenitriles, which are also accessible from methyl pentenoates. 3-Pentene nitrile, made from 1,3-butadiene hydrocyanation[116,117] on a large scale in industry by DowDuPont (Figure 21),[118,119] can be methoxycarbonylated using the Pd/1,2-DTBPMB system. In doing so, 5-cyanovaleric acid is produced within 5 h at 100 °C with 97% conversion and 98% linear selectivity, as patented by Bunel and Clark in 2002/2003.[120,121]

Taking all intermediate reactions into account, obtaining 5-cyanovaleric acid from the Pd/1,2-DTBPMB-mediated methoxycarbonylation of pentenenitriles is a significant improvement for subsequent synthesis of ε-caprolactam upon hydrogenation in an overall selectivity of 90% based on butadiene.[103] In addition, the stability of the nitrile function toward the methoxycarbonylation is remarkable. Conversely, it is noticeable that the Pd/1,2-DTBPMB system is inert toward the

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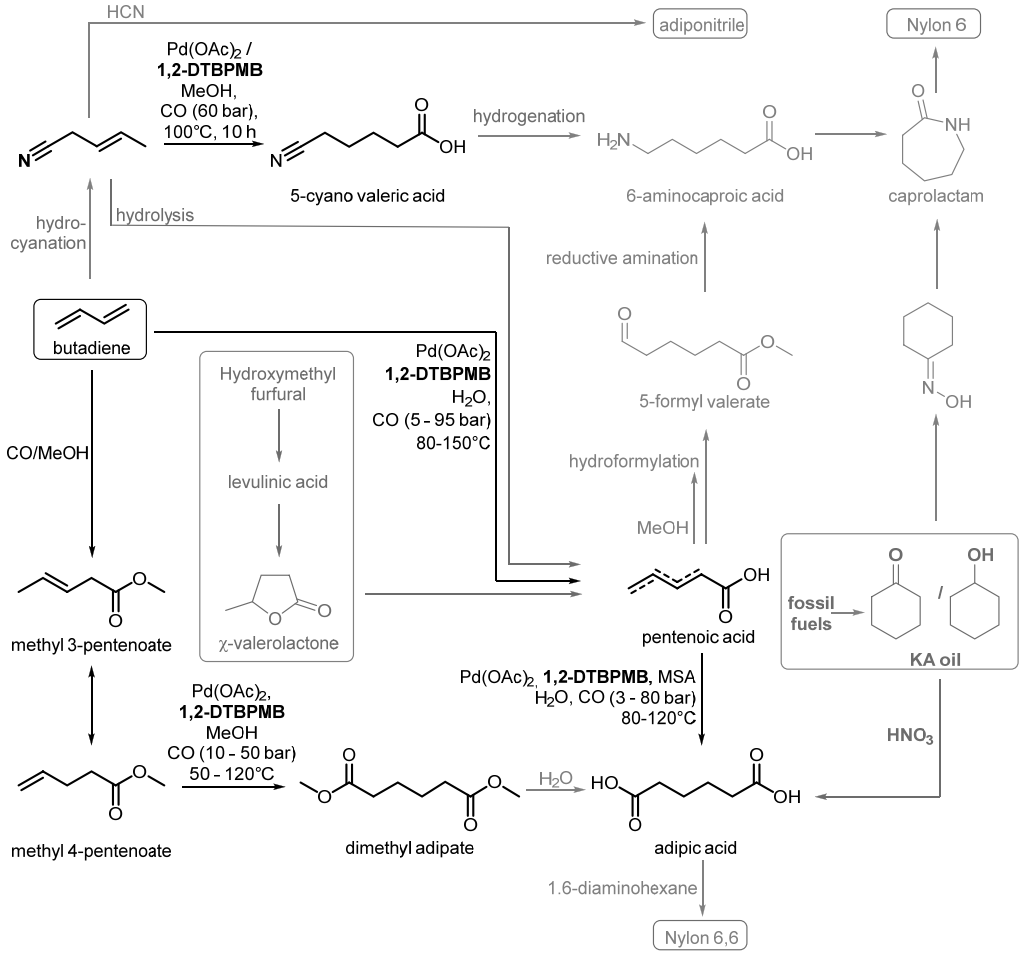

Figure 21. Role of 1,2-DTBPMB for the production of C6 polymer building blocks. For references, see text.

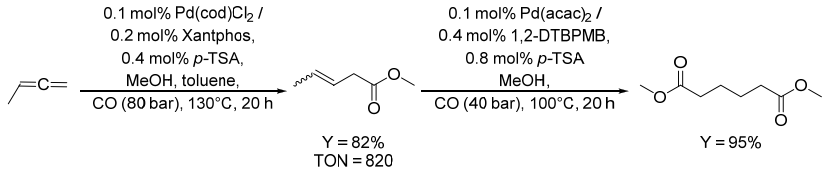

Figure 22. Xantphos-mediated methoxycarbonylation of 1,2-butadiene and subsequent 1,2-DTBPMB-mediated methoxycarbonylation of the intermediate pentenoic acid ester. Adapted from ref 124. Copyright 2015 American Chemical Society.

nitrile function, showing its versatility and tolerance for reactive functional groups and its potential key role in ε-caprolactam production. As an alternative, methyl pentenoates can undergo hydroformylation and subsequent reductive amination toward 6-aminocaproic acid, which is converted to ε-caprolactam through cyclization. In this route, the carbonylation of butadiene suffers from methyl 2-pentenoate formation with 10−25% selectivity, lowering the selectivity in hydroformylation. Although selectivity had been improved,[122] the overall selectivity toward ε-caprolactam in this 1,3-butadiene route is only 75%,[103] raising interest in the suggested Pd/1,2-DTBPMB-mediated path.

Although Pd/1,2-DTBPMB-mediated methoxycarbonylation of the unsaturated C5 esters/acids is highly selective, the formation of those intermediates from butadiene using the same reaction system has a low rate. Therefore, a high concentration of palladium is needed, which leads to rapid catalyst deactivation.[114] Additionally, telomerization and dimerization of butadiene can occur as competing side reactions. In 2002, Beller and co-workers found a suitable ligand using 1,4-bis(diphenylphosphino)butane (DPPB), leading to a yield of 3-methyl pentanoate of 69%.[123]

In 2015, Beller, Liu, and co-workers reported the pentenoic acid/ester intermediates to be accessible from methoxycarbonylation of 1,2-butadiene as a representative allene. A ligand screening for the alkoxycarbonylation of propa-1,2-dienylbenzene showed by far the best yield (90%) toward the linear ester using Xantphos. Although 1,2-DTBPMB showed higher activity compared to DPPB, triphenyl phosphine, and all other studied ligands, only a moderate yield of 60% was available. Finally, dimethyl adipate could be obtained in 95% yield by applying the Pd/Xantphos system for allene methoxycarbonylation, followed by Pd/1,2-DTBPMB-mediated methoxycarbonylation of methyl 3-pentenoate (Figure 22).[124]

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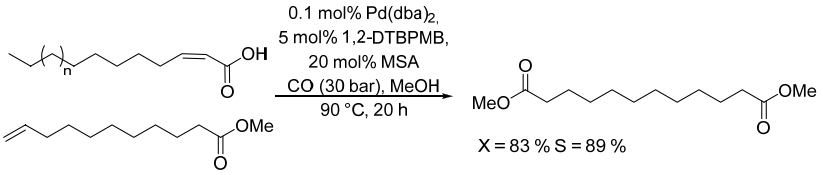

Figure 23. Methoxycarbonylation of unsaturated C11 (n = 1, yield (Y) = 84%, terminal selectivity (S) = 92%) and C16 (n = 6, Y = 79%, S = 90%) acid or esters. Reproduced with permission from ref 127. Copyright 2013 Royal Society of Chemistry.

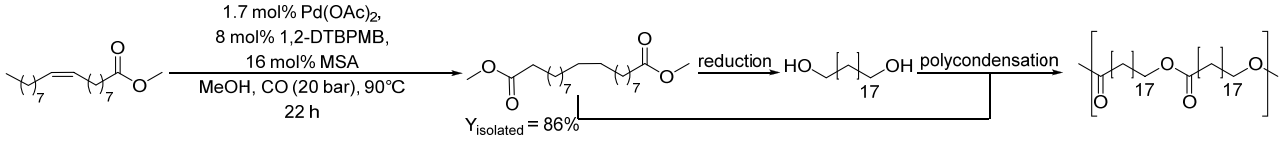

Figure 24. Pd/1,2-DTBPMB-mediated isomerizing methoxycarbonylation of methyl oleate and subsequent polymerization.

At this point, the reader is referred to recent works by Beller and co-workers, who developed a novel promising ligand (see section 8.1), derived from 1,2-DTBPMB, for the direct carbonylation of 1,3-butadiene[125] since none of the described procedures using 1,2-DTBPMB for C6 polymer building block synthesis have found their way into an industrial process.

In summary, several approaches for the development of a sustainable production of C6 polymer building blocks were investigated. However, so far, the described routes using 1,2-DTBPMB have not been up-scaled to be competitive on an industrial scale due to low catalyst stability and efficiency and, finally, most crucial for industry, the cost of a corresponding process.

3.2.2. Oleochemicals as Unsaturated Esters. Potential chemical compounds that make use of the isomerization ability of 1,2-DTBPMB to be converted into α,ω-bifunctional chemicals require a terminal functional group and an internal double bond. Therefore, the application of oleochemicals is highly attractive, especially in terms of sustainability.

3.2.2.1. Methyl Oleate and Methyl Linolenate. In principle, the alkoxycarbonylation of renewable resources such as unsaturated fatty acids and their esters should produce α,ω-diesters, diacids, and other derivatives. These products might be applied in, especially, linear polyesters, which exhibit melting points in the range of thermoplastics.[10] So far, long-chain C18 esters are accessible through self-metathesis of methyl oleate, and C11 diesters and derivatives are obtained through cross metathesis of methyl oleate with methyl acrylate, dimethyl maleate, or dimethylfumarate.[126] However, in terms of atom economy, only 50% of the C atoms of methyl oleate appear in the final product. In the case of self-metathesis, this proportion is lowered to 33% because the reaction reaches equilibrium. Therefore, a new approach making efficient use of renewable resources, in the production of polymer building blocks, is of special interest. Since the challenging substrates are often long chain, functionalized, and internally unsaturated, the application of 1,2-DTBPMB has considerable potential. Linear molecules of high purity are favored for the synthesis of high-grade polymers, making the target quite challenging.

As part of the pioneering work by Eastham, Cole-Hamilton, and co-workers (as outlined in section 3.2.1.2) on the methoxycarbonylation of internally unsaturated compounds,[98] the Pd/1,2-DTBPMB-mediated isomerizing methoxycarbonylation of methyl oleate to dimethyl 1,19-nonadecanedioate was carried out with quantitative conversion and >95% selectivity to the α,ω-diester under relatively mild conditions (20 bar CO, 40 °C, 20 h). For this case, the double bond was isomerized over nine carbon atoms. This demonstrates further potential of 1,2-DTBPMB, even if further double bonds are present or the double bond is deep in the chain.

The double bond also has to move over 8 atoms, this time out of conjugation, in the successful methoxycarbonylation of 2-undecenoic acid,[127] available as the methyl ester from metatheses of methyl oleate with dimethyl maleate.[128] Similar conversion and selectivity are obtained but at a faster rate using methyl 11-undecenoate[127] which can be made by cracking castor oil.[129] The furthest double bond isomerization observed so far is in the methoxycarbonylation of 2-hexadecenoic acid to dimethyl heptadecanedioate, where the double bond must be drawn out of conjugation and isomerize over 14 C atoms before being selectively carbonylated in the terminal position.[127] These reactions are summarized in Figure 23.

Plant-oil based substrates already contain long CH_2 chains, which are crystallizable so that semicrystalline long-chain polyesters are a subject of interest. In 2010, this approach was taken up by Mecking and co-workers, who purified dimethyl 1,19-nonadecanedioate, obtained from isomerizing methoxycarbonylation of methyl oleate, by crystallization, resulting in 99% purity. This approach was recently extended to a recycling technique by Seidensticker and co-workers (see section 6).[130] By subsequent reduction, initially with $LiAlH_4$ and polycondensation, a linear polyester was obtained (Figure 24).[131] This biobased polyester synthesis and application of the products was patented in 2013.[132] In 2014, the same group successfully carried out the procedure even on a 100 g scale and investigated the properties of the polyesters toward their potential application as packaging materials, nonwovens and moldings.[133]

For a technical application, the usage of high oleic sunflower oil instead of pure methyl oleate is more advantageous since transesterification prior to methoxycarbonylation is avoided. As already shown by Eastham and Cole-Hamilton (see section 3.2.1.2), the methoxycarbonylation reaction conditions are also suitable for esterification of carboxylic acids.[98] In 2011, Walther et al. extended and successfully implemented this approach in the tandem methanolysis/isomerization/methoxycarbonylation reaction of high oleic sunflower oil using Pd/1,2-DTBPMB at 30 bar of CO and 80 °C.[134] With a reaction time of 32 h, the reaction is slower in this case, but the formation of glycerol, with impurities such as free fatty acids in

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Chem. Rev. 2021, 121, 6610−6653

the substrate or traces of water in the solvent, do not inhibit the reaction. Finally, up to 97% yield and selectivity toward dimethyl 1,19-nonadecanedioate are obtained, even if upscaled to a 12 L batch. There were additional attempts to hydrolyze the diester to the diacid directly from high oleic sunflower oil, resulting in no conversion.[134] Nevertheless, dimethyl 1,19-nonadecanedioate serves as a substrate for the corresponding diacid, diol, and diamine as valuable building blocks for novel polymers based on renewables. In 2012/2013, Furst et al. also applied further natural oils such as olive, sunflower, and rapeseed oil[134] or nonfood tall oil,[127] which is a byproduct of paper manufacturing by the Kraft process available at 2 M tonnes per year,[135] successfully to Pd/1,2-DTBPMB-mediated methoxycarbonylation.

In terms of sustainability, the reduction toward the diol is preferably carried out using catalytic hydrogenation instead of conventional $LiAlH_4$. This has successfully been achieved using a variety of ruthenium complex catalysts.[10,134,136] 1,19-Diaminononadecandioate can also be produced by hydrogenation of the diester in a two-step, one-pot process involving initial hydrogenation to diol and reaction with ammonia, both steps being catalyzed by a ruthenium complex containing 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos).[137]

The low solubility of fatty compounds in water is the reason for their challenging hydroxycarbonylation. However, in 2016, Mecking and co-workers showed that by choosing a suitable solvent the Pd/1,2-DTBPMB-mediated isomerizing hydroxycarbonylation of oleic acid results in the formation of 1,19-nonadecanedioic acid. Due to the volatility, easy removal, and good miscibility, the hydroxylation of oleic acid was carried out in THF. In doing so, up to 88% conversion with 93% selectivity toward the linear diacid was obtained (Figure 25). Trifluoromethanesulfonic acid and 1,2-DTBPMB form the diprotonated ligand $[(1,2\text{-dtbpmbH}_2)(OTf)_2]$ to stabilize the Pd catalyst (see section 3.3) and significantly increase the conversion. Thereby, a turnover number (TON) of 107 is reached through application of the diprotonated form $[(1,2\text{-dtbpmbH}_2)(OTf)_2]$ in contrast to a TON of 36 using the unprotonated ligand and trifluoromethanesulfonic acid. Finally, high oleic sunflower oil was applied, giving similar results.[138]

These publications on Pd/1,2-DTBPMB-mediated isomerizing hydroxy-/alkoxycarbonylation of fatty acids and esters emphasize the great tolerance for the internal double bond deeply buried in a long hydrocarbon chain. In conclusion, a novel wide field of applications to oleochemicals for 1,2-DTBPMB is found in the synthesis of biodegradable, sustainable polymers.

3.2.2.2. Erucic Acid and Derivatives. In addition to methyl oleate and oleic acid, erucic acid, available from rapeseed oil, is of interest due to its longer 22 carbon atom chain (Figure 26).

Quinzler and Mecking described a similar alkoxycarbonylation/crystallization approach as for methyl oleate,[131] but since methyl erucate is not soluble in methanol, ethoxycarbonylation

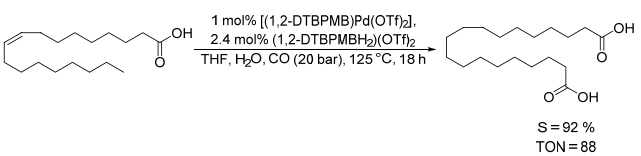

Figure 25. Pd/1,2-DTBPMB-mediated isomerizing hydroxycarbonylation of oleic acid in THF.[138]

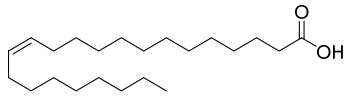

Figure 26. Erucic acid.

of ethyl erucate was carried out instead. The linear diester product crystallizes in a yield of 79% with excellent purity.[131] This diester can be used for preparing polyesters with a very long carbon chain, having a melting point of 90 °C. Mecking and Quinzler claimed that such a polyester is biologically degradable within 6 to 10 weeks.[139] However, this was not experimentally shown. In 2008, Heise, Joosten, and co-workers studied similar polymers, such as polyhexadecalactone but found no hydrolytic or enzymatic degradation due to the high crystallinity and hydrophobicity of the polymers.[140]

Additionally, the isomerizing hydroxycarbonylation using the diprotonated ligand $[(1,2\text{-dtbpmbH}_2)(OTf)_2]$ was transferred to erucic acid. Compared to 10-undecenoic acid and oleic acid, a decreasing conversion with increasing carbon chain length is observed (47% for erucic acid and 95% for 10-undecenoic acid[138]).

3.2.2.3. Methoxycarbonylation of Multiply Unsaturated Fatty Acids. In 2005, Eastham and Cole-Hamilton also investigated multiple unsaturated fatty acid esters in the methoxycarbonylation. Interestingly, they reported that methyl linoleate and methyl linolenate were quantitatively converted to the saturated linear dimethyl 1,19-nonadecanoate with 82% and 83% selectivity. The authors assumed a transfer hydrogenation of the remaining double bonds was occurring.[98] However, high occurrence of transfer hydrogenation in the presence of CO was subsequently shown not to occur, and the saturated diester was obtained in small amounts only.[127] Instead, from methoxycarbonylation of methyl linoleate, the linear diester containing one more double bond distributed along the carbon chain was identified as a product. Additionally, the branched triester, containing all regioisomers, was formed (Figure 27).

According to the reaction rate, the turnover frequency (TOF) of methoxycarbonylation of methyl oleate is 12 h^{-1}, while methoxycarbonylation of methyl linoleate is much slower with a TOF of 2 h^{-1}.[141] Nevertheless, it was shown that Pd/1,2-DTBPMB-mediated methoxycarbonylation of multiple unsaturated fatty acids, as they appear in natural oils such as commercial olive, canola, or sunflower oils, is possible with the yield of dimethyl 1,19-dimethyl nonadecanoate, corresponding to complete conversion of the oleic component of the triglyceride esters. Furthermore, food oils could be avoided by using Tall Oil fatty acids, which are side products from the paper industry.[135] A sample containing linoleic (72%) and oleic (28%) acids was investigated by Cole-Hamilton and co-workers.[127] The initial product contains 1,19-nonadecandioate (from oleic acid) and 1,19-dimethyl nonadecenoate (with the double bond in all possible positions) together with trimethyl 1,*n*,19-nonadecanetrioate ($1 < n < 19$) from linoleic acid. For the diunsaturated ester, one double bond isomerizes to the end

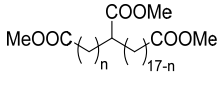

Figure 27. Branched triester obtained from methoxycarbonylation of methyl linoleate.

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Chem. Rev. 2021, 121, 6610−6653

of the chain and reacts to methoxycarbonylation, and the other double bond isomerizes randomly in the carbon chain and eventually reacts to form the third ester group, resulting in a mixture of all regioisomers as shown above (Figure 27). A competing reaction of the conjugated diunsaturated acid with water leads to ketone formation. This could be controlled by carrying out methyl ester formation of the Tall Oil fatty acids, followed by drying, methoxycarbonyation, and hydrogenation (using Pd/C) to give an unoptimized isolated yield of dimethyl 1,19-nonadecandioate of 49% (Figure 28).

Another highly interesting natural oil originates from microalgae. Its production is also noncompetitive with food production and simply grows from CO_2, water, and sunlight. The fatty acid content is 20−50%, making it a potential candidate for biopolymer production via methoxycarbonylation. In 2014, Kroth and Mecking reported that besides dimethyl 1,19-nonadecanoate also dimethyl 1,17-heptadecanedioate, resulting from palmitoleic acid that does not occur in traditional plant oils, is formed from the crude microalgae through methoxycarbonylation using the Pd/1,2-DTBPMB system at 20 bar of CO and 90 °C.[142] Further approaches, using a CO-free methoxycarbonylation of microalgae,[143] will be discussed in section 5.1.

3.2.3. Various Natural Substrates. The robustness of the Pd/1,2-DTBPMB system has been proven in its use with various substrates, especially with unpurified natural oils. Nevertheless, the carbonylation reaction is not limited to these natural oils as biobased substrates. For instance, cardanol, derived from thermal decarboxylation of anacardic acid, a side product from the cashew nut processing industry, was used for preparing bifunctional monomers by Cole-Hamilton and co-workers in 2016.[144] The overall process leads to a 65% yield of the desired linear methyl 16-(3-hydroxyphenyl)hexadecanoate, which was later used for preparing lactones and polymers (Figure 29). The spacer between the phenol and the ester functionality could be varied by metathesis of cardanol with ethene, 2-butene, or 3-hexene followed by Pd/1,2-DTBPMB-catalyzed methoxycarbonylaton.[144] Whether a macrocyclic lactone or a polymer is formed on attempted condensation polymerization catalyzed by $Ti(OBu)_4$ depends on the chain length, although for cardanol both are formed.[144]

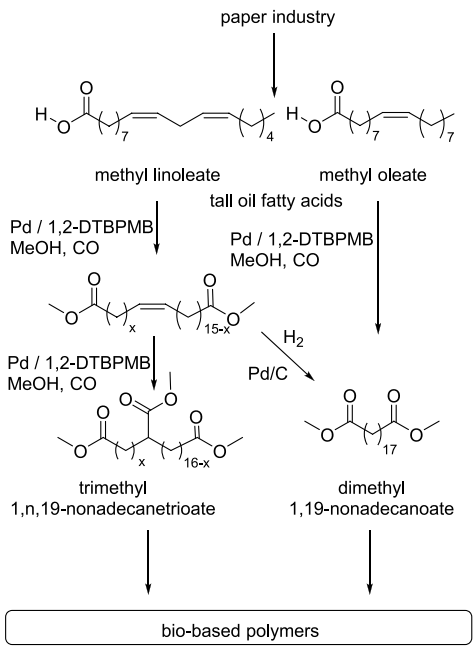

Figure 28. Role of 1,2-DTBPMB in the production of biobased polymers from tall oil.[127]

Similarly, the methoxycarbonylation reaction was carried out on a terpene, citronellic acid, by Mecking and co-workers in 2014.[145] This reaction was significant because, as with some branched pentenes (section 3.1.3), the double bond isomerizes through a tertiary center before carbonylation occurs. The catalyst used, [{1,2-dtbpmb-Pd$(OTf)_2$], provides 97% selectivity to the desired linear dimethyl-3,7-dimethylnonanedioate. The latter could be used for preparing high molecular weight poly[3,7-dimethylnonanediyl-3,7-dimethylnonanedioate] (Figure 29).

3.2.4. Dienes. *3.2.4.1. Alkoxycarbonylation of Isoprene.* Although methoxycarbonylation of 1,3-butadiene seems challenging using the Pd/1,2-DTBPMB system (see section 3.2.1.2), other conjugated dienes such as isoprene or piperylene have successfully been carbonylated using this or other catalyst systems. The latter have been reviewed.[146]

The synthesis of β,γ-unsaturated esters leads to versatile products from alkoxycarbonylation depending on the alcohol source. Therefore, Beller and co-workers attempted the alkoxycarbonylation of isoprene with several alcohols, such as geraniol, resulting in 98% yield. However, based on their ligand screening toward alkoxycarbonylation of isoprene with benzyl alcohol, the Pd/1,2-DTBPMB system, as for all other screened bidentate ligands, gives no conversion at all to the desired product in this case. For their study, the ligand of choice in this precise reaction was Xantphos, the only outstanding bidentate ligand.[147] However, these investigations were carried out in the absence of acid to mitigate the conditions. Therefore, since the application of acid, respectively, methanesulfonic acid, is mandatory for stabilization of the active catalyst as previously mentioned (see section 2.2.1.3 for more details), potential application of 1,2-DTBPMB for the alkoxycarbonylation of isoprene should be considered in the presence of acid.

3.2.4.2. Alkoxycarbonylation of Piperylene. Similar to isoprene, piperylene is a challenging substrate in the alkoxycarbonylation as shown by Brewis[148] and Bordenca[149] et al. in the 1960s, resulting in the linear and branched ester with low selectivity and yields below 42%. However, these early studies demonstrated that piperylene offers some potential for chemical conversions apart from simple hydrogenation into *n*-pentane, and finding some way for sufficient alkoxycarbonylation was a subject of interest. Using 1,2-DTBPMB as a ligand, although the linear diester was not obtainable, in 2015, Behr and co-workers investigated selectivity control toward the linear monoester, which is applicable to aromas and fragrances. They discovered a three-step autotandem-catalyzed reaction, including a selective hydrogenation of piperylene to obtain 1- or 2-pentene with the Pd/1,2-DTBPMB/methanesulfonic acid catalyst and subsequent isomerizing methoxycarbonylation without change in conditions (Figure 30). A methyl hexanoate (79%) *n*:*iso* ratio of 12.6 was obtained at 40 bar. Reducing the pressure resulted in lower linearity.[150] Remarkably, neither hydrogenation using 1,2-DTBPMB nor alkoxycarbonylation using 1,2-DTBPMB under a syngas atmosphere is inhibited. However, Pd/1,2-DTBPMB-mediated methoxycarbonylation of conjugated dienes seems only feasible via preceding hydrogenation.

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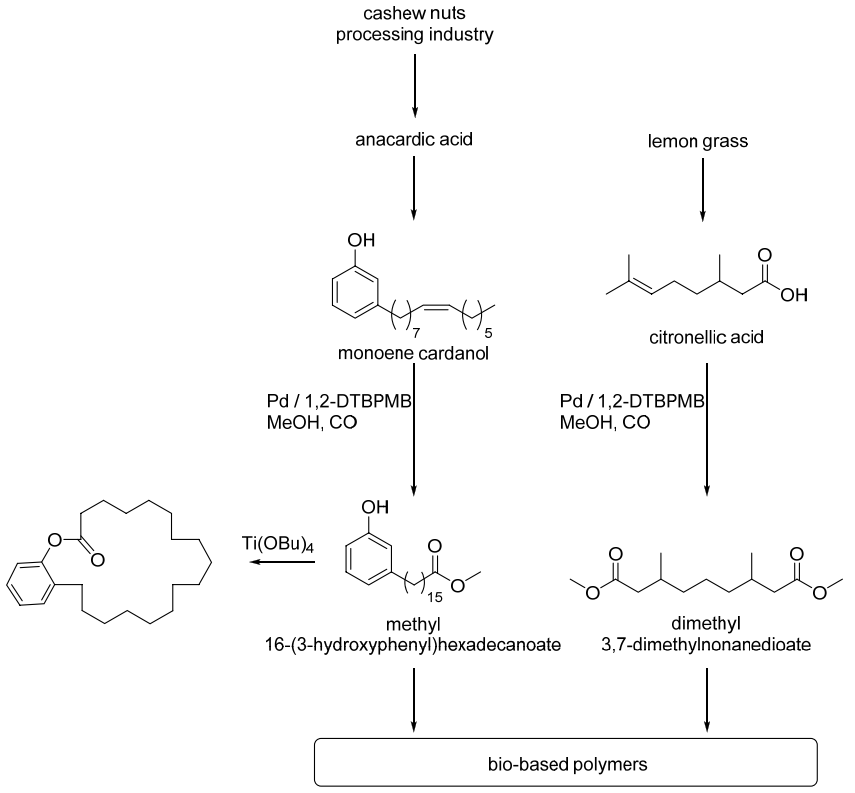

Figure 29. Pd/1,2-DTBPMB-mediated methoxycarbonylation of natural oils.[144,145]

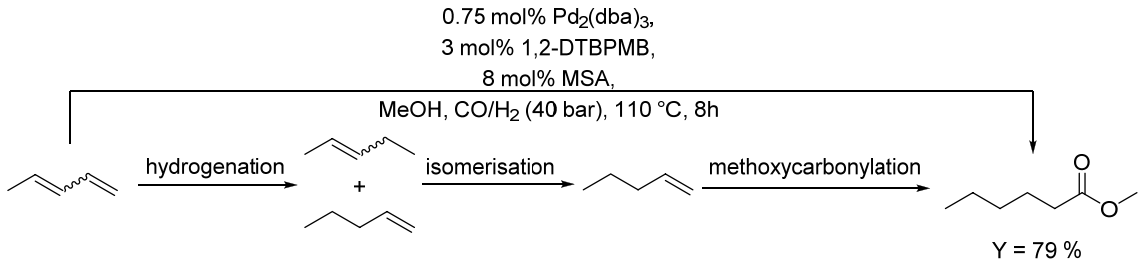

Figure 30. Three-step autotandem-catalyzed hydrogenation/isomerizing methoxycarbonylation of piperylene. Adapted with permission from ref 150. Copyright 2015 Elsevier.

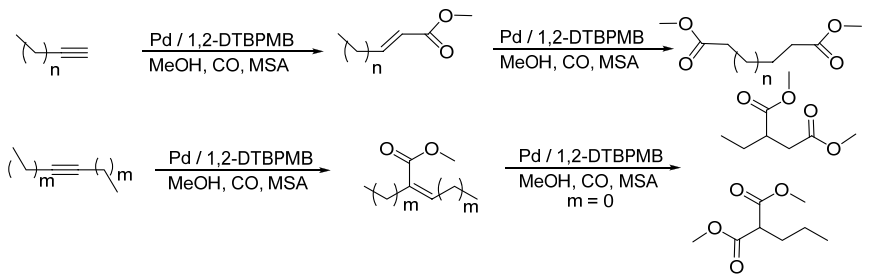

Figure 31. Methoxycarbonylation of alkynes. n = 1, 2, or 5; m = 0 or 2. Adapted with permission from ref 5. Copyright 2010 Royal Society of Chemistry.

3.2.5. Alkynes. *3.2.5.1. Linear Alkynes.* Chemical conversion of alkynes has been the focus of research for a long time, with palladium catalysts playing a crucial role, as reviewed by Chinchilla and Nájera in 2014.[151] Also the methoxycarbonylation of alkynes, especially propyne, has been the subject of research to produce the branched ester, methyl methacrylate. A first efficient palladium catalyst for this purpose was described by Drent et al. in 1993/1994, applying 2-pyridylphosphine as the ligand.[49,152] Based on these investigations, similar systems were described in 1998[153] and 1999 by Edwards and co-workers.[154] In 2014/15, Bühl and co-workers investigated the corresponding mechanism based on density functional theory.[155,156] In addition, bidentate phosphine ligands, such as 1,3-bis(di-*sec*-butylphosphino)-

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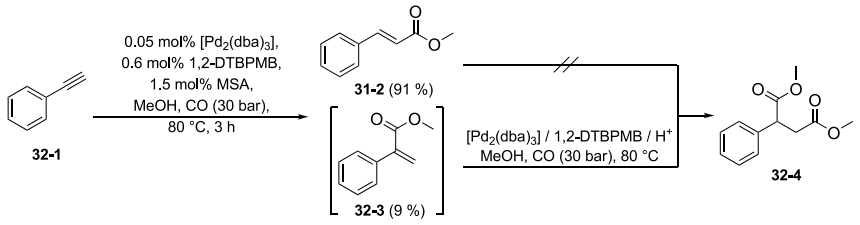

Figure 32. Pd/1,2-DTBPMB-mediated methoxycarbonylation of phenylacetylene. Adapted with permission from ref 5. Copyright 2010 Royal Society of Chemistry.

propane,[157] were applied. However, to the best of our knowledge, the methoxycarbonylation of alkynes applying 1,2-DTBPMB as a ligand was first reported by Cole-Hamilton and co-workers in 2010.[5]

The authors investigated the methoxycarbonylation of linear aliphatic alkynes yielding linear unsaturated esters in the case of 1-butyne, 1-pentyne, and 1-octyne, however, only at short reaction time or at low catalyst loading.[5] Longer reaction time gives saturated diesters with a predominance of the α,ω-species. Indeed, a cascade reaction happens: The initially formed unsaturated diester, in which the double bond is predominantly in the α,β-position conjugated to the carbonyl group, undergoes isomerization of the double bond all along the chain. The double bond is only trapped by methoxycarbonylation when it is in the least thermodynamically favored terminal position. The selectivity to the α,ω-diesters is >99% for dimethyl adipate from 1-butyne, 92% for dimethyl heptanedioate from 1-pentyne, and 87% for dimethyl decanedioate formed from 1-octyne, where the double bond must travel out of conjugation and seven positions along the chain. This is an unusual example of a compound with only one functional group leading to a product with functional groups at both ends of a chain. Internal alkynes generally give monomethoxycarbonylation at one end of the triple bond (e.g., methoxycarbonylation of 4-octyne, Figure 31), although longer reaction times lead to products that have one terminal ester function and one internal when starting with shorter-chain alkynes such as 2-butyne.[5]

3.2.5.2. Phenylacetylene. Contrary to the methoxycarbonylation of styrene, which can give high selectivity to branched saturated ester,[81] the methoxycarbonylation of phenyl acetylene **32-1** with this catalyst system provides a selectivity of up to 99% toward the linear ester **32-2** in excellent yield (Figure 32), as shown in the work of Cole-Hamilton and co-workers in 2010. Indeed, the branched ester **32-3** is formed in small amounts during the reaction but is quantitatively converted to the diester **32-4**. **32-2** is inert to further carbonylation.[5]

In 2018, Beller and co-workers further investigated the potential of 1,2-DTBPMB for the 1,2-dicarbonylation of terminal alkynes for the synthesis of 1,4-dicarboxylic acids. In accordance with the proposed mechanism (see section 3.3), the internal double bond resulting from the first methoxycarbonylation at the terminal position is not converted due to steric hindrance of the bulky ligand 1,2-DTBPMB. Instead, another ligand, 1,3-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)-propane (Figure 33), containing pyridyl substituents (see section 8.3 for pyridyl group containing 1,2-DTBPMB derivatives), better serves this purpose.[158]

In the work of Cole-Hamilton, the total acid yield from hydroxycarbonylation of phenyl acetylene was 88% with 99% selectivity to the linear unsaturated acid (Figure 34).

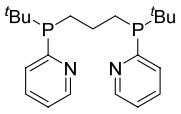

Figure 33. 1,3-Bis(*tert*-butyl(pyridin-2-yl)phosphanyl)propane.

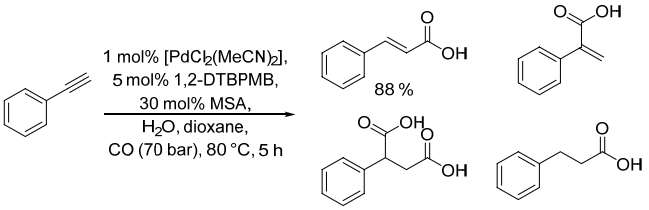

Figure 34. Pd/1,2-DTBPMB-mediated hydroxycarbonylation of phenyl acetylene. Adapted with permission from ref 5. Copyright 2010 Royal Society of Chemistry.

Additionally, also the saturated linear acid and diacid were observed in small amounts, presumably as a result of hydrogenation. The required hydrogen is assumed to result from a water–gas shift reaction.[5] Generally, this work confirms the high preference for linear hydroxycarbonylation provided by the Pd/1,2-DTBPMB/MSA system for alkynes as well as alkenes.

Recently, Jiang, Bi, and co-workers investigated the mechanism of Pd-catalyzed alkyne methoxycarbonylation by use of a computational study using phenyl acetylene as the model substrate.[159] The authors assume a catalytic cycle involving hydrometalation, CO insertion, and methanolysis (similar to the palladium-hydride mechanism in alkoxycarbonylation of alkenes, Figure 7) to be more likely than a cycle involving highly unstable palladium alkyloxycarbonyl complexes. In the hydrometalation stage, migratory insertion and ligand-assisted electrophilic addition can compete, depending on the characteristics of the ligand. During migratory insertion

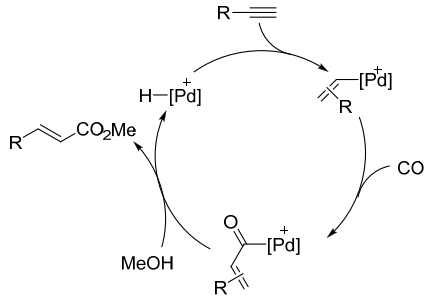

Figure 35. Mechanism for 1,2-DTBPMB-mediated alkoxycarbonylation of alkynes. Reproduced from ref 159. Copyright 2020 American Chemical Society.

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Chem. Rev. 2021, 121, 6610–6653

(Figure 35), anti-Markovnikov selectivity is favored due to the steric effect of 1,2-DTBPMB. Additionally, the authors found the two *tert*-butyl groups and the large bite angle of 1,2-DTBPMB to inhibit methanolysis for the formation of the diester.

3.3. Mechanistic Considerations for Isomerizing Methoxycarbonylation Reactions

The DTBPMB catalyst system has proven to be efficient for isomerizing methoxycarbonylation of unsaturated compounds only undergoing methanolysis when the acyl group bears a linear chain, thus giving terminal esters. This seems quite surprising at first sight due to the thermodynamically disfavored existence of the terminal alkene vs internal alkenes.[160]

In 2004, mechanistic studies were carried out by Cole-Hamilton and co-workers on the methoxycarbonylation of 1-octene using the Pd/1,2-DTBPMB/$MeSO_3H$ system.[77] The authors describe two pathways leading to the linear product. First, direct methoxycarbonylation of the terminal alkene occurs, and second, there is a tandem isomerization−methoxycarbonylation of the isomerized alkene since isomerization of the terminal alkene is observed. Gas uptake measurements showed two different regions of kinetics with the rate of the isomerization−methoxycarbonylation (second phase) being 44% that of direct methoxycarbonylation (first phase). Both reactions were first order in substrate. In the later part of the reaction (second phase), all possible isomers of octene were present as an equilibrium mixture, with 1-octene only being present at about 5%. These results were interpreted as being attributable to fast methoxycarbonylation of 1-octene, accounting for the first phase of the gas uptake kinetics, accompanied by isomerization of 1-octene to give mixed octenes, which were responsible for the second, slower phase of the kinetics.

To provide further mechanistic information, reactions were carried out in MeOD. First, the isomerization of 1-octene was studied in the absence of CO.[161] Fast isomerization occurred, and GCMS analysis showed that the equilibrium mixture of alkenes was formed with no detectible incorporation of deuterium in any of the octenes. These results were interpreted as showing that Pd−H/D exchange with the solvent is slow compared with reversible migration of H from Pd to the alkene and reversible alkene coordination. The very first migration (of Pd-D onto 1-octene) and β-H abstraction of H will give Pd−H and 1 mol of D_1-1 or 2-octene, which will be lost in solution, and all the other cycles will have H on Pd. This amount of D incorporation (<1%) will not be sufficient to detect by GCMS.

Quite different results were obtained for methoxycarbonylation reactions in MeOD.[77,161] GCMS analysis showed that isotopomers containing 0−16 D atoms of methyl nonanoate were produced when the reaction was carried out in pure MeOD at 30 bar and 80 °C (conditions **1**, Table 3). Reducing the methanol concentration gives less D incorporation with similar results using 1- (conditions **2**, Table 3) or 2-octene (conditions **3**, Table 3), while a reaction in MeOD:toluene 1:4 (1 bar, 25 °C, conditions **4**, Table 3) incorporated only 0−4 D atoms, with D_1-methyl nonanoate accounting for 60% of the product. Overall, there was an approximately Gaussian distribution of the isotopomers except that the one containing 1 D atom was enhanced. Unreacted isomerized alkenes (2-octene analyzed in detail, Table 3) showed similar labeling to the carbonylated product but without enhancement of the monodeuterated isotopomer. The D_1 product must arise from direct methoxycarbonylation of 1-octene, whereas the other isotopomers must arise from isomerized alkenes with exchange of free and bound alkene, reversible migration of H/D onto the alkene, and exchange of Pd−H with MeOD all being rapid compared with carbonylation. The slower rate of reaction of the internal alkenes was interpreted as arising because of a slower rate of isomerization compared with methoxycarbonylation. However, as suggested by Mecking and Müller in 2013, bulky diphosphines especially influence productivity since formation of the active catalyst species is facilitated, and therefore, isomerization using 1,2-DTBPMB is faster than using other phosphines[162] and also faster than rate-determining methanolysis.[98] The slower rate of methoxycarbonylation of internal alkenes than of terminal ones then arises because the concentration of the linear acyl complex in the system at any one time is very low, making the overall rate of reaction of the internal alkenes slower. This interpretation follows that of Mecking, Caporaso, and co-workers for the lower rate of methoxycarbonylation of longer-chain alkenes than of ethene.[141]

The relative rates of methoxycarbonylation and isomerization are further confirmed from Table 3.[161] In these experiments, isomerization and methoxycarbonylation of 1-octene are in direct competition. The direct methoxycarbonylation product only accounts for ca. 8% of the overall product under condition **1**, assuming that the GCMS response factor is the same for all isotopomers. However, for the related dimethyl nonanedioate, the response factor of the protio form is 1.5× that of the isotopomer containing 6 D atoms in the methyl groups.[163] So, in our study the rate of methoxycarbonylation is only about 5% that of isomerization under conditions **1** (Table 3). Interestingly, the rates of the two reactions are much more

Table 3. Deuterated Products from the Methoxycarbonylation and Isomerization of 1-Octene (1, 2, and 4) or 2-Octene (3) in the Presence of MeOD-Catalyzed by Pd/1,2-DTBPMB Complexes under Different Conditions (1−4) as Determined by GCMS[a,161]

	methyl nonanoate				trans-2-octene			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**
D_0	2.1	5.4	5.6	25.8	-	2.1	2.5	12.5
D_1	7.7	16.3	16.1	59.7	-	9.6	9.6	26.1
D_2	4.9	20.2	20.1	10.0	-	18.8	17.8	34.1
D_3	4.7	21.4	21.7	4.5	-	24.4	23.4	27.3
D_4	4.6	17.8	17.5		-	21.8	20.3	
D_5	4.9	10.9	11.6		-	13.7	14.2	
D_6	5.7	5.8	5.6		-	6.6	9.6	
D_7	7.0	2.3	1.9		-	2.5	2.5	
D_8	5.2				-	0.5		
D_9	9.7				-			
D_{10}	11.5				-			
D_{11}	11.2				-			
D_{12}	9.5				-			
D_{13}	6.7				-			
D_{14}	3.4				-			
D_{15}	1.1				-			
D_{16}	0.1				-			

[a]Individual entries correspond to % total GCMS peak height in parent ions. **1**: 80 °C, 30 bar, 0.75 h, MeOD. **2**: 80 °C, 30 bar, 3 h, MeOD:toluene (1:4). **3**: 2-octene, 80 °C, 30 bar, 3 h, MeOD:toluene (1:4). **4**: RT, 1 bar, 4.25 h.

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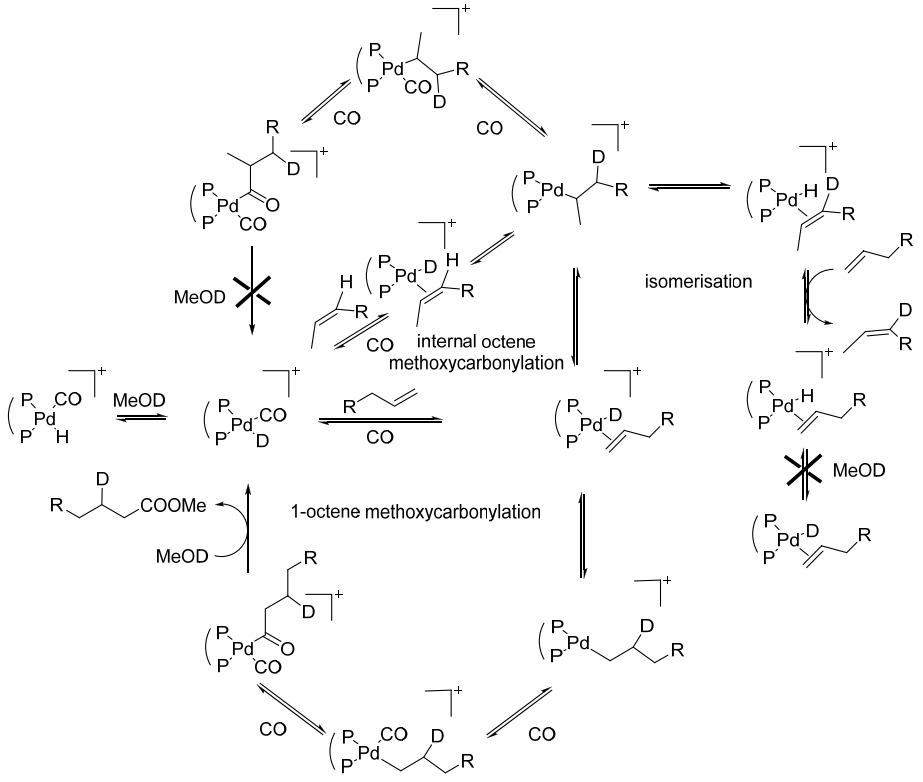

Figure 36. Reactions occurring during the tandem isomerization−methoxycarbonylation reaction of alkenes catalyzed by Pd complexes of 1,2-DTBPMB. Based on refs 77 and 161.

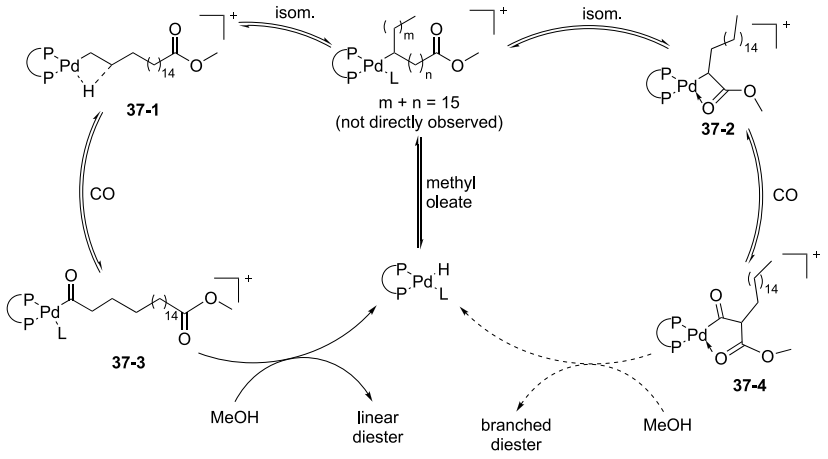

Figure 37. Proposed isomerization and alkoxycarbonylation mechanism of methyl oleate.[164] P′—P = 1,3-bis(di-*tert*-butylphosphino)propane. Reproduced from ref 164. Copyright 2012 American Chemical Society..

similar at room temperature and 1 bar of CO (conditions **4**, Table 3). This is presumably because of the negative order in p_{CO} for the methoxycarbonylation reaction. As outlined in section 3.2.2.1, Furst, Seidensticker, and Cole-Hamilton found methoxycarbonylation of the terminal double bond in methyl 10-undecenoate to be faster than methoxycarbonylation of the internal double bond in 2-undecenoic acid.[127] Again, this is attributable to the lower standing concentration of the terminal acyl intermediate in the reaction mixture, especially at the start of the reaction, when starting from the conjugated substrate.

The observation of significant amounts of undeuterated methyl nonanoate in the product mixture (Table 3) confirms that a hydride mechanism is operating (see section 2.2.1.3). When the methoxycarbonylation of 1-octene was carried out under the same conditions but in a mixture of MeOD:toluene 1:4, a similar labeling pattern was found for the methyl nonanoate except that there was no amplification of the monodeuterated isotopomer.[77] This suggests that the rate of methoxycarbonylation of 1-octene has been slowed down relative to isomerization and that methanolysis of the acyl complex is rate determining in methoxycarbonylation as for the reaction with ethene (see section 2.2.1.3). The lower incorporation of D in the products under condition **3** compared with **1** (Table 3) reflects the lower overall concentration of D in the system.

The origin of the various products from the deuterium-labeling studies is shown in Figure 36.

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Chem. Rev. 2021, 121, 6610−6653

Since terminal alkenes are thermodynamically disfavored relative to internal double bonds, the real origin of the very useful selectivity of 1,2-DTBPMB toward linear alkoxycarbonylation was finally fully clarified by the work of Mecking and co-workers in 2012. Methyl oleate was used as a model substrate and 1,3-bis(di-*tert*-butylphosphino)propane as a model ligand for 1,2-DTBPMB.[164] The model ligand was chosen since a hydride complex could be successfully isolated unlike for 1,2-DTBPMB, allowing for mechanistic studies.

As for 1-octene, isomerization of methyl oleate to all isomers was observed in a mixture of CD_3OD/CD_2Cl_2 containing catalytic amounts of the deuterated hydride species $[(P\text{^}P)\text{-}PdD(CD_3OD)]^+(OTf)^-$. In the presence of CO, isomerization also occurs, even at low temperature. Additionally, CO insertion was shown to occur into the linear and branched alkyl species. The key mechanistic steps are presented in Figure 37. However, in the isomerization equilibrium, the terminal linear alkyl species **37-1** is predominant, with the branched species not being observed. Nevertheless, the branched species **37-2** exists in a similar amount as the linear species due to chelate stabilization of the adjacent ester group, which does not occur in the linear pathway.[164]

An explanation for this difference is confirmed through density functional theory (DFT) studies (Figure 38), which also explain the importance of the steric demand of the phosphine ligand. Investigations on the smaller dimethyl-substituted phosphine ligand showed that a five-membered ring such as in **38-5a** is more stable than the more strained four-membered ring such as in **38-5**. In contrast, the analogous species with 1,2-DTBPMB is more stable, forming a four-membered ring as in **38-2** due to the very bulky *tert*-butyl substituents. Larger chelate isomers with less ring strain are not observed.[141,164]

Both linear and branched species **37-1** and **37-1** can insert CO. The methanolysis of the linear product **37-3** yields the linear diester. However, species **37-4** resists the methanolysis step. It was shown that the path leading to **36-4** does not constitute a dead end but preferentially a resting state, which can convert again to species **37-2** by loss of CO and isomerizes to the "productive" catalytic cycle (left cycle on Figure 37). In conclusion, the insertion of CO is reversible. In additional DFT calculations, the methanolysis rate was proven to be much faster for the linear acyl species **36-3** (barrier of $\Delta G^{\ddagger}$ = 29.7 kcal mol^{-1}) than for the branched acyl species **37-4** (barrier of $\Delta G^{\ddagger}$ = 37.7 kcal mol^{-1}).[164] Additionally, due to the bulky substituents of 1,2-DTBPMB, all branched acyl species are destabilized compared to the linear acyl.[141]

Finally, the full mechanism of the reaction methanolysis/isomerization/methoxycarbonylation yielding a linear diester from sunflower oil was entirely described by Walther et al. The methoxycarbonylation of both methyl oleate and sunflower oil was subjected to a temperature screening to determine the reaction rate as a function of temperature. From the resulting Arrhenius plots, both activation barriers were found to be similar so that a common rate-determining step was concluded to be the methanolysis of the acyl species, also validated from calculations. However, the acid was postulated not to be involved in the mechanism, although an acidic environment is required.[71] Therefore, substitution of methanesulfonic acid by cheaper sulfuric acid is possible, if used in twice the concentration.[165] The final proposed mechanism is given in Figure 39.

The active Pd species is a hydride **39-0**, formed easily from 1,2-DTBPMB-coordinated Pd complexes in methanol.[141] A hydride species, $[(1,2\text{-dtbpmb})PdH(H_2O)]^+$, had been reported by Heaton and co-workers in 2002 from a water/THF mixture.[63] In 2016, Caporaso, Mecking, and co-workers further investigated the formation of the active Pd hydride species under the reaction conditions of hydroxycarbonylation, being significantly faster at higher temperature. More precisely, 10% of the hydride was formed within 20 min at 50 °C. The authors propose a two-step process for hydride formation, including reductive elimination of a diaqua complex and subsequent oxidative addition of the diprotonated ligand,

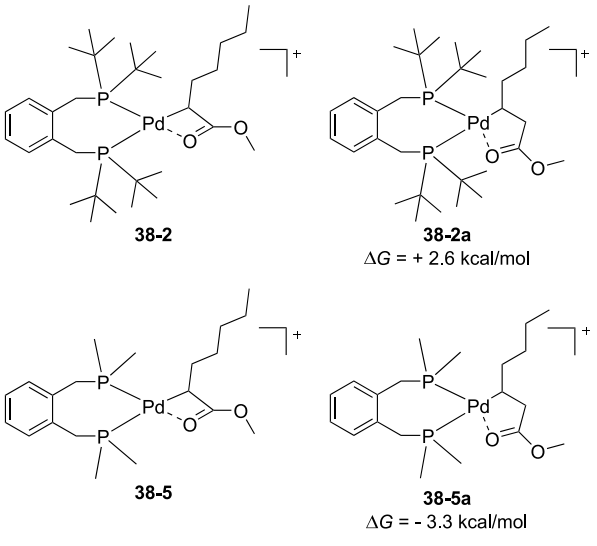

Figure 38. DFT calculations on Pd alkyl species for 1,2-DTBPMB (**38-2/2a**) and 1,2-bis(dimethylphosphinomethyl)benzene (**38-5/5a**). Reproduced from ref 164. Copyright 2012 American Chemical Society.

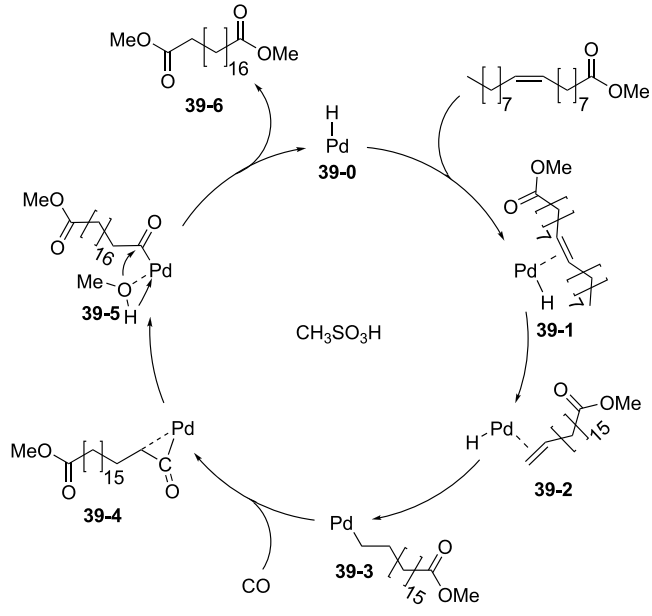

Figure 39. Proposed full mechanism for the isomerizing methoxycarbonylation of methyl oleate. Reproduced from ref 165. Copyright 2013 American Chemical Society.

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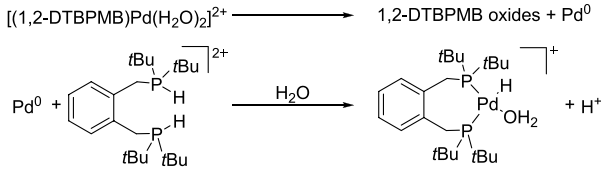

Figure 40. Formation of a Pd/1,2-DTBPMB hydride species as a two-step process in the hydroxycarbonylation.[138]

whereby CO can act as a reducing agent to generate Pd^0 (Figure 40).[138]

After coordination to give **39-1**, isomerization of the double bond occurs (**39-2**), although the terminal double bond is less thermodynamically stable. CO is preferably inserted at this position, due to the bulkiness of 1,2-DTBPMB. After coordination of CO to **39-4**, it is inserted into the Pd−C bond, and methanol is added (**39-5**). Finally, the diester **38-6** is released, and the Pd hydride **39-0** is regenerated. A microkinetic model was developed to determine activation barriers in accordance with that from thermodynamics and experiments, validating the proposed mechanism.[71] Insertion of alkene into the Pd alkyl or Pd acyl species is not observed, so a homotopic catalyst is assumed. Although deactivation of the catalyst occurs, Mecking and co-workers postulated formation of the active Pd hydride species through an excess of diprotonated ligand $(1,2\text{-dtbpmbH}_2)(OTf)_2$ from inactive Pd black, such as Pd nanoparticles and bulk.[72] CO plays the role of stabilizer toward the active hydride species. In conclusion, they found catalyst deactivation to be completely reversible.

As a final point, in 2014, Mecking, Caporaso, and co-workers showed by calculations that the transition state of the rate-determining methanolysis step is much lower in the case of ethene than for higher alkenes so that shorter-chained substrates are converted faster.[141] This is simply due to statistics since a longer chain length of the substrate results in a lower portion of linear Pd-acyl species, which can further be reacted in methanolysis. However, the position of the double bond has no influence. Since activity is similar for different substrate isomers, it is validated once more that isomerization is not rate-determining.

In summary, due to the bulkiness of 1,2-DTBPMB, only one branched Pd acyl species is potentially formed, while all other branched species are highly destabilized compared to the linear Pd acyl species. Although CO insertion is possible into the branched alkyl species and the formed acyl intermediate is stabilized by chelation, subsequent methanolysis is highly hindered sterically. Finally, CO insertion is reversible, and isomerization to the thermodynamically disfavored terminal position occurs. Thus, the bulk of 1,2-DTBPMB is the key for its outstanding isomerization ability and linear selectivity in the alkoxycarbonylation.

4. OTHER CARBONYLATIONS

As previously reported, 1,2-DTBPMB has shown to be successfully involved in the alkoxycarbonylation of alkenes, no matter where the position of the double bond is, and alkynes. However, the activity of this ligand is by no means limited to alkoxycarbonylation as it is also applicable to some other reaction types. Although some of them are better performed using other ligands, there are several approaches to push the boundaries of 1,2-DTBPMB.

4.1. Aminocarbonylation

Amides offer wide applications such as in detergents, in thickeners, or as monomers for polyamides and polyester amides in the chemical, pharmaceutical, and agrochemical industry. During conventional Schotten−Baumann reaction, which is base-catalyzed esterification or amidation of anhydrides or acyl halides with an alcohol or primary/secondary amine, stoichiometric amounts of halide or acid waste are produced.[166] An atom-efficient alternative is aminocarbonylation, the analogue to alkoxycarbonylation, using an amine as nucleophile.

The very first attempt at using the Pd/1,2-DTBPMB system for producing amides was in 2013 by Beller and co-workers; however, it was unsuccessful, and only traces of products were found using 0.5 mol % of $Pd(acac)_2$ as a precursor and 1 mol % of 1,2-DTBPMB.[167] In 2014, Cole-Hamilton and co-workers realized a promising synthesis, using relatively high catalyst loadings of 3.3 mol % of $PdCl_2$ and 4.16 mol % of 1,2-DTBPMB. While Beller and co-workers had used *p*-TsOH as an acidic promotor,[167] quantitative conversion and similar selectivity toward the linear amides for the reaction of 1-, 2-, and 4-octene with CO and aniline were achieved in this approach without the addition of acid (Figure 41).[168]

It was then shown that simply replacing the alcohol, necessary for the alkoxycarbonylation, by an amine is inefficient and leads to only traces of amides at lower catalyst loading. However, addition of 2-naphthol promotes the synthesis of the desired amide. This additive attacks the acyl palladium species and then generates the hydropalladium species and an aryl ester. The latter reacts with an amine, producing the desired amide regenerating 2-naphthol (Figure 42). The reaction was successful with various alkenes and functionalized alkenes in the presence of methanesulfonic acid.[168]

Beller and co-workers showed in 2014 that amino-carbonylation of 1,3-dienes was feasible as well[169] using an extremely low ligand:Pd ratio of 2:1. This seems to be the lowest ratio ever used successfully for a carbonylation reaction using a Pd/1,2-DTBPMB system. Trifluoroacetic acid was generated from the precursor, palladium trifluoracetate $(Pd(TFA)_2)$. The aminocarbonylation of isoprene with a wide range of aromatic amines was realized without any extra additive and yielded up to 98% of the desired aromatic amide, with a linear selectivity of 97%. The role of 1,2-DTBPMB is also to control chemoselectivity. Depending on the applied

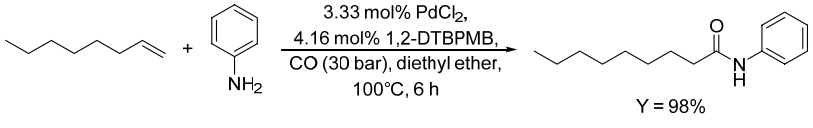

Figure 41. Pd/1,2-DTBPMB-mediated aminocarbonylation of 1-octene. Adapted with permission from ref 168. Copyright 2014 Royal Society of Chemistry.

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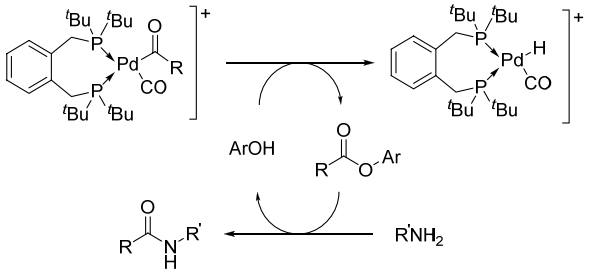

Figure 42. Role of 2-naphthol in Pd/1,2-DTBPMB-mediated aminocarbonylation. Reproduced with permission from ref 168. Copyright 2014 Royal Society of Chemistry.

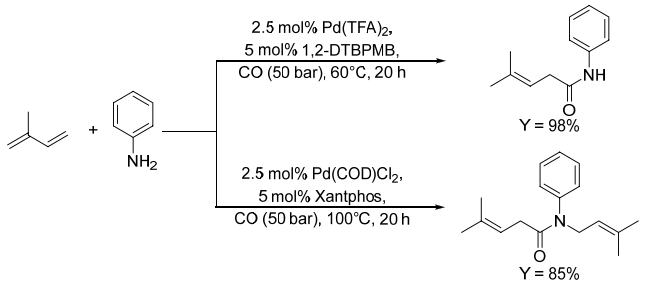

Figure 43. Role of 1,2-DTBPMB in aminocarbonylation of dienes. Adapted from ref 169. Copyright 2014 American Chemical Society.

catalyst/ligand system, the diene:amine 1:1 adduct, resulting from carbonylation, or 2:1 adduct, resulting from tandem hydroamination−carbonylation, is formed (Figure 43). This interesting result has to be compared to the inefficiency of the Pd/1,2-DTBPMB system for the alkoxycarbonylation of isoprene (see section 3.2.4.1).[147]

4.2. Carbonylative Cross-Coupling of Aryl Halides

The alkoxycarbonylation of aryl halides (ArX) would result in aryl esters. For X = I or Br, the reaction proceeds well, but reaction of aryl chlorides is challenging due to the less active C−Cl bond in oxidative addition to zerovalent palladium, requiring harsher conditions. However, chlorides are low cost, easy to prepare, highly stable, and widely available, so that an efficient catalyst system is of special interest. Due to its high activity in other systems, a Pd/1,2-DTBPMB was implemented by Cole-Hamilton and co-workers in 2005.[170] No acid is added, but instead, a base such as KO^{t}Bu or triethyl amine is applied to neutralize released HCl. As a result, aromatic chlorides are found to be converted poorly to the corresponding esters, if the aromatic ring is electron poor as in 4-chlorocyanobenzene, which is converted to the desired methyl ester 4-cyanomethylbenzoate in 30% yield. Chloromethylbenzoate was converted to dimethyl terephthalate with 16% yield. Otherwise, low nucleophilicity alcohols are required, such as 2,2,2-trifluoroethanol, to avoid side reactions such as nucleophilic aromatic substitution, reductive dehalogenation, or transformation of the methylketone into a methyl ester. In doing so, 4-chloroacetophenone is methoxycarbonylated selectively (90%) at quantitative conversion (Figure 44).

In 2009, McNulty et al. confirmed the efficacy of the Pd/1,2-DTBPMB for carbonylative cross-coupling of aryl bromides and iodides.[171] For butoxycarbonylation, high yields of butyl ester were obtained from 4-iodomethylbenzene (95%) and 4-bromomethylbenzene (84%). For the corresponding aryl chloride, only 27% isolated yield was obtained. Amino-

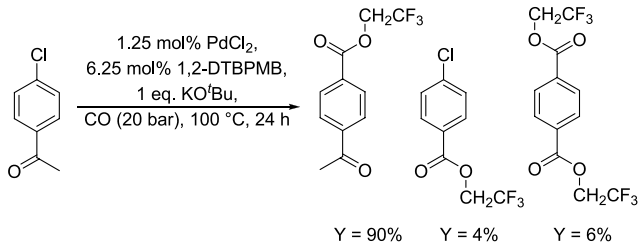

Figure 44. Pd/1,2-DTBPMB-mediated alkoxycarbonylation of 4-chloroacetophenone. Adapted with permission from ref 170. Copyright 2005 Royal Society of Chemistry.

carbonylation (see section 4.1 for more details) of 4-bromonitrobenzene with diethylamine as a nucleophile resulted in the highest yield (86%).

Vinyl halides were also efficiently carbonylated with this catalyst system. In summary, a range of aryl and vinyl substrates are tolerated in Pd/1,2-DTBPMB-mediated hydroxy-, alkoxy-, and aminocarbonylation reactions (Figure 45), while chlorides are of limited scope.

4.3. Carbonylative Cyclopropanation

The stereoselective synthesis of cyclopropanes offers many opportunities in pharmaceutical applications. For more functionalized cyclopropanes, Marder, Wu, and co-workers recently developed a synthesis of boronate derivatives through copper-catalyzed carbonylative cyclopropanation of alkenes.[172] Several ligands were initially examined. While using Xantphos and Sixantphos, a moderate yield of 71% of the desired borocyclopropane could be achieved, and the application of 1,2-DTBPMB resulted in a yield of only 11%. Using the novel 1,2-DTBPMB ligand derivative **80-1** (see section 8.3), traces of the product were obtained (Figure 46).

4.4. Hydroformylation

Hydroformylation is carried out using, mostly, homogeneous rhodium or cobalt catalysts for the formal addition of synthesis gas to alkenes to give aldehydes as valuable intermediates for bulk alcohols, esters, and amines.[173] Especially the formation of linear aldehydes is of interest. Due to the excellent linear regioselectivity, the idea of complexing rhodium with 1,2-DTBPMB for such a reaction was undertaken. In 2005, Eastham, Cole-Hamilton, and Jimenez showed the Rh/1,2-DTBPMB system to be efficient toward the hydroformylation of 1-hexene (100%) and 1-octene (89%).[174] However, contrary to the outstanding selectivity in alkoxycarbonylation, the selectivity to the desired linear aldehyde was very poor, only being improved using a chloride-containing catalyst precursor (Figure 47). With other ligands, *n*:*iso* selectivity of 19 and above is possible as reviewed by Börner and co-workers in 2012,[173] showing some limitation for the Rh-catalyzed hydroformylation using 1,2-DTBPMB.

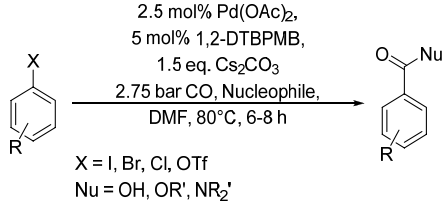

Figure 45. Carbonylative cross-coupling reaction. Adapted with permission from ref 171. Copyright 2009 Elsevier.

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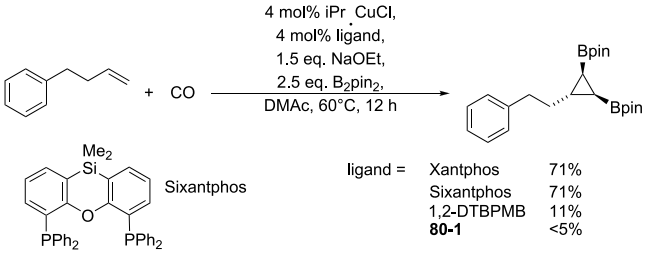

Figure 46. Carbonylative cyclopropanation. Adapted from ref 172. Copyright 2020 American Chemical Society.

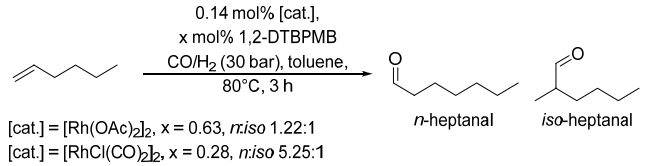

Figure 47. Hydroformylation of 1-hexene using 1,2-DTBPMB as ligand.[174]

4.5. Alcohol Carbonylation

Nowadays, the carbonylation of methanol is the most important route for the production of acetic acid.[175] The process of methanol carbonylation is highly atom efficient and traditionally carried out with an iridium catalyst in the Cativa process or a rhodium catalyst in the Monsanto process.[23] To accelerate the reaction rate and enhance the stability of the Rh catalyst, bidentate ligands had been reported to serve well.[176−178] Also 1,2-DTBPMB was investigated for complexation with rhodium in a Monsanto-type system. In 2007, Cole-Hamilton and co-workers showed that Rh(1,2-DTBPMB)Cl(CO)] is formed initially from $[RhCl(CO)_2]_2$ and 1,2-DTBPMB, improving the reaction rate of methanol carbonylation. However, the active species is not stable under the reaction conditions and rapidly decomposes to the Monsanto catalyst. It is likely that the rhodium forms a complex with 1,2-DTBPMB, which gives a higher rate of oxidative addition, but that the complex is unstable toward quaternization of the 1,2-DTBPMB (Figure 48).[175]

In 2017, Beller and co-workers reported the carbonylation of secondary and tertiary alcohols toward methyl esters, this time using a Pd catalyst. However, the carbonylation of *tert*-butanol using 1,2-DTBPMB leads to a small yield (14%) of the desired ester, while a pyridyl-modified ligand performs much better (PYTBPX, see section 8.3). Although the reaction is carried out in the presence of *p*-toluenesulfonic acid (*p*-TSA), Pd black formation cannot be avoided using 1,2-DTBPMB. The authors assume a low tolerance to water which is *in situ* generated from dehydration of the substrate.[179] This is surprising, considering successful hydroxycarbonylation with water using Pd/1,2-DTBPMB (see section 2.2). However, in 2016, Caporaso and Mecking observed Pd black formation at low water concentration and assumed catalyst stabilization in the presence of a certain, higher water concentration.[138] This observation is in accordance with hydroxycarbonylation conditions, patented by Drent and Jager in 2004, setting the ratio of substrate to water between 2:1 and 1:2.[105]

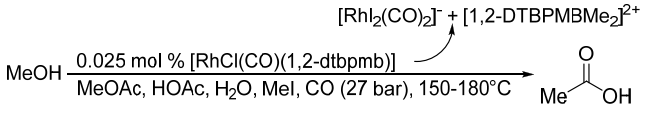

Figure 48. Rh/1,2-DTBPMB-mediated methanol carbonylation to acetic acid and decomposition to the Monsanto catalyst.[175]

4.6. Thiocarbonylation

Sulfur-containing reagents are often known as poisons for palladium catalysts. Nevertheless, the palladium-catalyzed thiocarbonylation of styrene has been fruitfully realized using *N*-formylsaccharine as a CO surrogate (see section 5 for further works on CO-surrogate based carbonylations) by Fleischer and co-workers in 2016.[180] The thiocarbonylation of styrene has been realized with 79% yield using 1,2-DTBPMB as a ligand (Figure 49).

However, in this case the Pd/1,2-DTBPMB system was shown not to be the most efficient, and the ligand 1-diphenylphosphino-1′-(di-*tert*-butylphosphino)-ferrocene (DTBDPPF) shown in Figure 50 was superior, resulting in 88% yield. This novel ligand will be introduced in section 8.2 as one of the new generation 1,2-DTBPMB derivatives.

5. ALTERNATIVE CARBON MONOXIDE SOURCES FOR CARBONYLATION

Carbonylations require the use of toxic carbon monoxide under pressure. In order to avoid its utilization and the possible dangers of leakages, several ways of replacing CO were attempted. For achieving such a performance, two ways of *in situ* CO synthesis have been developed. One method consists of introducing a species, which will decompose into CO under the reaction conditions. The second method is based on a two-chamber reactor, one containing the reaction mixture and the other one containing a CO-generating species, allowing CO to be continuously fed to the first reactor chamber. In the following, some CO-free systems making use of 1,2-DTBPMB as a ligand are discussed, showing analogous behavior of the ligand to that in conventional carbonylations.

5.1. Methoxycarbonylation

Formic acid derivatives are cheap and readily available. As liquids and due to avoidance of initial pressure, they are easy to handle and therefore promising CO surrogates as already reviewed by Jenner in 1995.[181] For example, methyl formate decomposes under the typical Pd/1,2-DTBPMB-mediated methoxycarbonylation conditions (100 °C and the presence of a strong acid) and leads to the *in situ* formation of CO and methanol, which allows the methoxycarbonylation reaction to take place, as shown by Beller, Franke, and co-workers in 2013[182] and patented afterward.[183,184] Remarkably, 1,2-DTBPMB is the only ligand in an initial screening, giving significant amounts of desired product.[182] The reaction was proved to be feasible with various aromatic formates, in some cases allowing a selectivity to linear species up to >99%. Regarding the mechanism for CO-free methoxycarbonylation, two principle ways are possible: first, a compound can

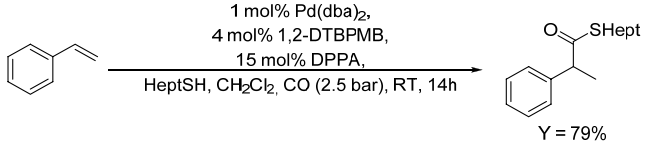

Figure 49. Pd/1,2-DTBPMB-mediated thiocarbonylation of styrene. Adapted from ref 180. Copyright 2016 American Chemical Society.

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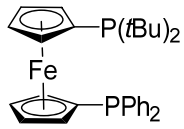

Figure 50. DTBDPPF as the optimized ligand for successful thiocarbonylation of styrene.

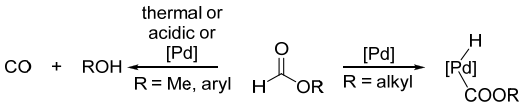

Figure 51. Activation of formates. Adapted with permission from ref 182. Copyright 2013 John Wiley and Sons.

decompose and release CO, or second, it can be catalytically activated and form an active, e.g., palladium hydrido-(carboalkoxy) species, as shown in Figure 51.[182]

As mentioned in section 3.2.2.3, the Pd/1,2-DTBPMB catalyst was shown to be efficient for methoxycarbonylation of microalgae, which results in the formation of biobased long-chain diesters. Adapted from the previous works using formates, in 2018, Mecking and co-workers described a similar CO-free system using Pd/1,2-DTBPMB for methoxycarbonylation of microalgae, obtaining quantitative conversion and selectivity toward the linear C17 and C19 diesters of 96%.[143]

In 2015, Beller and co-workers realized a further improvement by using methanol and paraformaldehyde, which decompose under the reacting conditions and release CO *in situ*. These inexpensive substrates provide excellent yield and selectivity to esters, starting from functionalized or unfunctionalized alkenes such as 1-, 2-, and 4-alkene, styrene, and several others.[185]

Recently, Geitner and Weckhuysen investigated the depolymerization of paraformaldehyde as a CO surrogate using a Pd/1,2-DTBPMB catalyst system.[186] The catalyst was found to increase the activation energy of depolymerization. The authors reason that paraformaldehyde chain ends coordinate with the Pd(1,2-DTBPMB)$^{2+}$ fragment (Figure 52), which leads to a reduced concentration of reactive groups. Since depolymerization starts at the chain end, such a behavior drastically inhibits the reaction. In contrast, this effect was not observed using dppp as a ligand, which exhibits a less rigid backbone and a lower electron-donating effect due to the *tert*-butyl substituents being altered. In conclusion, this behavior of 1,2-DTBPMB must be considered when using paraformaldehyde as a CO surrogate.

In 2015, Fleischer and co-workers managed to use the most suitable and nontoxic CO surrogate: carbon dioxide.[187] This procedure involves using *N*-formylsaccharin (NFS) simultaneously as a CO_2 capturer and a CO releaser. NFS is synthesized by Rh-catalyzed CO_2 hydrosilylation, providing silyl formate, which can be converted into an anhydride

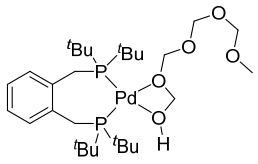

Figure 52. Exemplary coordination of MeO$(CH_2O)_4$H as a model compound to Pd/1,2-DTBPMB. Adapted from ref 186.

through transacylation and is finally reacted in a formamidation with saccharin. Although this route allows for CO_2 capture and conversion, the yield of 57% NFS is significantly improved through the use of formic acid instead of CO_2, starting with transacylation (Figure 53).

For methoxycarbonylation with NFS as a CO surrogate, the authors describe a two-chamber reactor. Herein, CO is generated *ex situ* in one chamber and used in the second one to achieve the Pd/1,2-DTBPMB-mediated methoxycarbonylation. *N*-Formylsaccharin is then regenerated and can be used for CO_2 capture once again (Figure 53).

In 2018, Fleischer and Hirschbeck applied the same CO-surrogate system to the first intramolecular alkoxycarbonylation of alkenylphenols using 1,2-DTBPMB for the production of benzofuranones,[188] which are applied as pharmaceuticals or antioxidants in polymer synthesis. First, they optimized the reaction system for the conversion of 2-vinylphenol (Figure 54), yielding 73% of the desired ester through the application of 1,2-DTBPMB. However, another ligand, DPPDTBPF (see section 4.6, Figure 50), is slightly more promising, yielding 81%, so that the conditions were further optimized to achieve 94% yield.

However, methoxycarbonylation generally shows a high tolerance of 1,2-DTBPMB toward CO surrogates, so that under appropriately optimized conditions the ligand could contribute to the future development of CO-free, potentially more sustainable carbonylation processes.

5.2. Aminocarbonylation

Replacing methyl formate by dimethylformamide (DMF) was attempted in order to produce amides from alkenes by Vorholt, Seidensticker, Furst, Vondran, and others in 2015.[189] Acid-catalyzed decomposition of DMF into CO and dimethylamine under acidic conditions is a necessary step but leads to a dead end, the dimethylamine being unable to achieve the nucleophilic attack. Addition of imidazole as a cocatalyst is necessary, the latter one realizing a nucleophilic attack on the palladium/1,2-DTBPMB complex, regenerating the active catalytic species and yielding an imidazoyl intermediate, which is immediately transaminated by dimethylamine, yielding the expected aliphatic amide (Figure 55). In doing so, 1-alkenes of varying chain length were converted successfully using Pd/1,2-DTBPMB, but also 4-octene was converted to the linear amide in 94% selectivity, validating the isomerization ability even under modified conditions.

6. STABILITY OF 1,2-DTBPMB AND RECYCLING APPROACHES IN CARBONYLATIONS

Many phosphine palladium complexes show high initial activity in methoxycarbonylation reactions but are unstable over time so would not be suitable for use in commercial processes. Work by Tooze and co-workers has shown that most phosphines are methylated at P in acidic methanol to give the quaternary phosphonium salt.[60] This irreversible reaction removes the phosphine from the system and leads to the catalyst instability. In contrast, 1,2-DTBPMB is a sufficiently strong base because of the electron-donating power of the *tert*-butyl groups to be fully protonated under the reaction conditions, where, importantly, excess acid is present (see section 2.2.2.2).[87] The protonated form is not a nucleophile so does not react with protonated methanol. The P−H bond is, however, able to add across Pd(0) to form the required Pd−H and Pd−P bonds (see section 2.2.2.2).[87] This addition can

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Chem. Rev. 2021, 121, 6610−6653

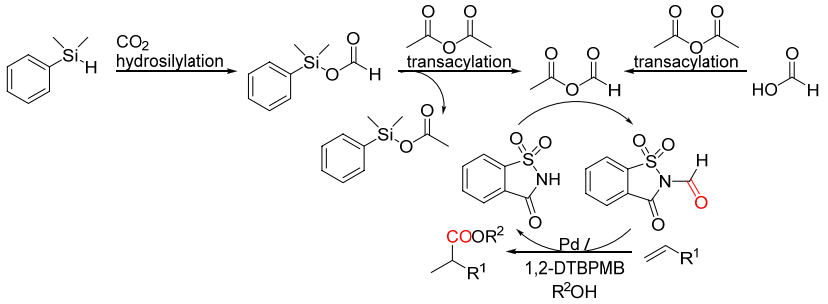

Figure 53. *N*-Formylsaccharin as a CO surrogate in the Pd/1,2-DTBPMB-mediated methoxycarbonylation. Adapted with permission from ref 187. Copyright 2015 Royal Society of Chemistry.

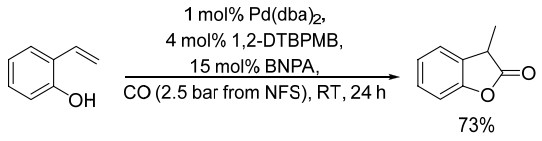

Figure 54. Pd/1,2-DTBPMB-mediated intramolecular methoxycarbonylation of 2-vinylphenol using *N*-formylsaccharin as the CO surrogate. Adapted with permission from ref 188. Copyright 2018 John Wiley and Sons.

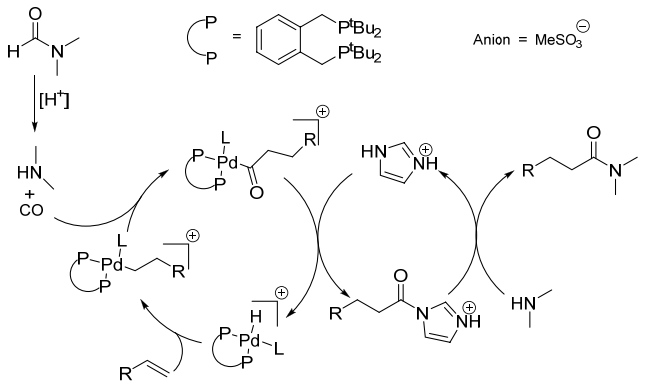

Figure 55. Proposed mechanism for the CO-free Pd/1,2-DTBPMB-mediated aminocarbonylation. Reproduced with permission from ref 189. Copyright 2015 John Wiley and Sons.

even occur across palladium black, thus reversing a deactivation pathway that would usually be terminal.[72] These unusual properties explain the very high stability of the catalytic system based on 1,2-DTBPMB compared to other phosphine ligands and the potential for recycling. However, the significant cost of the Pd/1,2-DTBPMB catalyst system led some groups to investigate the possibility of recycling the catalytic system in order to decrease its operability cost.

In the Alpha process, which produces relatively volatile methyl propanoate, the product can be separated by continuous distillation of a methyl propanoate−methanol azeotrope. However, for longer-chain substrates, the boiling points of the products are usually too high for direct distillation from the reaction mixture. Several catalyst recycling techniques for alkoxycarbonylation in general have been reviewed by Deelman and co-workers in 2006, including immobilization and biphasic systems.[190] Especially formation of Pd black as an inactive catalyst species is a major problem to be solved for sufficient catalyst recycling. In 1996, Tooze and colleagues studied the recyclability of 1,2-DTBPMB and bis(di-*tert*-butylphosphino)propane (DTBP) in the methoxycarbonylation of ethene via extraction.[11] While use of DTBP resulted in rapid Pd black precipitation and deactivation, 1,2-DTBPMB was successfully reused once with the same activity (TON > 50 000, mole of methyl propionate per mole of phosphine) as initially observed. However, in 2001, Eastham and colleagues reported deactivation over time and proposed the application of poly(acrylic acid) as a polymeric dispersant in the Pd/1,2-DTBPMB-mediated alkoxycarbonylation of ethene to stabilize the catalyst.[191] Although this approach was successful in terms of no Pd black precipitation and a TON of up to 34 000 within 4 h (mole of methyl propionate per mole of Pd), the process suffers from polymeric impurities in the product and extra cost. In 2013, Parton and Janssen claimed that addition of product, such as dimethyl adipate in the methoxycarbonylation of methyl pentenoate (see section 3.2.1.2), also functions as a stabilizer over several recycling runs to avoid Pd black precipitation. The TOF is slightly increased from 1000 to 1280 (measured at 20% conversion).[79] As mentioned in section 2.2.2.1, the addition of methyl nonanoate in the methoxycarbonylation of octene also reduces Pd black formation.

Assuming a stable catalyst over time, several recycling approaches have been undertaken. In 2005, Ooka, Tanaka, and co-workers were the very first to successfully achieve the recycling of the catalytic species containing Pd/1,2-DTBPMB in the methoxycarbonylation of styrene and vinyl acetate. The catalyst was immobilized on insoluble polymeric supports.[81] Using a Wang-type resin loaded with SO_3H groups, the TON was increased from 500 (without immobilization) to 3500. By using vinyl acetate as a substrate, the catalytic system was recycled three times without any loss in activity.

As outlined in the context of production of C6 polymer building blocks (see section 3.2.1.2), another recycling approach for the methoxycarbonylation made use of crystallization. This approach strongly depends on the crystallization ability of the product in the reaction mixture, although the catalyst should remain in the filtrate. In 2006, Drent and Jager reported sufficient Pd/1,2-DTBPMB catalyst recycling in the methoxycarbonylation toward adipic acid, with low catalyst leaching.[101] However, they did not describe total turnover numbers, and the filtrate was only recycled after removal of side product, so that it seems like crystallization is not selective.

Recently, Seidensticker and co-workers investigated selective product crystallization in the methoxycarbonylation of methyl oleate using the Pd/1,2-DTBPMB catalyst system. In contrast to the other recycling approaches, there is no need for any auxiliary (solvent, support, etc.), contributing to Green chemistry.[130] The linear product selectively crystallizes upon

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Chem. Rev. 2021, 121, 6610−6653

cooling the reaction mixture. Thereby, a TON of >2800 was achieved at an average selectivity of 88% toward the linear ester. However, the influence of recycled branched byproducts is not yet understood, and the strategy of crystallization is limited to those reactions that produce crystalline and low solubility products.

Another recycling strategy is to use Brønsted acid ionic liquids (BAILs). This was successfully investigated by Riisager and co-workers in 2014.[192] The authors reported that using 1.2 equiv of ligand with respect to palladium was detrimental to the process because the system cannot be reused due to the formation of palladium black. This is consistent with numerous other reports underlining the inefficiency of the system with low amounts of ligand. Using 5 equiv, the procedure using BAILs allowed the catalytic system with ethene as the substrate to be recycled 14 times, yielding methyl propionate in >97% selectivity each time.

The same group investigated supported ionic liquid phase (SILP) catalysts for the continuous gas-phase methoxycarbonylation of ethene, applying the Pd/1,2-DTBPMB system. Activity and stability were also strongly related to the 1,2-DTBPMB:Pd ratio. By increasing this ratio up to 30, a TON of almost 70 000 was reached. However, Pd black formation was observed after longer reaction times.[193]

In addition, an elegant recycling strategy is the application of a thermomorphic multiphase system (TMS), ensuring a homogeneous mixture at reaction temperature and a multiphasic mixture at the separation temperature, whereby the product is separated and the homogeneous catalyst can be recovered and recycled. Thus, the temperature-dependent miscibility gap is controlled through the choice of solvents.[194] Such an approach was taken for the Pd/1,2-DTBPMB-mediated methoxycarbonylation in 2013. For first attempts using a TMS recycling in the methoxycarbonylation, Behr and co-workers decided upon a Pd/Xantphos system, since precipitation using 1,2-DTBPMB in this approach occurred.[195] However, regioselectivity toward the linear product using Xantphos-type ligands is highly reduced compared to application of 1,2-DTBPMB.

Finally, a methanol/dodecane solvent system was employed in the Pd/1,2-DTBPMB-mediated methoxycarbonylation of the renewable feedstock methyl 10-undecenoate by Vorholt and co-workers in 2016[196,197] and completed by Sadowski and Lemberg with some phase equilibria investigations.[198] The total catalyst leaching is 1% (2 ppm Pd) into the organic product layer,[197] and an efficient recycling over 8 runs with no loss in selectivity was observed, when methanesulfonic acid was refreshed before each run. Refreshment of acid is required because acid leaches into the product phase. This was proven by the observation that Pd black precipitation is caused by too high acid concentration and does not occur in this recycling study.[196] A detailed comprehensive picture of the mechanism of methoxycarbonylation using a TMS was drawn by Stein and co-workers in 2019, analyzing the effects of polar and nonpolar solvents on each catalytic step.[199] They found that nonpolar solvents support methanol coordination to the Pd-acyl species as well as methanolysis, while polar solvents significantly facilitate catalyst activation and product dissociation. The TMS was also transferred to the Pd/1,2-DTBPMB-mediated methoxycarbonylation of 1-decene, being investigated experimentally and modeled by Gerlach et al. in 2018.[200] Some inhibition effect of the substrate on the reaction rate and some inhibition of CO on the isomerization rate were found, concluding that lower CO partial pressures are needed for conversion of long-chain alkenes in a TMS.

In conclusion, a few approaches including crystallization, ionic liquids, and TMS show some potential for recycling of the Pd/1,2-DTBPMB system. However, apart from when ethene is the substrate, catalyst deactivation is an issue that has not been completely overcome, which is one reason why upscaling a corresponding chemical process using a substrate other than ethene is not yet cost-effective.

7. NONCARBONYLATIVE REACTIONS WITH 1,2-DTBPMB

In addition to carbonylations, also some specific noncarbonylative reactions were investigated using 1,2-DTBPMB. Although some of them were successful, examples are rare, showing that systems using other ligands are often superior or that industrial applications are not required. In this section, we include some competing ligands that perform better than 1,2-DTBPMB (see section 8 for 1,2-DTBPMB derivatives). However, the versatility of reactions to which 1,2-DTBPMB has been applied is impressive.

7.1. Reduction

7.1.1. Transfer Hydrogenolysis. Conventional methods for the reduction of C−O to C−H bonds often suffer from harsh reaction conditions and high concentrations of reducing agents, which lead to low selectivity and waste production. Catalytic transfer hydrogenolysis is an attractive alternative, also avoiding the use of highly flammable hydrogen gas and the need for special equipment to handle high pressures. In 2018, Ciszek and Fleischer reported the first homogeneous palladium-based transfer hydrogenolysis of benzylic alcohols with formic acid using 1,2-DTBPMB as the ligand (Figure 56).[201]

Only 1,2-DTBPMB results in the formation of significant amounts of product compared to the other tested ligands, such as DPPDTBPF. By chance, the authors found that the addition of small amounts of oxidized 1,2-DTBPMB is beneficial, and it is assumed to stabilize the active catalyst. In addition, they successfully widened the scope to several primary, secondary, and tertiary alcohols and found that esterification of the alcohol through formic acid occurs first as an intermediate step.[201] This is in accordance with previously described esterification of acids in the presence of Pd/1,2-DTBPMB (see section 3.2.1.2).[98]

7.1.2. Reductive Rearrangement. Biobased substrates are often highly functionalized and need suitable strategies for conversion. Recently, in 2020, Fleischer and co-workers published their work on Pd/1,2-DTBPMB-catalyzed reductive rearrangement of glycol derivatives as lignin model compounds.[202] 1,2-DTBPMB was found to be the most suitable compared with several others, including Xantphos or

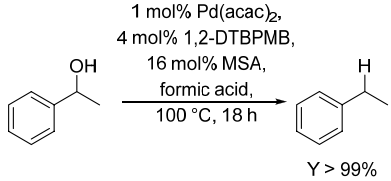

Figure 56. Pd/1,2-DTBPMB-mediated transfer hydrogenolysis of benzylic alcohols. Adapted with permission from ref 201. Copyright 2018 John Wiley and Sons.

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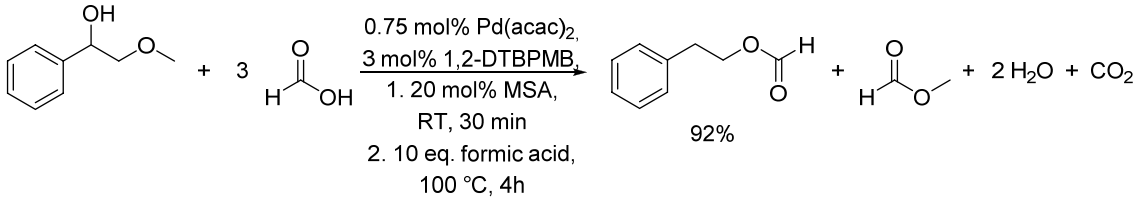

Figure 57. Pd/1,2-DTBPMB-mediated reductive rearrangement of 2-methoxy phenylethanol.[202]

DPPDTBPF, resulting in up to 92% yield starting from 2-methoxy phenylethanol (Figure 57) using $Pd(acac)_2$ as s catalyst precursor and methanesulfonic acid as an additive. The authors postulated a Brønsted acid promoted rearrangement step, followed by a Pd-catalyzed reduction of an intermediate aldehyde. However, the role of 1,2-DTBPMB was not specifically addressed except for the suspected formation of a hydride complex under the reaction conditions. Finally, the substrate scope was extended to several phenolic glycol derivatives.

7.2. Polymerization

Polymer dispersions have gained interest due to their potential application in environmentally benign coatings and paints for sensitive substrates or nanocomposites. Although often prepared by free-radical emulsion polymerization, nonradical, catalytic routes have also been investigated.[203] In 2010, Mecking and Huber described the preparation of aqueous poly(arylacetylene) dispersions using bidendate phosphine/palladium catalysts at 25 °C overnight. 1,2-DTBPMB showed excellent activity toward the phenylacetylene polymerization (96% conversion), although it was shown not to be the best ligand for the catalytic system, bis(di-*tert*-butylphosphino)-propane (DTBP), yielding full conversion and a slightly higher turnover number. Comparing DTBP and 1,2-DTBPMB, both have bulky *tert*-butyl substituents, which are held responsible for the generally good catalyst performance. However, they differ in the size of the chelate ring that is formed due to coordination to Pd. Similar to the explanation for the outstanding selectivity of 1,2-DTBPMB in the isomerizing alkoxycarbonylation, mentioned in section 3.3, the role of ligand in this work is also attributed to the relative stability of the chelate rings within the catalyst complex. The authors argue that DTBP should form a more stable six-membered chelate complex, while 1,2-DTBPMB would form a slightly less stable seven-membered ring, which is still relatively stable due to the stiff backbone, compared to, e.g., bis(di-*tert*-butylphosphino)butane (Figure 58).

Recently, Rosen, Klosin, and co-workers evaluated a broad range of 53 bisphosphine ligands for selective ethylene oligomerization toward 1-hexene and 1-octene.[204] They also included 1,2-DTBPMB in their high-throughput experiments using a Cr catalyst but found instead the formation of high-density polyethylene with 90% selectivity. However, activity was rather low [6000 g of product (g of Cr h)$^{-1}$] compared to other ligands.

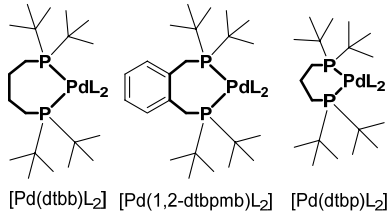

Figure 58. Ring strain in Pd complexes of DTBB (left), 1,2-DTBPMB (middle), and DTBP (right).

7.3. Double Bond Isomerization

Due to the efficiency of the Pd/1,2-DTBPMB system for isomerizing the C=C bond (section 3), it was employed by Sereinig et al. in 2013 for isomerizing substituted alkenes such as ricinoleic acid for preparing methyl 12-oxostearate.[205] The C=C bond is isomerized next to the hydroxyl group, resulting in a keto−enol equilibrium yielding 100% selectivity and excellent conversion to the desired oxoester product (Figure 59). Conventionally, Raney-Ni is used as catalyst at a temperature >200 °C. However, selectivity decreases with increasing temperature. Only 61% of the desired oxoester was obtained at 210 °C, applying a Raney-Ni catalyst. Thus, the Pd/1,2-DTBPMB offers a selective alternative at lower temperature.

Moreover, in 2012/2015, Cole-Hamilton and co-workers showed the catalyst to be efficient for isomerizing the C=C bond on monounsaturated anacardic acid to the benzylic position, yielding isocardanol after decarboxylation.[206,207] The equilibrium position from the monoene contains 67% of the desired styrene, with other double bond positional isomers making up the remainder. However, the conversion of cardanol was only 40%, the remaining products being random double bond isomers of cardanol.[206] This equilibrium yield is less from cardanol because it does not bear the acid group of anacardic acid, which participates in conjugation. The diunsaturated acid, which accounts for 18.3% of the anacardic acid content, most probably leads to the minor product benzolactones, having a potential medicinal value in anticancer and anti-inflammatory agents.[207] In combination with a metathesis catalyst, 3-propylphenol, an attractant that can be used in tsetse fly traps (Figure 60), can be synthesized from cardanol, a nonfood byproduct from the cashew nut industry.[206] Although some interesting applications are reported herein for the Pd/1,2-DTBPMB-mediated double bond isomerization, conversion and selectivity are not satisfactory and would require some improvement. Indeed, high yields of 3-propenyl or 3-vinylphenol can be obtained by isomerizing metathesis where isomerization and metathesis catalysts work together in the same solution, but the isomerization catalyst based on Pd/1,2-DTBPMB was not as effective a Pd^{I} dimeric catalyst.[97]

In 2017, Mecking et al. reported the "chain doubling" strategy for synthesis of ultralong-chain α,ω-diesters.[208] Self-metathesis of a fatty acid, such as oleic acid, results in the formation of a C18 diacid, which is then esterified with methanol. Afterward, a Pd/1,2-DTBPMB catalyst is applied for catalytic dynamic isomerization crystallization, pushing the double bond to the α,β-position. Thus, consecutive cross-metathesis with short-chain olefins from petrochemical waste and self-metathesis of the monoester result in the formation of

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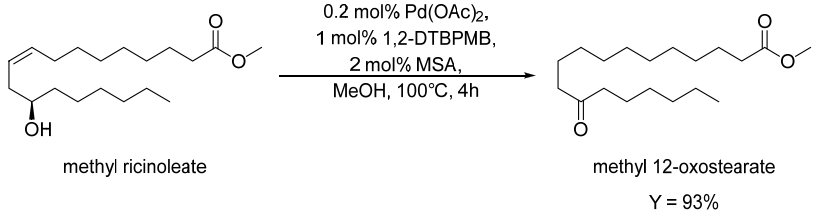

Figure 59. Pd/1,2-DTBPMB-mediated double bond isomerization of methyl ricinoleate.[205]

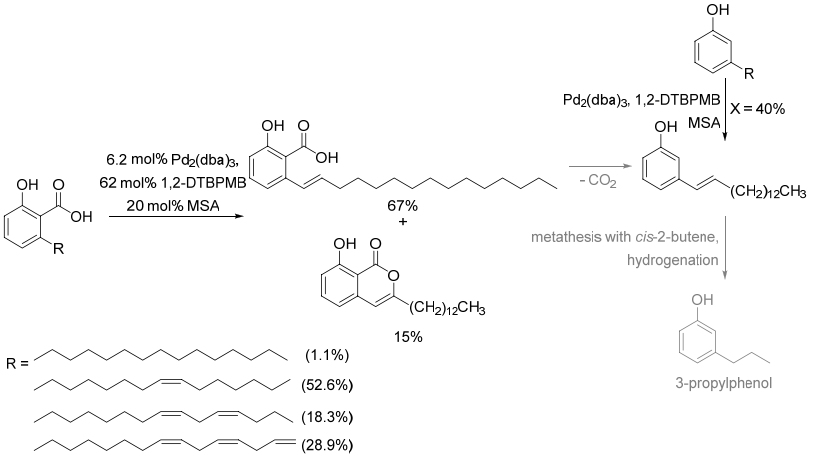

Figure 60. Pd/1,2-DTBPMB-mediated isomerization of anacardic acid and cardanol.[206]

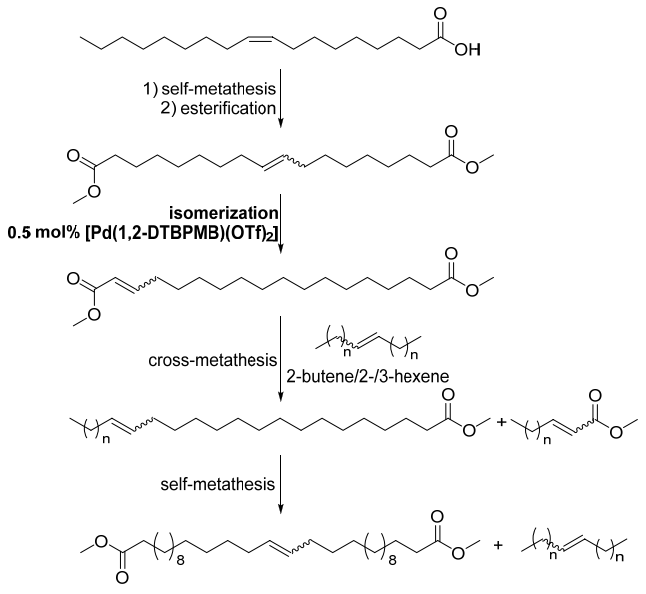

Figure 61. Metathesis and isomerization of fatty acids (methyl esters) for the synthesis of ultralong-chain α,ω-diesters (n = 0, 1, and 2). Adapted with permission from ref 208. Copyright 2017 John Wiley and Sons.

a C32 diester, which could be converted to high melting polyesters or thermoplastic elastomeric block copolymers. This approach allowed the production of C48 α,ω-diesters (Figure 61).[208] Hence, it capitalizes upon the specific virtues of 1,2-DTBPMB, namely, high reactivity toward internal double bonds, compatibility with functional groups, and catalyst stability.

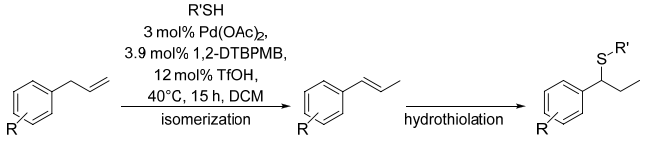

Figure 62. Pd/1,2-DTBPMB-mediated tandem isomerization/hydrothiolation of allylarenes. Adapted from ref 209. Copyright 2019 American Chemical Society.

In 2019, Kathe and Fleischer reported tandem isomerization/hydrothiolation of allylarenes for the synthesis of benzylic thioethers using 1,2-DTBPMB (Figure 62).[209] The branched thioethers are biologically relevant for antiasthma drugs or antihyperlipidemic agents. Again, application of 1,2-DTBPMB resulted in high yields for various substrate allylarenes and excellent regioselectivity. The occurrence of anti-Markovnikov regioisomers was avoided by the use of a freshly distilled thiol compound. The authors also extended the approach to longer-chain substrates with a terminal double bond. In this system, $[PdCl_2(PhCN)_2]$ was additionally necessary for double bond migration toward β-substituted styrenes, and the 1,2-DTBPMB ligand was subsequently added with acid and thiol for the hydrothiolation.

7.4. Defunctionalization

7.4.1. Decarboxylation. Decarboxylation is a helpful synthetic tool for highly selective routes toward novel organic molecules. The presence of specific functional groups often improves the mostly desired C−C bond formation. However, these groups need to be finally removed. In 2009, Cole-Hamilton and co-workers showed Pd/1,2-DTBPMB-mediated decarboxylation to be efficient on 4-hydroxybenzoic acid.[210] Initially, several phosphine ligands were investigated. Highly electron-donating phosphines with a medium bite angle in case

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Chem. Rev. 2021, 121, 6610−6653

of diphosphines were advantageous. Although the monodentate ligand tri-*tert*-butylphosphine resulted in the highest yield in the ligand screening (78% vs 72% using 1,2-DTBPMB), the authors decided upon 1,2-DTBPMB for a subsequent optimization study, finally yielding up to 85% phenol at 140 °C (Figure 63). This reaction opens the path for smooth decarboxylation of sensitive compounds, as the decarboxylation usually occurs at temperatures higher than 200 °C.

According to the mechanism (Figure 64), after formation of the active Pd/1,2-DTBPMB species **64-1**, oxidative addition of 4-hydroxybenzoic acid would generate a hydride **64-2**, which is decarboxylated to the aryl palladium species **64-3**. Reductive elimination of the phenol would lead to regeneration of the catalyst.

In 2018, the decarboxylation was also investigated in the synthesis of pharmaceutically attractive benzo-fused nine-membered heterocyclic alkenes using Pd/1,2-DTBPMB by Shibata and co-workers.[211] However, in this approach, no yield was obtained using 1,2-DTBPMB; instead, triphenylphosphine was the ligand of choice, resulting in 91% yield (Figure 65).

7.4.2. Desulfonation. Strongly related to decarboxylation, also desulfonation usually requires harsh conditions using strong mineral acids for hydrolysis[212,213] or stoichiometric reductive agents like Raney-Ni[214] to give good conversion. The Pd/1,2-DTBPMB system was investigated by Cole-Hamilton and co-workers toward desulfonation of 4-hydroxybenzenesulfonic acid, providing a good yield (70%, Figure 66).[210]

However, by application of the monodentate tri-*tert*-butylphosphine, 83% yield was obtained.[210] Nevertheless, using 1,2-DTBPMB, the system was further improved, resulting in 93% yield by application of $[Pd(MeCN)_4][BF_4]_2$ as a precursor instead of $Pd(OAc)_2$.[210] In conclusion, the Pd/1,2-DTBPMB catalyst was proven active in the desulfonation/decarboxylation at relatively low reaction temperature, but its performance is not as outstanding as in alkoxycarbonylation since a simple, sterically hindered monophosphine seems equally suitable for this purpose.

7.5. Coupling Reactions

7.5.1. Cross-Coupling. C−C and C−heteroatom bond-forming reactions are known to be catalyzed by Pd−phosphine complexes, using sterically hindered electron-donating ligands such as tri-*tert*-butylphosphine.[215] In addition to the carbonylative cross-coupling (see section 4.2), noncarbonylative cross-coupling reactions making use of 1,2-DTBPMB have been attempted as well. For instance, several C−C and C−N bond-forming reactions were investigated by Wills and co-workers in 2007,[216] wherein 1,2-DTBPMB was shown not to be the most efficient ligand for making such a coupling since, e.g., 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(di-*tert*-butylphosphino)butane (DIOP derivative) was more efficient for all studied examples. However, especially in the Sonogashira reaction, quantitative conversion of an electron-poor substrate such as *para*-iodonitrobenzene was obtained using 1,2-DTBPMB within 6 h (Figure 67). In contrast, the electron-rich substrate 4-iodoanisole was converted with only 33% yield after the same reaction time, while the DIOP derivative or even DPPB resulted in quantitative conversion and yield.

In addition, the Suzuki−Miyaura reaction catalyzed by Pd/1,2-DTBPMB (Figure 68) was described by McNulty and co-workers in 2009 to extend the scope and specifically to investigate the effect of bulky xylylphosphines.[171] The scope of the Suzuki−Miyaura cross-coupling reaction is shown to be quite broad, and it is efficient with aryl iodides, bromides, and

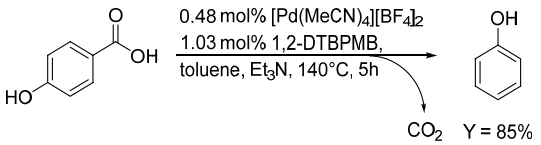

Figure 63. Decarboxylation of 4-hydroxybenzoic acid. Adapted with permission from ref 210. Copyright 2009 Royal Society of Chemistry.

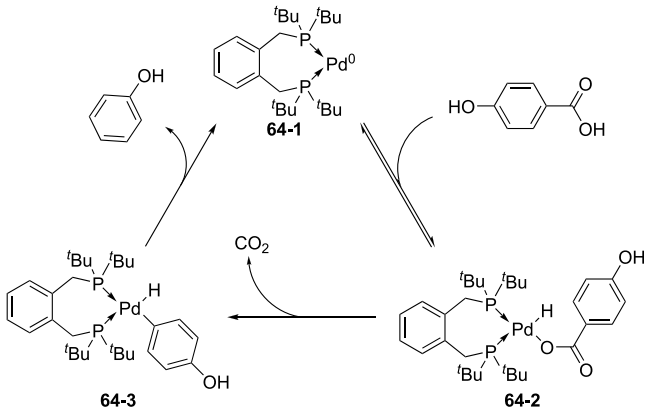

Figure 64. Proposed mechanism for the Pd/1,2-DTBPMB-mediated decarboxylation of 4-hydroxybenzoic acid. Reproduced with permission from ref 210. Copyright 2009 Royal Society of Chemistry.

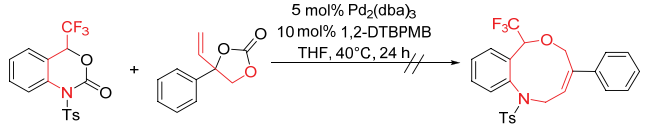

Figure 65. Approach of Pd/1,2-DTBPMB-mediated double decarboxylative cycloaddition. Adapted with permission from ref 211. Copyright 2018 Royal Society of Chemistry.

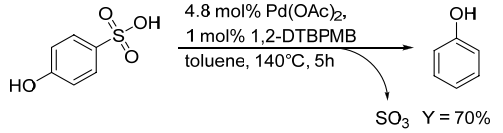

Figure 66. Desulfonation of 4-hydroxybenzenesulfonic acid. Adapted with permission from ref 210. Copyright 2009 Royal Society of Chemistry.

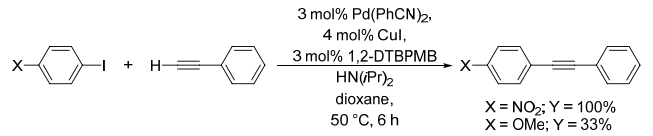

Figure 67. Pd/1,2-DTBPMB-mediated Sonogashira reaction. Adapted with permission from ref 216. Copyright 2007 Elsevier.

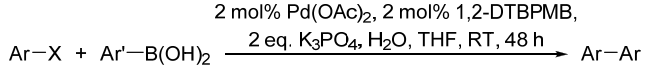

Figure 68. Pd/1,2-DTBPMB-mediated Suzuki−Miyaura cross coupling. Adapted from ref 171. Copyright 2009 Elsevier.

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activated aryl chlorides, allowing for up to 94% yield. However, deactivated aryl chlorides are less reactive.[171] In a subsequent work, the group investigated some other P,N and P,O ligands that were also suitable for Suzuki−Miyaura cross coupling of deactivated aryl chlorides[217] and therefore preferred over 1,2-DTBPMB for this purpose.

7.5.2. Oxidative Esterification. The development of selective catalytic oxidations using molecular oxygen is of special industrial interest since it contributes to Green chemistry, reducing waste and toxic byproducts, respectively. In 2011, Beller and co-workers reported the catalytic oxidative cross-esterification using air as oxidant. Besides the ligand bis(1-adamantyl)butylphosphine, also 1,2-DTBPMB showed high performance in the oxidative homocoupling of various benzyl and heterobenzyl alcohols, resulting in the corresponding benzoate esters in 60 to 85% yields (Figure 69).

The authors demonstrated the wide feasibility of this reaction using an aliphatic alcohol, 1-octanol, in 72% conversion toward octyl octanoate. However, the excellent activity of 1,2-DTBPMB is surprising since the ligand is often described as air sensitive. In this work, parts of the ligand were detected to be oxidized, although this did not inhibit its highly selective oxidation ability.[218] The two suitable ligands have bulky nucleophilic substituents in common, so that a stable binding toward the palladium center is proposed by the authors, explaining the role of the ligand as a stabilizer against Pd agglomeration. Although generally suitable in this coupling reaction, oxidation of 1,2-DTBPMB could be an issue in terms of recycling.

8. 1,2-DTBPMB DERIVATIVES FOR OPTIMIZED PERFORMANCE

For two decades, 1,2-DTBPMB has been given much attention not only on (isomerizing) alkoxycarbonylation. As a result, limitations had been investigated deeply, leading researchers to aim for progress. Herein, we present several novel ligands, all derived from 1,2-DTBPMB. Most of them were highly focused on a potential industrial application, finally leading to a new generation of highly functional 1,2-DTBPMB derivatives.

Throughout this review, the remarkable properties of metal complexes and Pd complexes, especially bearing 1,2-DTBPMB as a ligand, have been described. 1,2-DTBPMB has proven to be very efficient toward the carbonylation of various unsaturated substrates, leading to a wide range of multiple products (esters, amides, acids...). Despite the outstanding selectivity regardless of the chain length or double bond position in the substrate, the catalyst suffers from instability over time and lower reaction rates for long-chain alkenes, so that it came to industrial application exclusively for the case of ethene methoxycarbonylation. Additionally, the methoxycarbonylation of sterically hindered alkenes such as tri- and tetra-substituted alkenes has not been reported. It was considered that 1,2-DTBPMB had possibly reached its maximum performance in catalysis, and the time had come to modify drastically the structure of the ligand, such as the phosphorus substituents or the aromatic backbone. Several ligands, including 1,2-DTBPMB and its derivatives, and their role especially in carbonylations were recently reviewed by Kathe and Fleischer.[219] The modified ligands exhibit different faces since the most important modifications include substitution of either two *tert*-butyl groups on one phosphorus atom leading to an unsymmetrical ligand or one *tert*-butyl group on each phosphorus atom. Additionally, modifications of the backbone are reported.

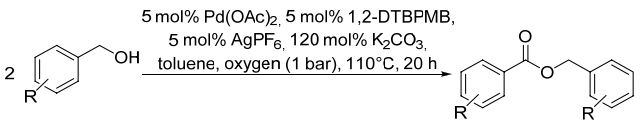

Figure 69. Oxidative esterification of benzylic alcohols. Adapted with permission from ref 218. Copyright 2011 John Wiley and Sons.

8.1. Unsymmetrical 1,2-DTBPMB Derivatives

Some authors have taken the challenge of modifying 1,2-DTBPMB in order to further enhance its capabilities. In 2010, Pringle and co-workers applied a modified ligand of higher stability. A different synthesis had been followed from scratch, resulting in a ligand with two phenyl groups structurally substituting the two *tert*-butyl groups at only one phosphorus atom.[37]

The first tests carried out on methoxycarbonylation of ethene were promising, so that catalyst lifetime was also studied. The TONs in the first two runs were similar, before the new ligand **70-1** (Figure 70) was recycled 9 times in total and 1,2-DTBPMB only twice. In contrast, replacing all *tert*-butyl groups by phenyl groups was detrimental to the methoxycarbonylation reaction, proving that at least one *tert*-butyl group is of high importance to the properties of the ligand. The authors assume that substitution of the two *tert*-butyl groups on only one phosphorus atom with phenyl groups results in a stronger Pd−P bond and therefore higher stability.

Further investigations on modifying the substituents on only one phosphorus atom have led the group to the synthesis of a derivative bearing two *o*-tolyl groups **70-2** and another one bearing a phospha-adamantane cage **70-3** in 2012.[38] While the original ligand 1,2-DTBPMB showed a selectivity of 99.9% on the methoxycarbonylation of ethene and a TON of 17 900, ligand **70-2** gave 99.5% selectivity and a TON of 32 200, and ligand **70-3** offered 99.9% selectivity and a TON of 40 200.

With the unsymmetrical phosphine ligands, the authors postulate the presence of two isomers for all catalytic species in contrast to the symmetrical phosphine ligand 1,2-DTBPMB, resulting in only one isomer involved in the mechanism (Figure 7, cycle A). However, the acyl group *trans*- to the *tert*-butyl-substituted phosphine is kinetically favored and facilitates high chemoselectivity toward methyl propanoate.[37,38]

This study demonstrated that methoxycarbonylation of ethene requires only one single bulky phosphine donor, which raises the question of which ligands are needed for methoxycarbonylation of more demanding substrates (see sections 8.2 and 8.3). Apart from methoxycarbonylation of ethene, the methoxycarbonylation of 1,3-butadiene was extensively reviewed for adipic acid (derivatives) production in section 3.2.1.2. 1,2-DTBPMB has not been implemented in an industrial process due to lacking stability and efficiency so far. Very recently, Beller and co-workers designed a novel ligand (HeMaRaphos) in which one *tert*-butyl group in 1,2-DTBPMB is substituted with a pyridyl group.

The application of pyridyl-substituted phosphines as ligands in carbonylation of ethene was already reported by Drent, Petrus, and Van Langen in 1987.[220] Later, Drent and co-workers reported 2-pyridyldiphenylphosphine (2-PyPPh$_2$) to be highly active and selective toward carbonylation of propyne.[49,152] The authors postulate the P,N hemilabile ligand

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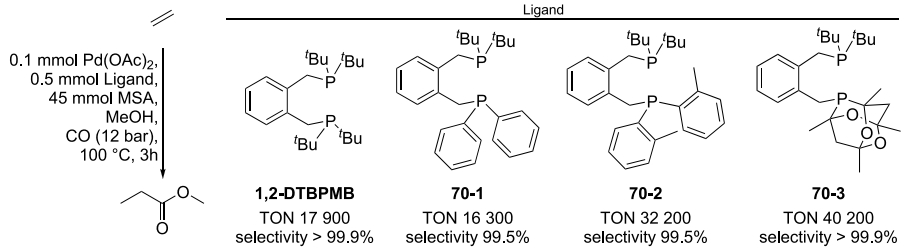

Figure 70. Comparison of 1,2-DTBPMB derivatives in the methoxycarbonylation of ethene.

to be crucial in the selectivity- and rate-determining step. Furthermore, its function is described to involve proton shuttling to the active palladium species. In 2014, Bühl et al. investigated the mechanism of Pd/(2-PyPPh$_2$)-mediated alkyne alkoxycarbonylation.[155,156] The authors postulate neither a carbomethoxy nor a hydride mechanism but rather a proton transfer from the ligand to the alkyne. Therefore, as the last step in the cycle, alcoholysis would be facilitated due to deprotonation of methanol by the pyridyl group, releasing free methoxide as a better nucleophile (see section 8.3 for a detailed mechanism using a pyridyl-substituted ligand in alkoxycarbonylation).

Regarding the novel HeMaRaphos ligand, the most important structural features of 1,2-DTBPMB and 2-PyPPh$_2$ were combined.[125] The bulky *tert*-butyl groups facilitate fast isomerization, while the *tert*-butyl-2-pyridyl group enhances formation of the palladium hydride species and final alcoholysis. Hence, direct butoxycarbonylation of 1,3-butadiene results in 97% selectivity and a TON of >60 000 (Figure 71).[125] In addition, the ligand was shown also to be active and highly selective for alkoxycarbonylation of 1,3-butadiene with various other alcohol compounds opening up a wide industrial potential.

8.2. Backbone-Modified Unsymmetrical 1,2-DTBPMB Derivatives

In order to develop an improved catalyst system for methoxycarbonylation of ethene in terms of stability and reaction rate, in 2004 Butler and co-workers additionally replaced the backbone by a ferrocene group, forming ferrocenylmethylphosphanes. The *tert*-butyl substituents were additionally replaced by adamantly or methyl substituents, resulting in comparable turnover numbers after 3 h and initial reaction rates as for the benchmark ligand 1,2-DTBPMB (Figure 72).[221,222]

To test stability, the ligand 1,2-bis(di-*tert*-butylphosphinomethyl)ferrocene was applied to a recyclability test, resulting in similar initial rate and TON after 3 h in the second run.[223] In 2008, further studies on the recyclability of the novel ferrocene ligands were patented by Eastham and Butler. However, activity and TON, respectively, decreased to only 17% of the initial TON over four recycling runs.[223]

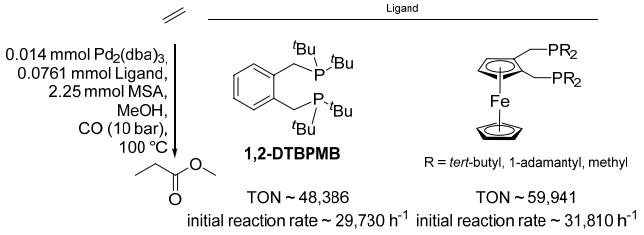

Figure 72. Comparison of 1,2-DTBPMB and ferrocenylmethylphosphanes in the methoxycarbonylation of ethene.[222]

In 2016, Holtzapfel and Bredenkamp additionally replaced the backbone by a ferrocene group, forming 1-(diphenylphosphino)-1′-(di-*tert*-butylphosphino)ferrocene (DTBDPPF) (Figure 73). The structure of the new ligand is very different from the original ligand, but its performance in terms of reaction rate is greatly enhanced since TOFs are doubled in methoxycarbonylation of alkenes compared to 1,2-DTBPMB. However, selectivity toward the linear product was much lower.[224] In conclusion, this modification is not helpful for selective methoxycarbonylation toward linear products.

8.3. Symmetrical 1,2-DTBPMB Analogues

In 2014, Caporaso, Mecking, and co-workers modified 1,2-DTBPMB in order to achieve high selectivity on the more challenging methoxycarbonylation of methyl oleate.[225] High selectivity toward the linear ester product would result from the difference in energy barrier between methanolysis of the linear and branched Pd acyl species, resulting from the bulky *tert*-butyl substituents in 1,2-DTBPMB. Therefore, they could only enhance selectivity by using a more sterically demanding substituent and decided upon replacing the four *tert*-butyl groups by adamantyl groups. A yield of 1,19-dimethylnonadecanedioate of up to 96% was achieved but only after a reaction

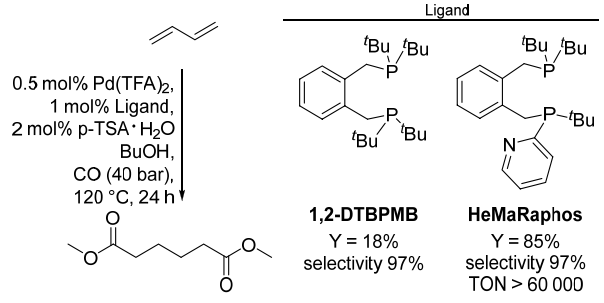

Figure 71. Comparison of 1,2-DTBPMB and HeMaRaphos in the butoxycarbonylation of 1,3-butadiene.

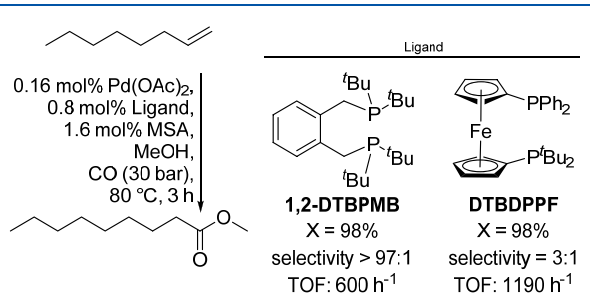

Figure 73. Comparison of 1,2-DTBPMB and DTBDPPF in the methoxycarbonylation of ethene.[224]

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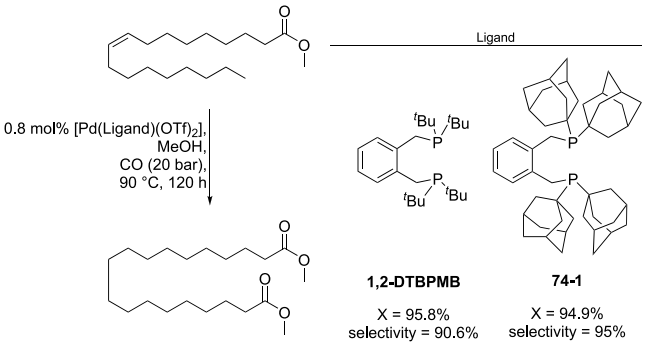

Figure 74. Comparison of 1,2-DTBPMB derivatives in the methoxycarbonylation of methyl oleate.[225]

time of 120 h (Figure 74). At shorter reaction times, significantly higher conversion is obtained using 1,2-DTBPMB, although the adamantyl derivative **74-1** is slightly more selective to the α,ω-product.[225]

In 2017, van Meurs and co-workers proposed that a rigid backbone, a bite angle of around 100°, and bulky *tert*-butyl substituents at the phosphorus atoms of the ligand are required to reach high selectivity in the isomerizing alkoxycarbonylation. Therefore, they developed the novel ligand 1,2-bis(4-phosphorinone)xylene (BPX).[226] As a model compound, trans-4-octene was converted, and BPX showed significantly higher activity than 1,2-DTBPMB (Figure 75). Although the new ligand BPX was found to isomerize double bonds significantly more slowly, the overall reaction rate was higher since it is not isomerization but methanolysis that is rate-determining. Finally, the substrate scope was extended to various alkenes, showing at least similar performance of BPX compared to 1,2-DTBPMB. The authors conclude that the phosphorus atoms constrained in a six-membered heterocycle, containing an electron-withdrawing ketone group, result in an improved electronic structure, which is necessary for the increased activity.

Another important step toward application of a novel 1,2-DTBPMB-modified ligand was achieved by Beller and co-workers in 2017.[227] Their intention was a selective isomerizing methoxycarbonylation of tetramethylethene (Figure 76) through the use of 1,2-bis((*tert*-butyl(pyridin-2-yl)-phosphanyl)methyl)benzene (PYTBPX). Two challenges are to be tackled with regard to the substituted substrate: first, the isomerization of the sterically hindered double bond and, second, avoidance of the acid-promoted formation of a methyl ether. Therefore, addition of a base was considered, facilitating alcoholysis as an intermediate step in methoxycarbonylation

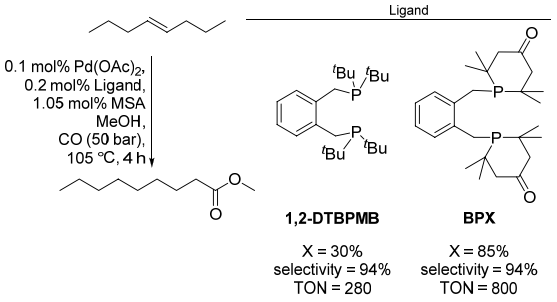

Figure 75. Comparison of 1,2-DTBPMB and BPX in the methoxycarbonylation of *trans*-4-octene.[226]

and inhibiting ether formation. However, also intermediate isomerization steps would be inhibited under basic conditions.

Hence, the ligand was modified with an amphoteric *o*-pyridine group on each phosphorus atom (as mentioned in section 8.1, pyridyl-substituted ligands offer special features for alkoxycarbonylation), while keeping its steric hindrance.

In doing so, the corresponding methyl ester was formed in 98% yield, while 50% of the undesired ether and no methyl ester were produced when using 1,2-DTBPMB. Also pharmaceutically interesting compounds such as diethylstilbestrol or cholesterol were converted very easily in high selectivity. Additionally, this novel modified ligand was investigated toward its performance in the methoxycarbonylation of ethene. While at 23 °C the Pd/1,2-DTBPMB system provides a 3% yield of methyl propanoate after 50 min, the new ligand allows 99% yield after the same time (Figure 77). For the first time, methoxycarbonylation proceeds at room temperature with such a high rate.[227] At 120 °C, a turnover number of 44 000 h^{-1} and a total turnover number of >1 425 000 for two runs were determined using PYTBPX.

The same ligand also showed outstanding activity in the carbonylation of secondary and tertiary alcohols directly to the corresponding methyl ester. As previously mentioned in section 4.5, 1,2-DTBPMB did not compete with the modified ligand PYTBPX in this case (Figure 78).[179]

In 2018, Mecking, Beller, and co-workers compared 1,2-DTBPMB and the novel ligands PYTBPX and BPX in terms of isomerizing alkoxycarbonylation of hyperbranched oligoethenes. These are extremely challenging substrates due to multiple substituents and branches that need to be overcome in isomerization.[228] Initially, inter alia, 1-heptene was applied as a model substrate (Figure 79). While all ligands were more selective toward the linear products, with PYTBPX also significant amounts of branched products were detected. In contrast, this less selective ligand showed higher activity especially with increasing degree of substitution of the double bond. In terms of rapid isomerization, 1,2-DTBPMB was most suitable even at room temperature, but this effect would be compensated at reaction temperature. Finally, BPX was found to combine high selectivity, activity, and durability at reaction temperature and was therefore chosen for the ongoing study wherein it was also found to be the key for ethoxycarbonylation of hyperbranched oligoethenes with sufficient reaction rates and good selectivity.

Coming back to ethene as a less demanding substrate, some final improvements were outlined in 2017 by Beller and co-workers. Learning from the previous works, wherein pyridine groups substituting one *tert*-butyl group at each phosphorus atom were shown to enhance selectivity[227] and a ferrocene backbone resulting in increased reaction rate,[224] the next generation of 1,2-DTBPMB was created as a combination. The ligand 1,1′-bis(*tert*-butyl(pyridin-2-yl)phosphanyl)ferrocene **80-1** provides the full methoxycarbonylation of ethene at 80 °C after 10 min and shows much higher activity in this industrially relevant carbonylation reaction (Figure 80). This effect was confirmed by investigating the apparent activation energy, which was much lower using the novel ligand **80-1** than using 1,2-DTBPMB.[229]

In 2018, Beller and co-workers undertook a mechanistic study of the novel ligand **80-1** and further investigations on the methoxycarbonylation of alkenes using this ligand.[230] The authors describe a Pd-hydride mechanism similar to 1,2-DTBPMB-mediated alkoxycarbonylation, which differs from

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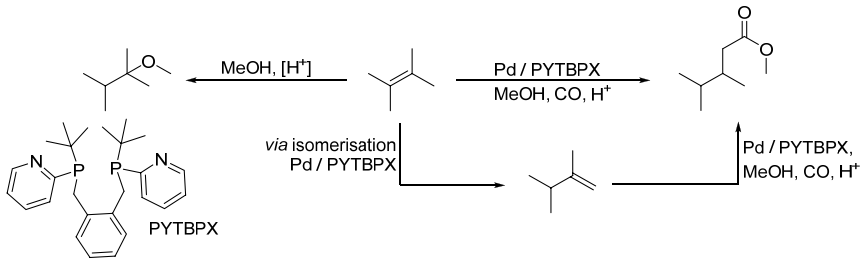

Figure 76. Pd/PYTBPX-mediated methoxycarbonylation of tetramethylethene.[227]

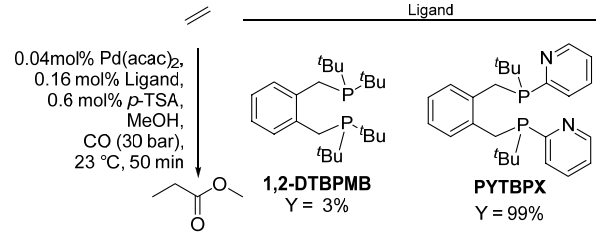

Figure 77. Comparison of 1,2-DTBPMB and its *o*-pyridyl derivative in the methoxycarbonylation of ethene at room temperature.[227]

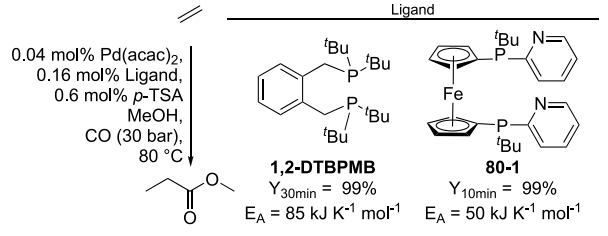

Figure 80. Comparison of 1,2-DTBPMB and the novel ferrocene derivative **80-1** in the methoxycarbonylation of ethene.[229]

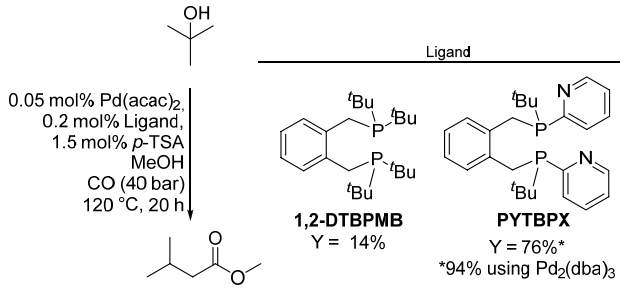

Figure 78. Comparison of 1,2-DTBPMB and its *o*-pyridyl derivative in the carbonylation of *tert*-butanol.[179]

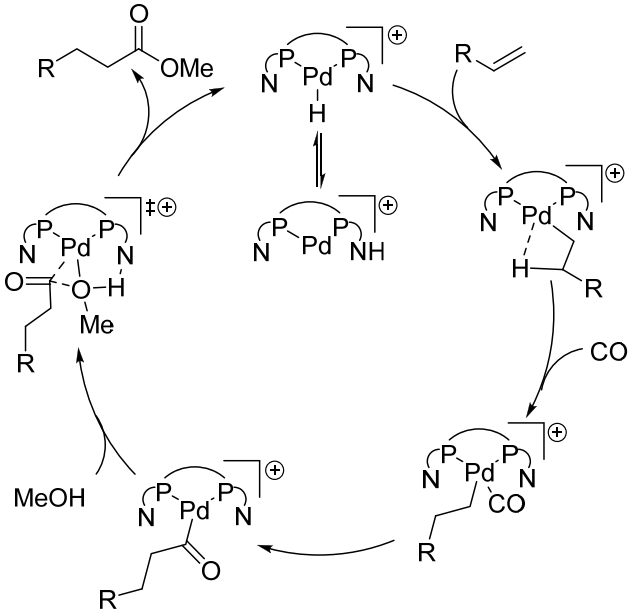

Figure 81. Proposed mechanism for the alkoxycarbonylation using ligand **80-1**. Reproduced with permission from ref 230. Copyright 2018 Royal Society of Chemistry.

1,2-DTBPMB in two superior properties of the new ligand. First, the N atom is able to hemilabily coordinate to the Pd center, improving the long-term stability of the catalyst. Second, methanolysis is N-assisted since the proton is transferred from the hydroxy group in methanol to the N atom of the pyridyl ring in the Pd acyl complex and then interacts with the methoxy group via hydrogen bonding, which leads to a special stabilization of this transition state (Figure 81). This mechanism is similar to the one postulated by Bühl (see section 8.1).[155,156]

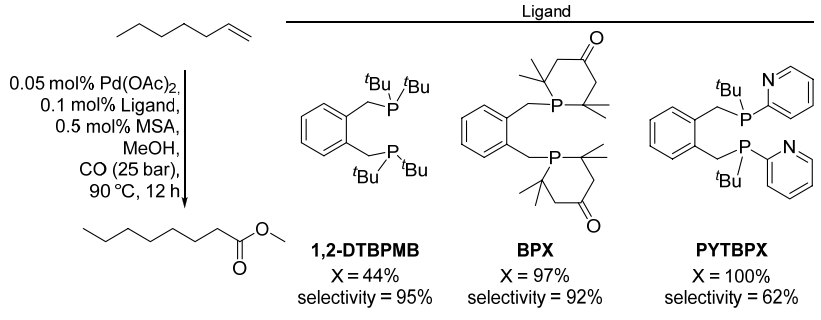

Figure 79. Comparison of 1,2-DTBPMB, BPX, and PYTBPX in the methoxycarbonylation of 1-heptene as a model compound for hyperbranched oligoethenes.[228]

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Chem. Rev. 2021, 121, 6610−6653

According to the performance, the new ligand was shown to be active even at 0 °C, obtaining full conversion of ethene after 24 h. Additionally, at a very low catalyst concentration of 1.6 ppm, the catalyst was used in four consecutive runs maintaining 99% selectivity. This corresponds to a TON > 1 100 000. Several terminal, internal, and functionalized alkenes were successfully converted quantitatively and with good linear selectivity for tri- or tetrasubstituted double bonds, underlining that this ligand probably represents the brand new state-of-the-art ligand for alkoxycarbonylation reactions. However, regioselectivity toward linear products was lower (around 75%) in the methoxycarbonylation/hydroxycarbonylation of internal or terminal alkenes than using 1,2-DTBPMB.[230] In conclusion, limited applicability of the novel ligand **80-1** is found for these longer-chain alkenes, underlining the special feature of 1,2-DTBPMB.

9. CONCLUSIONS

Due to their excellent atom economy, carbonylation reactions have been a focus of research since the invention of hydroformylation. For many years, several catalyst systems have been developed and steadily improved. Among homogeneous catalysts, ligands significantly codetermine activity and selectivity. 1,2-Bis(di-*tert*-butylphosphinomethyl)-benzene, a symmetrical diphosphine ligand, has become a role model. Bonded to palladium, it has been the ligand of choice in the alkoxycarbonylation of various substrates for more than two decades. The very first reactions were related to methoxycarbonylation of ethene, the simplest substrate leading to the industrially most relevant product from this reaction, methyl propanoate. Showing excellent activity, the large-scale, continuous ALPHA process using 1,2-DTBPMB for production of methyl propanoate was developed by Lucite International/Mitsubishi Chemical, leading to two (and in the future three) industrial plants which are distributed all over the world. Extending the substrate scope, longer-chain 1-alkenes were alkoxycarbonylated efficiently with very high selectivity to the terminal product. However, the special feature of 1,2-DTBPMB comes to light during alkoxycarbonylation of internal alkenes. As a result of its outstanding isomerization ability, excellent selectivity toward linear esters/acids compared to the branched products is obtained. Nowadays, it is well understood that this ability is due to the bulky *tert*-butyl substituents and the rigid xylene backbone. Although linear and branched intermediates are formed within the catalytic cycle, isomerization is much faster than rate-determining methanolysis, and finally, methanolysis is faster for the linear acyl species leading to the linear product. Therefore, the tandem isomerization/alkoxycarbonylation has been extensively studied for the development of sustainable adipic acid (derivatives) production, based on 1,3-butadiene or renewable resources. Although efficient to a certain extent, this approach using 1,2-DTBPMB is not competitive on an industrial scale and has never been upscaled. Especially methoxycarbonylation of conjugated dienes is known as a challenge. However, the wide field of applications had been shown once more, applying long-chain, multiply unsaturated fatty acid (esters) that could be converted selectively to linear di- or trifunctionalized compounds that are key intermediates for the formation of biobased polymers. Although rarely reported, also alkynes have been alkoxycarbonylated successfully to α,ω-disubstituted products, raising the question for limitations of this ligand. Several approaches applying 1,2-DTBPMB in other carbonylations, also using CO surrogates to substitute this toxic reagent, and noncarbonylative reactions were carried out. However, success does not come close to that of isomerizing alkoxycarbonylation. A common issue from palladium catalysis is Pd black formation and catalyst deactivation, also reported applying 1,2-DTBPMB. Herein, several approaches for stabilization and recycling have been described, but catalyst deactivation over time could not be fully overcome. In addition, product demand and catalyst separation from the product are a challenge. As a result, conversion of 1,2-DTBPMB-mediated reactions other than methoxycarbonylation of ethene to an industrial level has been elusive, while the latter is of such a high rate and the catalyst so stable that the industrial ALPHA process is profitable.

Although 1,2-DTBPMB has attracted much attention and has shown great potential for isomerizing alkoxycarbonylation of a large variety of substrates, some recent attempts have been made to design novel 1,2-DTBPMB replacements that serve better in terms of activity and durability at equal selectivity. Depending on the purpose, especially the symmetrical ligand PBX, PYTBPX and a ligand derived from PYTBPX with a ferrocene backbone and the unsymmetrical HeMaRaPhos have been reported as high performing. They all have the sterically demanding substituents in common but exhibit further, unique features, such as pyridyl groups, that allow for alkoxycarbonylation of challenging substrates and/or of ethene under relatively mild conditions with high activity. To date, there is not "the one" novel ligand but several 1,2-DTBPMB derivatives as potential candidates for large-scale applications. However, most of them cannot compete in terms of linear regioselectivity for longer-chain/internal alkenes. Therefore, the simplicity of 1,2-DTBMB and its excellent characteristics will make it a ligand of choice in some reactions for many years to come.

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Notes

The authors declare no competing financial interest.

Biographies

Johanna Vondran studied chemistry at TU Dortmund university from 2012 to 2017. Her bachelor thesis was on the Pd/1,2-DTBPMB-catalyzed aminocarbonylation using *N*,*N*-dimethylformamide as an in situ source of CO. Within her master studies, she did a three month internship in the workgroup of Dr. Polyzos on flow chemistry at the University of Melbourne. In her master thesis, she developed a homogeneously catalyzed reaction system for the amidotelomerization of butadiene with secondary amines. After her master studies, she got work experience in the industry through an internship at Covestro AG in Leverkusen. Since 2018, Johanna has worked as a Ph.D. candidate with Thomas Seidensticker at the Laboratory of Industrial Chemistry at TU Dortmund university under the supervision of Prof. Dr. Dieter Vogt. Her research interests are homogeneously catalyzed oxidations and the methoxycarbonylation of oleochemicals.

Marc R. L. Furst was a Ph.D. student at the University of St Andrews under the supervision of Prof. David J. Cole-Hamilton and received his doctorate in 2013. Then, he joined Prof. Udo Kragl and Dr. Eckard Paetzold in 2013 at the University of Rostock, in the field of renewable chemistry. Thereafter, he worked for Prof. Michael Clays in 2014 at the University of Cape Town, developing new analysis methods for the Fischer−Tropsch synthesis. Subsequently, he developed recyclable homogeneous catalysts in the team of Prof. Arno Behr in 2016 at the TU Dortmund University. He withdrew from research in 2017 to teach chemistry to high school students at the Athénée of Luxembourg

Graham Eastham received a first degree in biochemistry at the University of Kent, Canterbury (1982−86), before spending 18 months at Glaxo Pharmaceuticals Barnard Castle facility. He joined ICI Advanced Materials in 1988, working on the synthesis and applications of polyphosphazenes before transferring to ICI Acrylics, which later became Ineos, Lucite, Mitsubishi Cemicals, in 1991 and worked on developing new technologies for the production of methyl methacrylate (MMA) for use in making the transparent polymer Perspex/Lucite/Plexiglas. He carried out a part time Ph.D. in the group of Dr. Mel Kilner at the University of Durham on the Alpha process for MMA production. As a coinventor on the first project Alpha patent disclosing DTBPMB for use in the methoxycarbonylation of ethene, he had the unique position of taking this new technology from bench-scale experiments through pilot plant scale to commercial (120 ktonne) production in the Singapore plant. He was a key player in the successful realization of the process, ran many of the optimization reactions, and carried out key mechanistic studies both within the company and via numerous university collaborations. He is a coinventor on 20 plus patent families. His later years were spent leading a team looking at new technology for the sustainable production of MMA. He retired in 2019

Thomas Seidensticker studied chemistry at TU Dortmund University and received his master's degree in 2012. During his masters studies he was working at the University of St. Andrews/Scotland with Prof. David J. Cole-Hamilton. Thomas worked as a Ph.D. student at the laboratories of industrial chemistry starting in 2013 and received his doctorate in 2016 under the supervision of Prof. Dr. Arno Behr. Since 2017, he has been working on his independent career with Prof. Dr. Dieter Vogt. His research is dedicated to sustainable process design for homogeneous catalysts, including the development of innovative recycling methods and the conversion of renewable resources. Since January 2021, he has been setting up his own junior research group "renewlysis" at TU Dortmund University combining catalysis with renewable resources.

David Cole-Hamilton obtained his degrees (B.Sc. and Ph.D.) at Edinburgh University, before working with Nobel Laureate Sir Geoffrey Wilkinson at Imperial College, where he developed a strong interest in organometallic chemistry and especially homogeneous catalysis. His independent career started at Liverpool University (Lecturer and Senior Lecturer) before moving to be Professor of Chemistry at the University of St. Andrews in 1985. He became Emeritus in 2014. The majority of his work has been on the applications of organometallic chemistry in solving problems in homogeneous catalysis and materials chemistry including nanomaterials. He led a team at St Andrews which developed new catalytic reactions using DTBPMB as ligand. He was President of the European Chemical Society 2013−2017.

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ABBREVIATIONS

2-PyPPh$_2$	2-pyridyldiphenylphosphine
1,2-DTBPMB	1,2-bis(di-*tert*-butylphosphinomethyl)-benzene
70-1	di-*tert*-butyl(2-((diphenylphosphaneyl)-methyl)benzyl)phosphane
70-2	di-*tert*-butyl(2-((di-*o*-tolylphosphaneyl)-methyl)benzyl)phosphane
70-3	(1*S*,3*R*,5*R*,7*S*)-8-(2-((di-*tert*-butylphosphaneyl)methyl)benzyl)-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane
74-1	1,2-bis((di(adamantan-1-yl)-phosphaneyl)methyl)benzene
80-1	1,1′-bis(*tert*-butyl(pyridin-2-yl)-phosphanyl)ferrocene
ACH	acetone cyanohydrin
ArX	aryl halides
BAILs	Brønsted acid ionic liquids
BNPA	1,1′-bi-2-naphthol phosphoric acid
BPX	1,2-bis(4-phosphorinone)xylene
B_2 pin$_2$	bis(pinacolato)diboron
C4	isobutene
DCM	dichloromethane
DDPPI	1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis-(diphenylphosphino)-L-iditol
DFT	density functional theory
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMF	dimethylformamide
DPPA	diphenylphosphoric acid
DPPB	1,4-bis(diphenylphosphino)butane
DTBDPPF	1-diphenylphosphino-1′-(di-*tert*-butylphosphino)ferrocene
DTBDPPF	1-(diphenylphosphino)-1′-(di-*tert*-butylphosphino)ferrocene
DTBP	bis(di-*tert*-butylphosphino)propane

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Chem. Rev. 2021, 121, 6610−6653

HeMaRaPhos	2-(*tert*-butyl(2-((di-*tert*-butylphosphaneyl)methyl)benzyl)-phosphaneyl)pyridine
*i*Pr	isopropyl
KA	ketone alcohol
MCC	Mitsubishi chemical
MMA	methyl methacrylate
MSA	methanesulfonic acid
N_2O	nitrous oxide
NFS	*N*-formylsaccharin
NMR	nuclear magnetic resonance
o-$BrCH_2C_6H_4CH_2Br$	1,2-bis(bromomethyl)benzene
OMPO	1,3,5,7,9,11,13,15-octakis-[methylpropanoate]octasiloxane
p-TSA	*p*-toluenesulfonic acid
$PdCl_2(PhCN)_2$	bis(benzonitrile)palladium dichloride
$Pd(MeCN)_4$	bis(acetonitrile) palladium dichloride
$Pd(OAc)_2$	palladium acetate
$Pd(TFA)_2$	palladium trifluoroacetate
PH^tBu_2	di-*tert*-butylphosphine
POSS	polyhedral oligomeric silsesquioxanes
PYTBPX	1,2-bis((*tert*-butyl(pyridin-2-yl)-phosphanyl)methyl)benzene
rac-BNPA	racemic 1,1′-bi-2-naphthol-phosphoric acid
SAMAC	Saudi methacrylates
SILP	supported ionic liquid phase
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	thermomorphic multiphase system
TOF	turnover frequency
TON	turnover number

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