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Palladium Catalysis

Efficient Synthesis of Novel Plasticizers by Direct Palladium-Catalyzed Di- or Multi-carbonylations

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Dedicated to Dr. Christian Bruneau on the occasion of his 70th birthday

Abstract: Diesters are of fundamental importance in the chemical industry and are used for many applications, e.g. as plasticizers, surfactants, emulsifiers, and lubricants. Herein, we present a straightforward and efficient method for the selective synthesis of diesters via palladium-catalyzed direct carbonylation of di- or polyols with readily available alkenes. Key-to-success is the use of a specific palladium catalyst with the "built-in-base" ligand **L16** providing esterification of all alcohols and a high *n/iso* ratio. The synthesized diesters were evaluated as potential plasticizers in PVC films by measuring the glass transition temperature (T_g) via differential scanning calorimetry (DSC).

Introduction

Organic polymers find various applications in our daily life such as transportation, clothing, and communication.[1] Undoubtedly, they represent most important products of the chemical industry. In general, the specific property of a polymer is based on the respective feedstock(s) (monomers) and the process conditions including catalysts. In addition, utilization of various additives can significantly modify material features of plastics, for example, hardness, elastic modulus, viscosity, density, flexibility, durability, and so on. In this way, the applications of a given polymer material are significantly broadened.[2] Amongst the various additives, so-called plasticizers represent the most common class of compounds.[3] More specifically, the global annual production of plasticizers was around 6.4 million tons during the last decade.[4] By 2026, the worldwide demand of the plasticizers market is projected to reach $10.5 billion annually, which corresponds to more than 13.2 million tons per year.[5] Notably, the production of polyvinyl chloride (PVC) plastics accounts for about 80 % of all plasticizers produced.[6] Until now, the most commercially used plasticizers are phthalate diesters.[7] They are odorless liquids produced by reacting phthalic anhydride, phthaloyl chloride, or phthalic acid with an appropriate alcohol (Figure 1a). Phthalates are known as endocrine disruptors with potential adverse effects on heart, lung, liver, kidney, and reproductive systems in humans. Besides, they are toxic to aquatic life. Therefore, the use of plasticizer phthalates has been restricted in several countries.[8] Particularly, both European and American regulations banned phthalic diesters for content above 0.1 wt % in flexible PVC products.[4] Hence, the development of alternative non-phthalate based plasticizers is highly desired and remains an important topic in industry.[9] Indeed, the market for phthalate-free plasticizers is continuously increasing.[5,10] For example, several companies including BASF and Evonik provide diisononyl cyclohexane-1,2-dicarboxylate, which is obtained from the catalytic hydrogenation of the corresponding phthalate (Figure 1). However, diisononyl cyclohexane-1,2-dicarboxylate also features toxicity and is therefore labelled as regrettable

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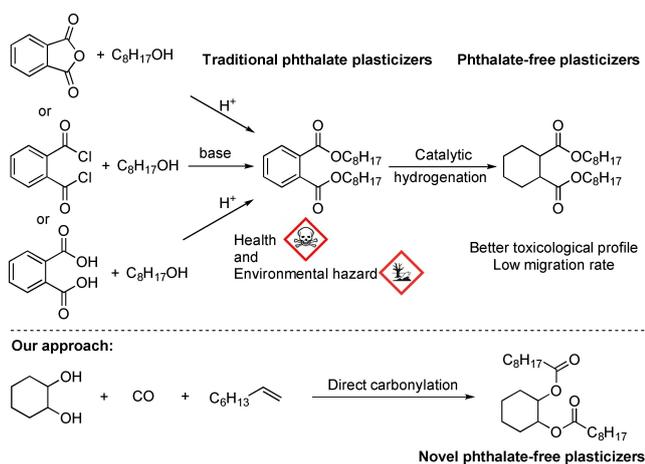[+] These authors contributed equally to this work.

Figure 1. Phthalate and phthalate-free plasticizers via catalytic hydrogenation vs. structurally related potential novel phthalate-free plasticizer via direct carbonylation.

Figure 2. Access to potential novel phthalate-free plasticizers.
a) Conventional synthesis of diesters from diols and acyl chlorides.
b) Known Pd-catalyzed carbonylation of diols with olefins only resulted in monoesters. c) This work: Straightforward synthesis of diesters via Pd-catalyzed direct dicarbonylation of diols with olefins.

substitution. Moreover, to access this non-phthalate plasticizer an additional hydrogenation step is needed.

Considering the mechanism of plasticization,[3,4] we assumed that structurally related diesters of cyclic diols and aliphatic carboxylates might have similar properties and offer great potential as non or less toxic plasticizers. It should be noted that in this approach the position of the carbonyl group is reversed (Figure 1). However, this simple structural change allows to efficiently synthesize a plethora of potential plasticizers by atom-efficient carbonylations. Conventional methods of 1,2-cyclohexanediol diester synthesis are esterification reactions of the diol with long-chain fatty acids available from vegetable oils, or the nucleophilic substitution reaction of acyl chlorides with the diol (Figure 2a). However, those approaches are often limited by the carboxylic acid source. For example, hydrolysis of renewable triglycerides yields only specific long-chain carboxylic acids.[11] The paraffin oxidation to carboxylic acids suffers from moderate product yields due to non-selective formation of acid mixtures.[12] Besides, C_4–C_{11} carboxylic acids are produced from alkenes by hydroformylation reaction with syngas,[13] and subsequent oxidation.[14]

Palladium-catalyzed alkoxycarbonylation reactions allow for a straightforward access to esters directly from readily available and low-cost olefins, carbon monoxide and alcohols. This transformation represents an important synthetic method both in organic synthesis and industry.[15] So far, this reaction has been widely investigated to produce monoesters.[16] Instead, multiple carbonylations of di- or polyols with olefins to get access to di- or multi-esters has been largely neglected. As an exception, Mecking and co-workers studied the alkoxycarbonylation of ethylene with carbon monoxide and cellulose.[17]

Later on, the Sauthier group reported the synthesis of several diesters from isosorbide, isomannide, and isoidide by using a $Pd(OAc)_2$/PPh_3/PTSA catalytic system. Notably, when applying other 1,2- and 1,3-diols, mixtures of mono- and dicarbonylated products were obtained (Figure 2b).[18]
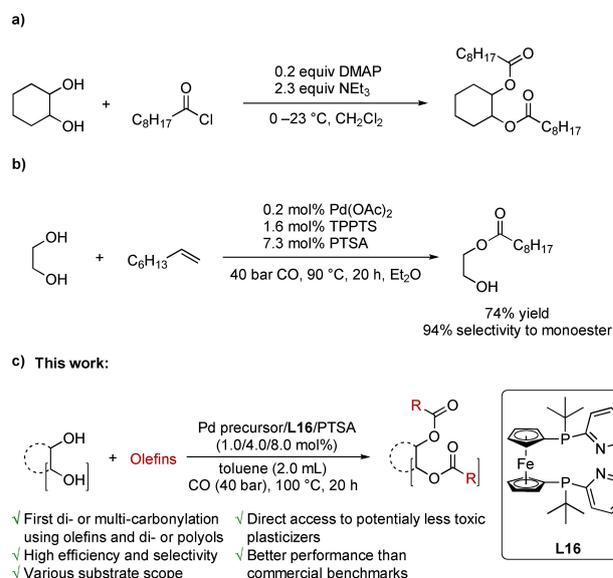
Obviously, this is a general challenge for all such transformations as the obtained product mixtures are difficult to separate. Previously, our group reported the dialkoxycarbonylation of 1,n-diols with conjugated 1,3-dienes to access a series of β,γ-unsaturated esters by using $Pd(COD)Cl_2$/XantPhos as the catalyst.[19] In addition, Sauthier and coworkers described the $Pd(OAc)_2$/PPh_3/benzoic acid catalyzed carboxytelomerization of 1,3-butadiene with bio-based polyols to synthesize unsaturated alkyl nona-3,8-dienoates.[20]

Based on our long-term interests in carbonylation reactions, herein we present the development of the first general applicable palladium catalyst system for the direct di- or multi-carbonylation of di- or polyols respectively with olefins, rather than conjugated dienes, providing di/polyester formation exclusively with high n/iso ratio (Figure 2c). The reactions proceed in general in high yields and selectivity. Selected diester products show interesting and promising properties as industrially relevant plasticizers.

Results and Discussion

At the beginning of our work, *trans*-1,2-cyclohexanediol (**1a**, 1 mmol) and 1-octene (**2a**) were chosen as model substrates for studying Pd-catalyzed dicarbonylations in the presence of different ligands and PTSA as acid co-catalyst (Table 1). In general, two equivalents of 1-octene were used as substrate and octene isomers were observed as side-products in the reaction mixtures. Notably, no clear relationship between ligand structure and catalyst activity as well as regioselectivity was observed. For example, typical monophosphines (**L1**–**L4**) provided diester **4aa** as the main

Table 1: Palladium-catalyzed dicarbonylation of *trans*-1,2-cyclohexane-diol **1a** with 1-octene **2a**: Ligand screening.
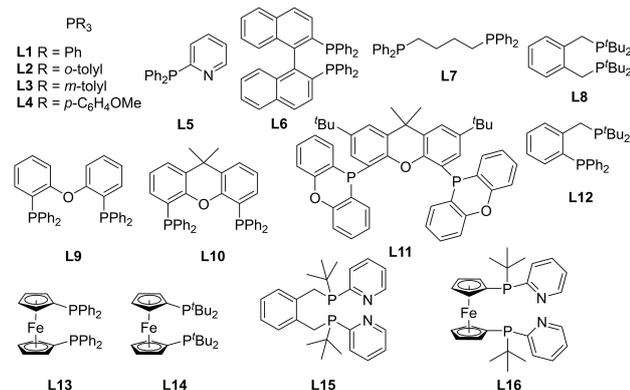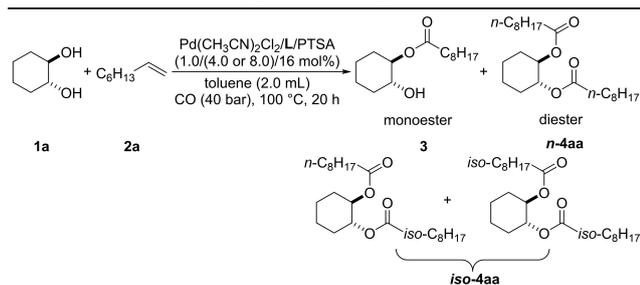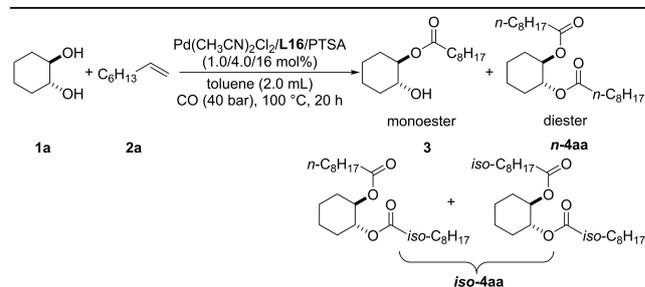

Entry	Ligand	Conversion **1a** [%]	Yield **3** [%] (*n/iso*)	Yield **4aa** [%] (*n/iso*)
1	**L1**	99	5 (84/16)	82 (45/55)
2	**L2**	46	11 (91/9)	28 (12/88)
3	**L3**	99	trace	84 (50/50)
4	**L4**	99	trace	90 (49/51)
5	**L5**	82	47 (37/63)	22 (22/78)
6	**L6**	68	45 (70/30)	4 (63/37)
7	**L7**	21	12 (1/99)	trace
8	**L8**	69	19 (81/19)	35 (62/38)
9	**L9**	90	70 (65/35)	18 (88/12)
10	**L10**	99	trace	81 (55/45)
11	**L11**	98	trace	88 (58/42)
12	**L12**	Trace	trace	0
13	**L13**	89	59 (83/17)	25 (62/38)
14	**L14**	57	51 (20/80)	3 (31/69)
15	**L15**	97	33 (93/7)	56 (90/10)
16	**L16**	99	4 (85/15)	89 (87/13)

Reaction conditions: **1a** (1.0 mmol), **2a** (4.0 mmol), Pd(CH$_3$CN)$_2$Cl$_2$ (1.0 mol%), monodentate ligand **L1–L5** (8.0 mol%) or bidentate ligand **L6–L16** (4.0 mol%), PTSA (16 mol%), CO (40 bar), toluene (2.0 mL), 100 °C, 20 h. The conversion of **1a**, yields of **3** and **4aa**, and ratios of *n/iso* isomers were determined by GC analysis using isooctane as the internal standard.

product with yields 28–90 %; however, the catalytic system didn't show any *n/iso* selectivity in the product formation (Table 1, entries 1–4). Monoester **3** was only formed as a minor product. In contrast, using Drent's ligand **L5**, the formation of **4aa** was decreased accompanied by an increased *n/iso* selectivity, and **3** was observed as the major product (Table 1, entry 5). Next, a selection of well-known bidentate phosphorus ligands was investigated. By using BINAP **L6** and alkyl chain-backboned ligand DPPB **L7**, monoester **3** was obtained as the major product with <5 %

4aa (Table 1, entries 6–7). Notably, d^{r}bpx **L8**, which is currently used for ethylene alkoxycarbonylation on multi-100 000 ton-scale,[21] afforded a mixture of **3** and **4aa** with moderate *n/iso* selectivity (Table 1, entry 8). DPEphos **L9**, which is also a widely used ligand in carbonylation reactions, provided high conversion of **1a**. Unfortunately, again a product mixture of **3** and **4aa** was attained, with **4aa** as the minor one (Table 1, entry 9). Interestingly, both Xantphos **L10** and its analogue **L11** showed high activity for the double carbonylation process and fully converted **1a** into the desired product **4aa** with yields 81 and 88 %, but both showed low *n/iso* selectivity (Table 1, entries 10–11). On the other hand, only trace conversion of **1a** was observed when applying **L12** (Table 1, entry 12). In addition, the ferrocenyl-backboned ligands **L13** and **L14** as well as the d^{r}bpx analogue **L15** gave no satisfactory results (Table 1, entries 13–15). Finally, a breakthrough was achieved when applying **L16**. Only this ligand provided **4aa** in high yield (89 %) and *n/iso* selectivity (87/13) (Table 1, entry 16).

Further explorations of the reaction conditions applying this optimal ligand **L16** (Supporting Information, Tables S2–4) revealed similar reactivity and selectivity in the model reaction for both Pd^{II} and Pd^0 precursors (Table 2, entries 1–3). In the presence of other strong acidic co-catalysts, a decrease in yield and/or selectivity was observed (Supporting Information, Table S5) and the best results can be obtained with 8 mol% PTSA (**4aa**: 93 % yield, 90/10 selectivity; Table 2, entry 6). Apart from toluene, various solvents were tested. When using the non-polar solvent

Table 2: Palladium-catalyzed dicarbonylation of *trans*-1,2-cyclohexane-diol **1a** with 1-octene **2a**: Variation of reaction conditions.

Entry	Variation of "standard conditions"	Conversion **1a** [%]	Yield **3** [%] (*n/iso*)	Yield **4aa** [%] (*n/iso*)
1	Pd(acac)$_2$ as [Pd]	99	trace	92 (87/13)
2	Pd$_2$(dba)$_3$ as [Pd]	99	trace	89 (87/13)
3	PdCl$_2$ as [Pd]	99	trace	93 (87/13)
4	CF$_3$SO$_3$H as acid	99	5 (72/28)	89 (79/21)
5	H$_2$SO$_4$ as acid	99	22 (93/7)	71 (89/11)
6	PdCl$_2$ as [Pd], and 8.0 mol% PTSA	99	trace	93 (90/10)
7	Heptane as solvent	96	48 (95/5)	41 (94/6)
8	MeCN as solvent	72	50 (81/19)	5 (78/22)
9	THF as solvent	99	13 (79/21)	74 (76/24)

Reaction conditions: **1a** (1.0 mmol), **2a** (4.0 mmol), [Pd] (1.0 mol%), **L16** (4.0 mol%), co-cat. acid (8.0 or 16 mol%), CO (40 bar), solvent (2.0 mL), 100 °C, 20 h. The conversion of **1a**, yields of **3** and **4aa**, and ratios of isomers were determined by GC analysis using isooctane as the internal standard.

heptane, high conversion of **1a** and excellent *n/iso* selectivity were achieved; however, **3** and **4aa** were obtained in similar amount (Table 2, entry 7). In contrast, in MeCN only moderate conversion was observed, and the monoester **3** was attained as the major product (Table 2, entry 8). In THF full conversion of **1a** was reached, but both formation of **4aa** and *n/iso* selectivity decreased compared to toluene (Table 2, entry 9).

Obviously, the physical properties of any plasticizer are strongly related to its molecular structure.[22] By variation of di- or polyols as well as olefins, a broad selection of potential candidates can be easily prepared. Hence, under the optimized reaction conditions, several di- and multi-carbonylations were performed (Scheme 1). To the best of our knowledge, none of those carbonylation reactions has been disclosed before.

Related to the model substrate **1a**, its *cis*-isomer **1b** was converted in a reaction with 1-octene (**2a**) in a similar yield and regioselectivity to **4ba**, revealing that this reaction is not influenced by the stereochemistry of the substrate. Comparably, other 1,3- and 1,4-cyclohexanediols were also fully converted, and the corresponding diesters *cis*-**4ca**, *trans*-**4ca**, *cis*-**4da**, *trans*-**4da** were isolated in good to excellent yields (87–96 %) with good regioselectivities. In addition, cyclic compounds, like *trans*-1,2-cyclopentanediol **1e** and *cis*-1,2-cyclooctanediol **1f** can be converted in a straightforward manner leading to diesters **4ea** and **4fa** in similar yields and selectivities after isolation. 1,n-diols with linear backbones represent an important class of compounds, and the produced diesters are of interest for further applications.[9,22c,23] Simple but industrially highly important ethylene glycol reacted smoothly without further optimization and the diester **4ga** was isolated in 80 % yield with

83/17 selectivity. Glycols with longer chains (C3 to C10) **1h**–**1l** reacted smoothly under the standard reaction conditions, giving the corresponding diesters **4ha**–**4la** in excellent yields (>94 %) and high regioselectivities, respectively.

Besides primary diols, secondary alcohols, which are more sterically hindered, were also tested. Using 1,2-propanediol **1m** as the parent substrate, the corresponding diester **4ma** was isolated in 87 % yield with 81/19 selectivity. Similar yield and selectivity were obtained with the longer chain 1,5-hexanediol substrate **1n**. Slightly lower yields were attained with hexyl- (**1o**), phenyl- (**1p**) or chloromethyl- (**1q**) substituted ethylene diol, but the selectivity remained very good. The methyl substituted 1,3-diol **1r** was also tested. To our delight, the corresponding diester **4ra** was obtained smoothly, too. As mentioned above,[17,19,20] only rare examples have been reported for multi-carbonylation reactions using polyols. Thus, selected polyols were also investigated applying this optimized catalytic system. As an example, glycerol can be converted into the corresponding triester **4sa** in 63 % yield with 73/27 *n/iso* selectivity. Glycerol is widely available as the major by-product in the manufacturing of biodiesel,[24] and the use of glycerol as the feedstock for preparing value-added products is therefore an attractive goal. Furthermore, even the tetraol pentaerythritol **1t** can be fully converted, and the corresponding tetraester **4ta** was isolated in 60 % yield with 72/28 *n/iso* selectivity. Bio-based erythritol[25] **1u** was also tested under the standard reaction conditions; however, in this case a mixture of mono-, di-, tri- and tetra-carbonylative products were obtained. Interestingly, when switching the olefin from 1-octene to 1-pentene, the tetraester **4ub** was obtained in 71 % yield. Finally, isosorbide **1v**, representing an industrially important chiral bicyclic diol[26] which has been used as a
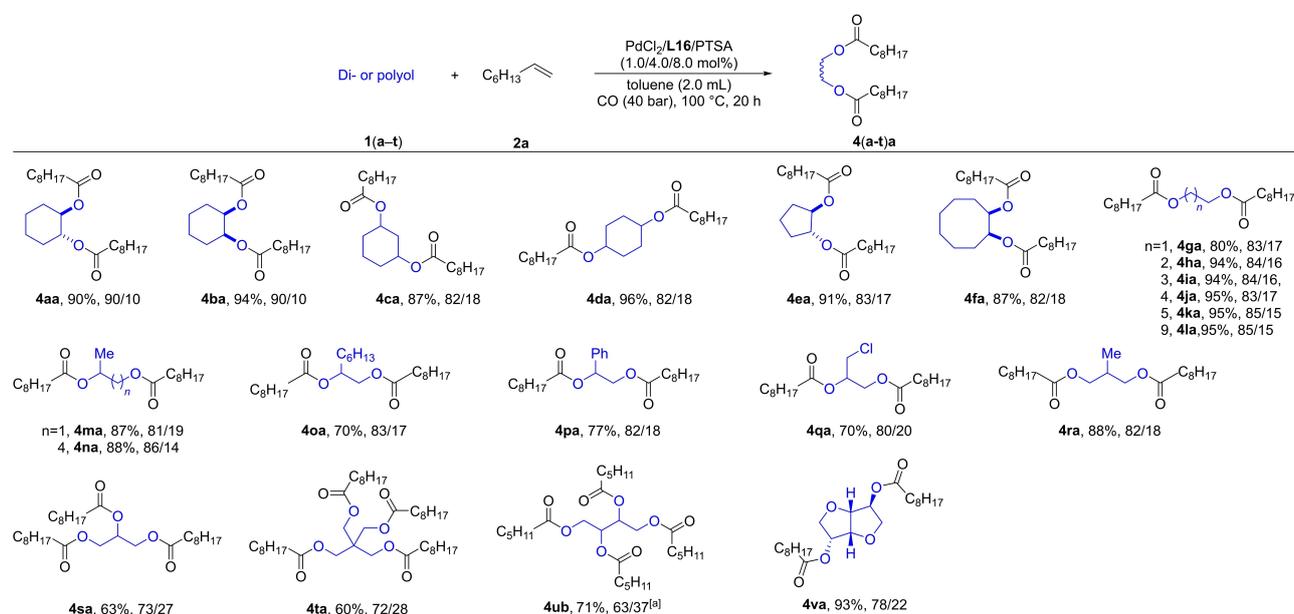
Scheme 1. Palladium-catalyzed di- and multi-carbonylations with 1-octene **2a** as the model substrate: Scope of di- or polyols. Reaction conditions: **1** (1.0 mmol), **2a** (4.0 mmol for **1a–r** and **1v**, 6.0 mmol for **1s**, and 8.0 mmol for **1t** and **1u**), PdCl₂ (1.0 mol %), **L16** (4.0 mol %), PTSA (8.0 mol %), CO (40 bar), toluene (2.0 mL), 100 °C, 20 h. Isolated yield. Ratios of isomers were determined by GC analysis using isooctane as the internal standard.[a] 1-Pentene **2b** instead of 1-octene **2a**.
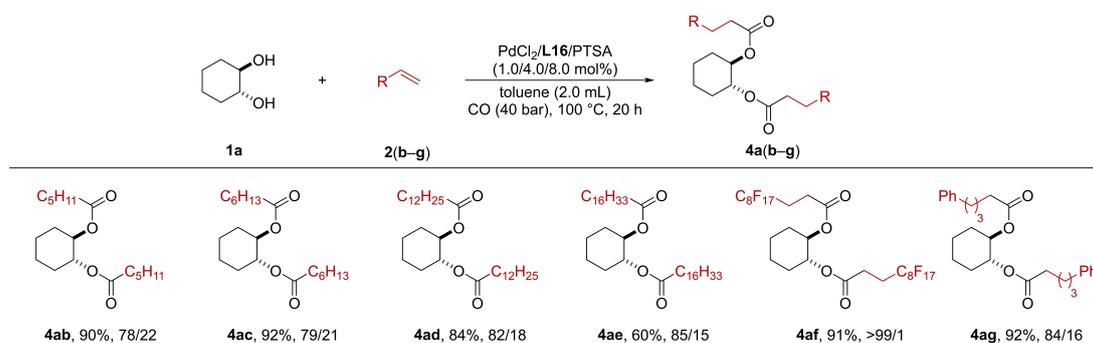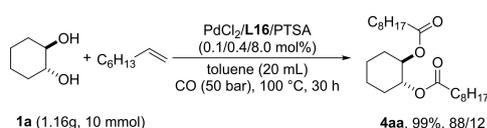
Scheme 2. Palladium-catalyzed dicarbonylation with *trans*-cyclohexane-1,2-diol as the model substrate: Scope of alkenes **2**. Reaction conditions: **1a** (1.0 mmol), **2** (4.0 mmol), PdCl$_2$ (1.0 mol%), **L16** (4.0 mol%), PTSA (8.0 mol%), CO (40 bar), toluene (2.0 mL), 100°C, 20 h. Isolated yield. Ratios of isomers were determined by GC analysis using isooctane as the internal standard.

precursor for the production of bio-based plasticizers,[27] is also compatible in this synthetic method, and the corresponding diester **4va** was isolated in 93% yield.

Subsequently, applying *trans*-1,2-cyclohexanediol (**1a**) a variety of olefins were tested under the standard reaction conditions (Scheme 2). Terminal olefins with varying chain length (**2b–e**) reacted smoothly to the corresponding diesters **4a(b–e)** in moderate to good yields with very good selectivity. Utilizing the fluorinated olefin **2f**, the corresponding linear diester **4af** was isolated in 91% yield with complete *n/iso* selectivity. Such compounds are of potential use as special plasticizers for fluoride-based polymer materials.[28] The reaction also went smoothly with a phenyl-substituted aliphatic olefin towards the corresponding diester **4ag** in excellent yield and selectivity. Furthermore, an internal alkene, i.e. 2-octene was tested, however, in this case no dicarbonylation occurred under the present reaction conditions.

In addition, the productivity of the optimal catalyst system was investigated by lowering the metal loading. In the presence of only 0.1 mol% palladium, the diester **4aa** was obtained in 90% yield with 89/11 *n/iso* selectivity (Supporting Information, Table S7). This reaction was easily scaled up to gram-level with 0.1 mol% catalyst loading and the diester was synthesized in 99% yield with 88/12 (*n/iso*) selectivity (Scheme 3).

As mentioned in the introduction, plasticized PVC has numerous industrial, technical, and everyday applications, such as in transport, building, packaging, electrical and life science applications.[29] Thus, the plasticizing effect of several prepared diesters **4** was tested for PVC. Since the primary role of plasticizers is to enhance the flexibility and the processability of plastics by decreasing the glass transition temperature (T_g), here the T_g is used as a preliminary

measure to evaluate the properties of those diesters via DSC measurement. Firstly, unplasticized PVC was measured as the reference (Table 3, entry 1), a T_g at 84.3°C was observed, which corresponds to known literature.[30] Next, commercial plasticizers and representative synthesized diesters were selected and blended with PVC at 10 wt% loading. Notably, all most tested diesters can be derived from renewables and their plasticizing properties are unexplored. Currently applied commercial plasticizers such as DINCH, DEHP, Octicizer, and DEHA showed glass transition temperatures between 56.0–75.9°C (Table 3, entries 2–5). Diesters derived from *trans*- and *cis*-1,2-cyclohexanediol (**4aa**, **4ba**, **4ac**, **4ad**) already decreased the T_g of the blended PVC, but to a less extent compared to most of the commercial derivatives (Table 3, entries 6–9). Interestingly, regioisomeric esters derived from 1,3- (*trans*- and *cis*-**4ca**) and 1,4-cyclohexanediols (*trans*- and *cis*-**4ad**), which are available from resorcinol or hydroquinone, provided better performances (Table 3, entries 10–13). Among them, the *trans*-**4ca** derived from 1,3-cyclohexanediol was found to be the best plasticizer candidate with the lowest T_g at 53.4°C (Table 3, entry 10). Notably, its performance is even better than the tested commercial benchmark plasticizers. Besides, C$_9$ esters with different ring sizes were studied and both

Scheme 3. Palladium-catalyzed dicarbonylation with *trans*-1,2-cyclohexanediol: Gram-level scale-up reaction.

Table 3: Thermal properties of neat PVC and PVC blends containing 10 wt% commercial benchmarks and synthesized plasticizer candidates **4**.

Entry	PVC and PVC blends	T_g [°C]	Entry	PVC and PVC blends	T_g [°C]
1	PVC	84.3	9	**4ad**	67.8
2	DINCH	57.7	10	*trans*-**4ca**	53.4
3	DEHP	56.0	11	*cis*-**4ca**	65.6
4	Octicizer	58.8	12	*trans*-**4da**	61.5
5	DEHA	75.9	13	*cis*-**4da**	59.7
6	**4aa**	66.5	14	**4ea**	59.4
7	**4ba**	75.8	15	**4fa**	57.1
8	**4ac**	80.8	–	–	–

Abbreviations/chemical names: DINCH (diisononyl 1,2-cyclohexane dicarboxylate), DEHP (di-2-ethylhexyl phthalate), Octicizer (2-ethyl-hexyl diphenyl phosphate), and DEHA (di(2-ethylhexyl) adipate).
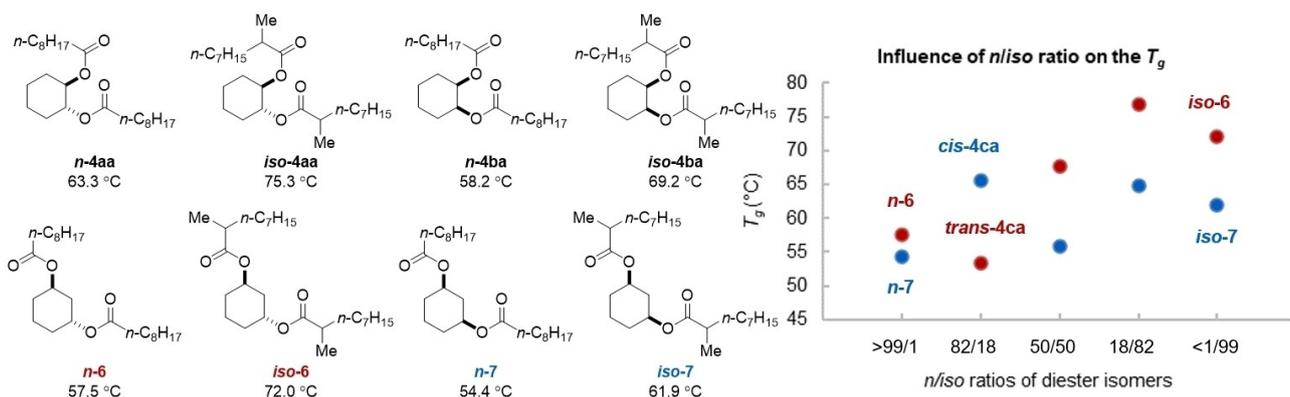
Figure 3. Synthesis of diesters as potential phthalate-free plasticizers. a) Pure *n*- and *iso*-isomers of diesters derived from *trans*- and *cis*-1,2- and 1,3-cyclohexanediols. b) Influence of different *n/iso* ratios on T_g values for mixtures of *n*-**6** and *iso*-**6**, and *n*-**7** and *iso*-**7**, respectively. *cis*-**4ca** and *trans*-**4ca** are mixtures of *n:iso* 82:18 as obtained from **4ca** via column chromatography (see Scheme 1).

esters **4ea** and **4fa** gave low T_g values (57.1–59.4 °C, Table 3, entries 14 and 15).

To study the impact of the degree of branching in the alkyl chain of the ester on the plasticization process,[31] pure *n*-/*iso*-diesters derived from *trans*-/*cis*-1,2-cyclohexanediols (*n*-**4aa**, *iso*-**4aa**, *n*-**4ba**, and *iso*-**4ba**) and 1,3-cyclohexane-diols (**4ca**, *n*-**6**, *iso*-**6**, *n*-**7**, and *iso*-**7**) were independently prepared, and their performances were investigated. As shown in Figure 3a, all those diesters showed plasticizing effects in PVC. PVC films blended with diesters derived from linear isomers always displayed lower T_g values compared to ones from branched isomers.

Finally, the influence of different *n/iso* ratios on T_g values for **4ca** isomers was studied as our protocol directly provides mixtures. As shown in Figure 3b, the blue dots are T_g values of PVC containing different *n/iso* ratios of *cis*-isomers of **4ca**, and the red dots are those of *trans*-isomers of **4ca**. Notably, the diester directly synthesized by dicarbonylation featuring an *n/iso* ratio of 82/18 provided the best performance in PVC for *trans*-**4ca**, while this is the reverse for *cis*-**4ca**. This interestingly shows that small amounts of another regioisomer impact the plasticizer properties significantly.

Conclusion

In conclusion, we present a new state-of-the-art palladium catalyst system for efficient and selective synthesis of di- or multi-esters from the corresponding alcohols. Key-to-success is the use of **L16**, which allows such transformations under otherwise typical carbonylation conditions. For the first time, a range of industrially important olefins directly react with a variety of di- and polyols including bio-based ones to give di- or multi-esters in good to very good yields with high *n/iso* selectivity. Representative examples of the synthesized diesters were evaluated as plasticizers in PVC films. All tested compounds showed plasticizing effects with decreased glass transition temperature (T_g) values of the plasticized

PVC films. Remarkably, the diester *trans*-**4ca** prepared by our method performs even better than commercial products, indicating that small amounts of *iso*-regioisomers significantly influence the plasticizing properties. In general, the presented catalytic system allows producing non-phthalates plasticizer analogues in straightforward manner under mild reaction conditions. We believe this work will inspire the development of more environmentally friendly and sustainable plasticizers in the future.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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