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Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes

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The direct carbonylation of 1,3-butadiene offers the potential for a more cost-efficient and environmentally benign route to industrially important adipic acid derivatives. However, owing to the complex reaction network of regioisomeric carbonylation and isomerization pathways, a selective practical catalyst for this process has thus far proven elusive. Here, we report the design of a pyridyl-substituted bidentate phosphine ligand (HeMaRaphos) that, upon coordination to palladium, catalyzes adipate diester formation from 1,3-butadiene, carbon monoxide, and butanol with 97% selectivity and 100% atom-economy under industrially viable and scalable conditions (turnover number > 60,000). This catalyst system also affords access to a variety of other di- and triesters from 1,2- and 1,3-dienes.

Carbonylation reactions are among the most important applications of industrial catalysis (*1*–*5*): Using carbon monoxide (CO) as a highly versatile C1 building block with olefins, more than 10 million metric tons of various carbonyl compounds (aldehydes, acids, and esters) are produced annually for numerous consumer products. CO is a central intermediate in the chemical industry that can be easily produced either from fossil-based resources (coal or gas) or from renewables (CO_2 or biowaste). Despite the initial discovery of homogeneously catalyzed carbonylation processes nearly 80 years ago (*6*–*15*), several unattained objectives remain, perhaps most saliently the direct dicarbonylation of 1,3-dienes. This reaction would enable more environmentally benign, atom-economical production of adipate esters, the building blocks of polyamides and polyesters currently produced on a multimillion–metric ton scale (*16*, *17*). More specifically, adipate diesters are used for plasticizers, perfumes, lubricants, solvents, several active pharmaceutical ingredients, and, with respect to scale, most importantly for the production of nylons. Now, the main industrial route to produce adipate diesters involves oxidation of a mixture of cyclohexanol and cyclohexanone by an excess of nitric acid, followed by esterification with the corresponding alcohols (*18*–*20*). This process requires special equipment owing to the acid's corrosiveness and produces stoichiometric amounts of nitrous oxide (N_2O) (*21*), which is a major scavenger of stratospheric ozone and has nearly 300 times the atmospheric heat-trapping capacity of CO_2 (*22*).

Over several decades, numerous companies all over the world, including BASF, Dupont, Shell, Dow, Kuraray, and Sinopec, investigated the prospect of accessing adipate esters via butadiene dicarbonylation. However, despite extensive explorations, no such industrially viable transformation was developed (*23*–*38*). Some pilot tests were implemented (*23*–*36*), but those processes all involved multistep reactions with insufficient selectivity (~60 to 80%) for the desired linear diester.

Here, we present a palladium-catalyzed dicarbonylation of 1,3-butadiene that provides dialkyl adipates in ≥95% yield and ≥97% selectivity. Key to success was the ligand design. Recently, we developed bidentate phosphine ligands for palladium-catalyzed alkoxycarbonylation reactions in which basic pyridyl substituents on phosphorus proved essential for high activity (*39*). On the basis of that work and our long-standing interest in carbonylation reactions (*40*), we proceeded to investigate the dicarbonylation reaction of 1,3-butadiene with butanol as a model for the direct synthesis of adipate diesters.

As shown in Fig. 1, there are multiple challenges associated with this catalytic process: (i) The catalyst must promote two different carbonylation reactions on the diene substrate (which could not be achieved previously); (ii) the linear dicarbonylation product must be

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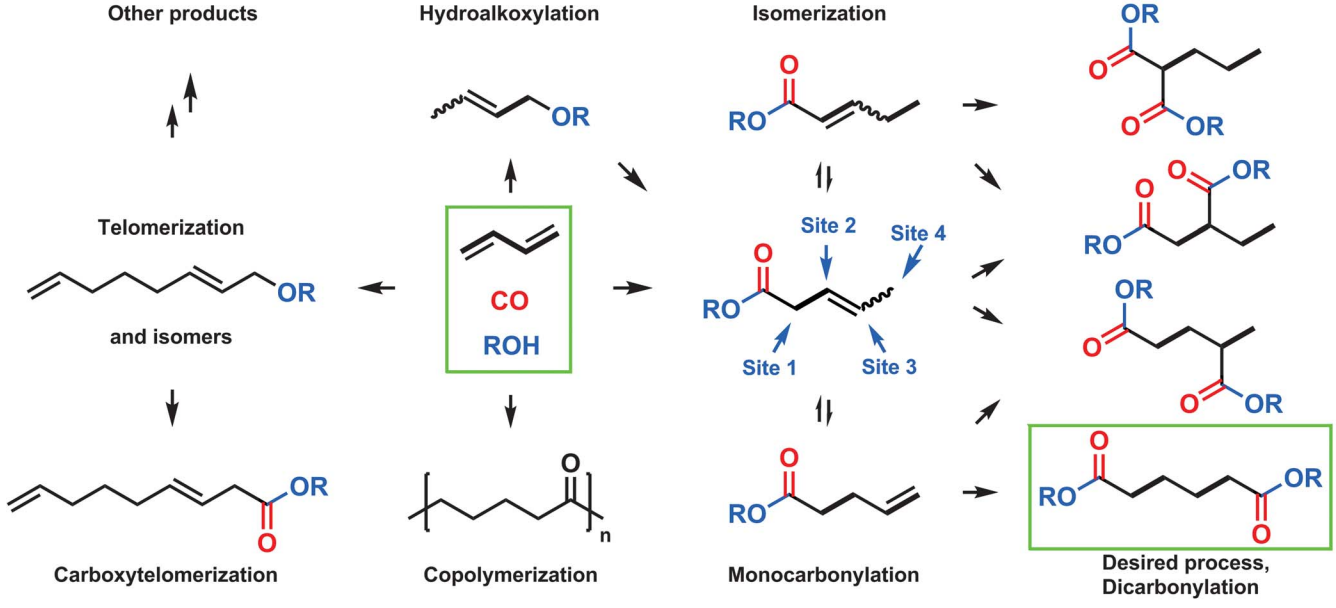

Fig. 1. Reaction network involved in synthesis of adipates from 1,3-butadienes. The green outlines indicate the starting materials (1,3-butadiene, carbon monoxide, and alcohol) and desired product adipic diester.

formed selectively, despite the fact that isomerization of the initially formed monocarbonylated intermediate to the terminal olefin is thermodynamically particularly unfavorable; and (iii) other side reactions such as telomerization (*41*), hydroalkoxylation, and (co)polymerization must be suppressed.

We sought to realize the selective dicarbonylation of 1,3-butadiene by using base-modified derivatives of the 1,2-bis[(di-*tert*-butylphosphino) methyl]benzene ligand (**L1**, dtbpx), which is used for the bulk production of methyl methacrylate (*42*). Initial optimization studies with this ligand (Fig. 2) showed slight activity but good selectivity to give the linear di-*n*-butyl adipate **4a** at 120°C and 40 bar CO with *p*-toluenesulfonic acid as a cocatalyst. To improve the catalyst performance, dtbpx derivatives **L2** and **L3** were tested. However, no increase of activity was observed. According to our hypothesis above, the incorporation of suitable basic groups on this specific ligand backbone should increase the activity of the corresponding palladium catalyst system in alkoxycarbonylation reactions. Indeed, using **L4** considerably increased activity and yield of diesters (77%) but at the expense of insufficient selectivity (48%). Considering the appropriate reactivity of **L4** and the suitable selectivity of **L1**, we designed the ligand **L5** (HeMaRaphos), which combines the two structural fragments of **L1** and **L4**: The bulky and electron-rich di-*tert*-butylphosphino fragment could promote fast isomerization of carbon-carbon double bonds (*43*–*45*) while the *tert*-butyl-2-pyridyl phosphino group facilitated formation of the active palladium hydride complex and accelerated the final alcoholysis step. Mixing **L5** and Pd(0) bis(dibenzylideneacetone) [$Pd(dba)_2$] in the presence of HCl resulted in the formation of a bright yellow palladium complex, which was suitable for x-ray crystallography (fig. S1). Although no coordination of the pyridine-N atom to the palladium center was observed in solid state, the durability of the catalyst in solution might be enhanced by such hemilabile binding. To our delight, the dicarbonylation of 1,3-butadiene proceeded in the presence of HeMaRaphos and Pd(II) trifluoroacetate [$Pd(TFA)_2$] to adipate diester with a yield of 85% and a linear selectivity of 97%. We benchmark the distinct behavior of **L5** in comparison with more than 70 other ligands, including well-known mono- and bidentate phosphines, in table S1.

To understand the performance of the palladium catalyst with HeMaRaphos, we conducted kinetic monitoring experiments (fig. S3). In the first half hour, formation of the active palladium hydride complex was observed in the in situ mixture of $Pd(TFA)_2$, **L5**, and *p*-toluenesulfonic acid (PTSA). Then, alkoxycarbonylation occurred to selectively produce *n*-butyl pent-3-enoate **3a**. This intermediate continuously accumulated to reach a maximum yield of about 50% after 90 min. Stopping the reaction at this time allowed isolation of **3a** from the reaction mixture. Meanwhile, the active catalyst also promoted olefin isomerization. The terminal olefin *n*-butyl pent-4-enoate **3c** could not be detected, which we attribute to its fast conversion into the linear adipate diester.

Next, detailed optimization studies on the effect of palladium precursor, acid, temperature, and pressure were performed to further improve the practicality of the process (tables S2 to S7). In particular, excellent catalyst turnover numbers (>60,000) were obtained using the presynthesized Pd(II)-HeMaRaphos complex under optimal conditions (table S9). Scaled-up reactions of 1,3-butadiene with methanol and *n*-butanol were then carried out at low catalyst loading [<0.5 mole % (mol %)] (table S8). The resulting esters were smoothly obtained in 88 to 95% yield and >97% linear selectivity. As an example, a reaction without additional solvent could be performed on a >200-g scale with a Pd loading of only 0.05 mol % (fig. S2 and table S8).

Beyond the specific importance of the dicarbonylation of 1,3-butadiene in the chemical industry, this methodology also offers

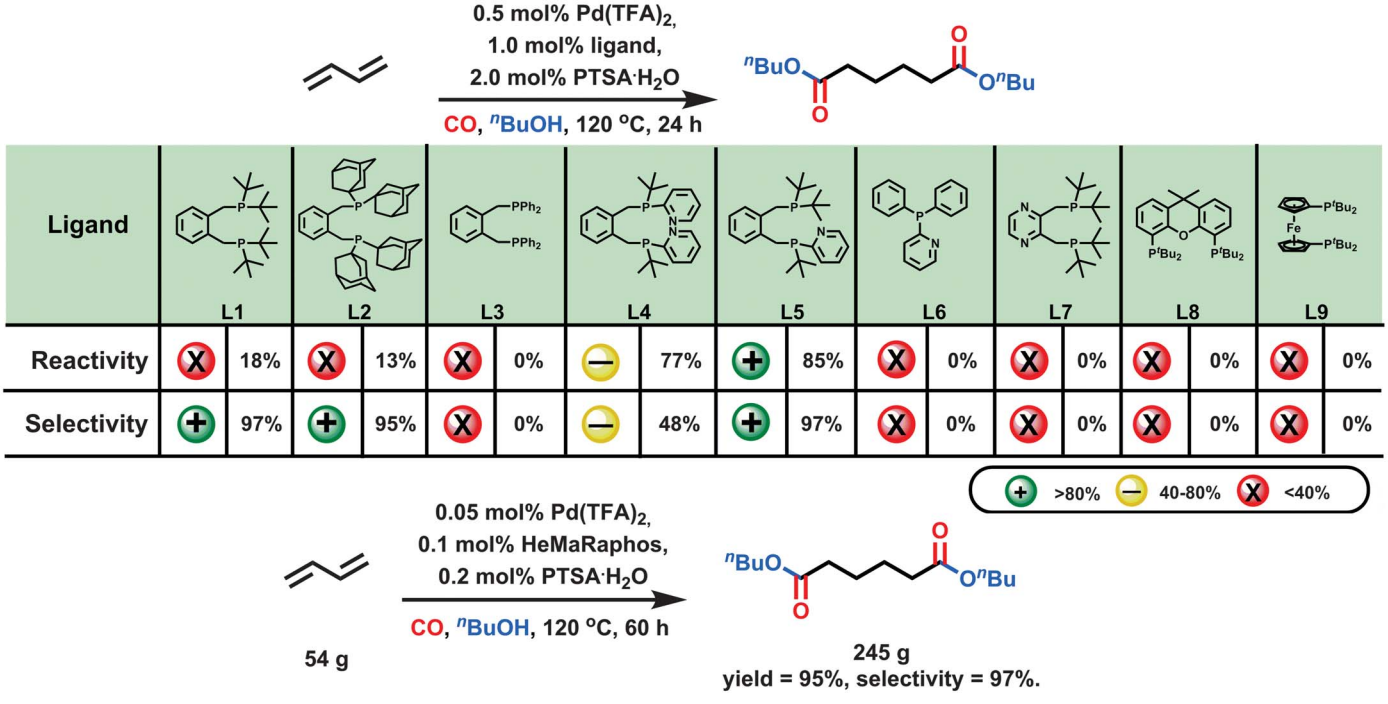

Fig. 2. Ligand optimization for palladium-catalyzed dicarbonylation of 1,3-butadiene. Reaction conditions for ligand optimization: butadiene (1.0 mmol, solution in toluene), $Pd(TFA)_2$ (0.005 mmol, 0.5 mol %), ligand (0.01 mmol, 1.0 mol %), PTSA•H_2O (2.0 mol %), ^{n}BuOH (2.0 ml), CO (40 bar), 120°C, and 24 hours; the ratio of products and yields were determined by gas chromatography analysis with mesitylene as the internal standard. Reactivity represents the yield of the diester. Selectivity represents the ratio of linear diester to all diesters. ^{n}Bu, *n*-butyl; ^{t}Bu, *tert*-butyl.

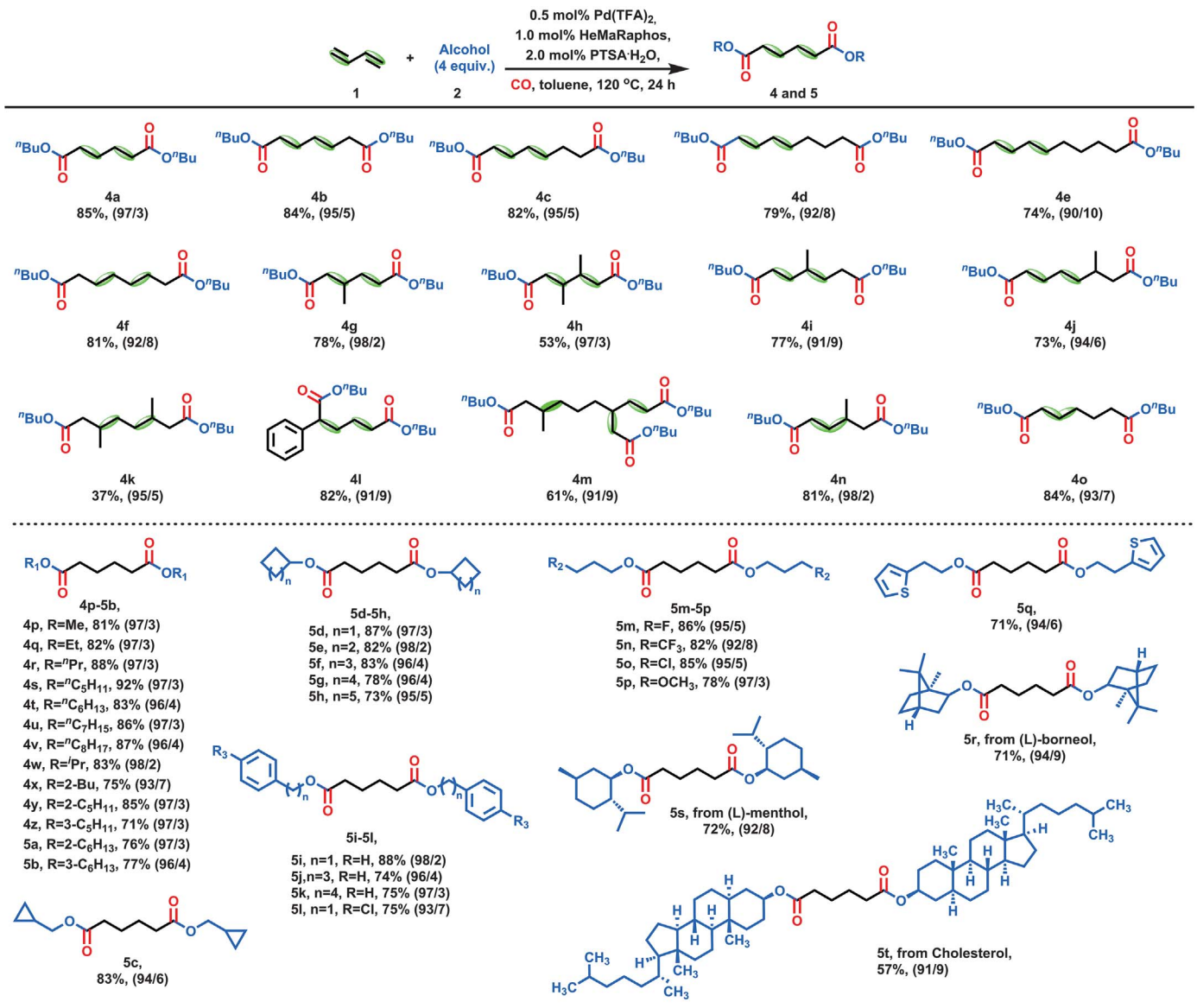

Fig. 3. Palladium-catalyzed dicarbonylation of 1,2- and 1,3-dienes. Me, methyl; Et, ethyl; ^{n}Pr, *n*-propyl; ^{i}Pr, isopropyl.

prospects for valorization of other dienes for fine chemical production (*46*–*48*). To showcase the generality of the catalyst system, 15 different dienes and more than 30 alcohols were converted in high yield and selectivity to the corresponding diesters (Fig. 3). For example, several linear conjugated dienes **1a** to **1f** showed excellent reactivity and regioselectivity. Even for internal conjugated double bonds (**1f**), isomerization reactions led preferentially to the terminal products. Increased steric hindrance on the carbon chain, including a tetra-substituted conjugated diene, influenced the reactivity; however, the regioselectivity to the corresponding linear diesters remained very high (**1g** to **1k**). 1-Phenyl–substituted 1,3-diene **1l**, for which the regioselectivity might be more difficult to control, afforded excellent 1,4-site selectivity. Using myrcene **1m** as an exemplary inexpensive, widely available natural diterpene, tri-alkoxycarbonylation was achieved smoothly. In addition to conjugated 1,3-dienes, 1,2-dienes **1n** and **1o** were converted to the corresponding linear diesters with similar activity and regioselectivity.

Numerous aliphatic alcohols (products **4p** to **4z** and **5a** to **5h**) were also tolerated by the catalyst system and gave diesters in high yields and selectivity (>93%). Various functional groups (products **5m** to **5p**)—including electron-withdrawing fluorine, chlorine, and trifluoromethyl, as well as electron-donating methoxy—were compatible. Furthermore, a heterocyclic derivative (**5q**) and hydroxylated natural products [(L)-menthol, (L)-borneol, and cholesterol] yielded the desired products with high regioselectivity.

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SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/366/6472/1514/suppl/DC1
Materials and Methods
Figs. S1 to S4
Tables S1 to S9
NMR and HRMS Spectra
References (*49*–*52*)

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A carbonylation path to a nylon precursor

Adipic acid and its esters are manufactured on a massive scale, primarily to produce nylon. However, the standard route requires large quantities of corrosive nitric acid. J. Yang *et al.* present an efficient alternative route whereby a palladium catalyst adds carbon monoxide to each end of butadiene (see the Perspective by Schaub). Both reactants are available at commodity scale, and the reaction produces no by-products. An optimized bidentate phosphine ligand bearing a pyridine substituent for proton shuttling proved key to attaining the necessary selectivity.

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