Palladium Catalysis

Efficient Palladium-Catalyzed Carbonylation of 1,3-Dienes: Selective Synthesis of Adipates and Other Aliphatic Diesters

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Abstract: *The dicarbonylation of 1,3-butadiene to adipic acid derivatives offers the potential for a more cost-efficient and environmentally benign industrial process. However, the complex reaction network of regioisomeric carbonylation and isomerization pathways, make a selective and direct transformation particularly difficult. Here, we report surprising solvent effects on this palladium-catalysed process in the presence of 1,2-bis-di-tert-butylphosphin-oxylene (dtbpx) ligands, which allow adipate diester formation from 1,3-butadiene, carbon monoxide, and methanol with 97 % selectivity and 100 % atom-economy under scalable conditions. Under optimal conditions a variety of di- and triesters from 1,2- and 1,3-dienes can be obtained in good to excellent yields.*

Introduction

Due to its availability and low price, carbon monoxide is a central intermediate in the chemical industry that is easily produced from fossil-based resources (coal, gas).[1] In the future, an increasing amount can be available from renewables (CO_2 or bio-waste).[2] Among the different carbonylations, specifically reactions of olefins with CO constitute the important applications of industrial homogeneous catalysis.[1,3] In fact, nowadays more than 10 million tons of carbonyl compounds, especially aldehydes via hydroformylation, are produced annually for many consumer products. In addition, the so-called alkoxycarbonylation reaction allows an atom-efficient access of esters and was industrially imple-

mented in the Lucite process as a reaction step for the methyl methacrylate process.[4]

Although the underlying reactions are known for nearly eighty years,[5] still important catalyst challenges exist in this area, for example, the direct dicarbonylation of 1,3-butadiene to give selectively adipate esters, which are intermediates for bulk polyamides and polyesters produced on multi-million ton-scale.[6] Currently, adipate diesters are used for plasticizers, perfumes, lubricants, solvents, several active pharmaceutical ingredients (API's), and with respect to scale most importantly for the production of polyamides (nylon).[7] So far, adipate diesters are mainly produced in industry by oxidation of a mixture of cyclohexanol and cyclohexanone (so-called KA-oil) with an excess of nitric acid, followed by esterification with the corresponding alcohols (Scheme 1a).[6a,8] Due to the corrosiveness of the mixture, this process requires special equipment, and produces stoichiometric amounts of nitrous oxide (N_2O), which has nearly 300 times the atmospheric heat-trapping capacity of CO_2.[9]

Due to the intrinsic problems of the present process and the potential benefits of a direct dicarbonylation process, several companies all over the world including BASF,
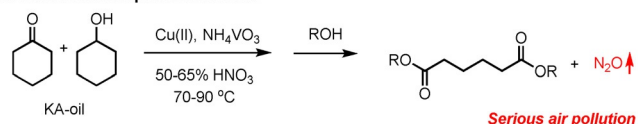
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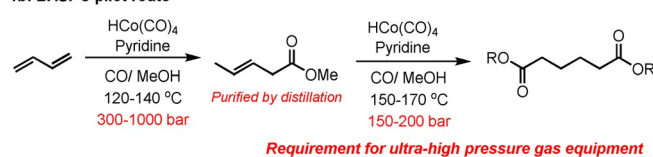Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum
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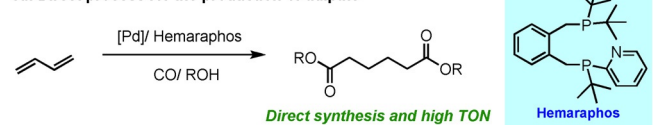
Scheme 1. Selected processes for making alkyl adipates.

Dupont, Shell, Dow, Kuraray and Sinopec investigated the synthesis of adipate esters from 1,3-butadiene.[10] Nevertheless, no industrially viable process has been developed yet, although some pilot facilities involving at least two-step reactions were realized (Scheme 1b and c).[12] Most notable, Drent and co-workers described a single-pot dimethoxycarbonylation of 1,3-butadiene in the presence of a single catalytic system.[10k] A drawback of these processes is the low regioselectivity for the desired linear diester, although high selectivity has been obtained in related hydroxycarbonylations.
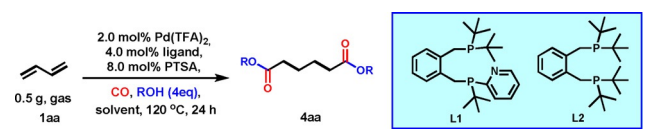
Recently, we discovered that a particular bidentate phosphine ligand (HeMaRaPhos) **L1** allowed the palladium-catalyzed dicarbonylation of 1,3-butadiene towards dialkyl adipates in $\geq 95\%$ yield and $\geq 97\%$ selectivity (Scheme 1d).[12] Crucial for the success of this ligand is the intrinsic basic pyridyl substituent combined with a *tert*-butyl group on one of the phosphorous atoms, which proved to be essential for high activity in other palladium-catalyzed alkoxycarbonylation reactions too.[13]

In order to understand the different reactivity of HeMaRaPhos and 1,2-bis-di-*tert*-butylphosphinoxylene (**L2**, d*t*bpx), we re-investigated the reactivity of the latter system in more detail. Notably, **L2** is commercially used in the alkoxycarbonylation of ethylene (Lucite α-process)[4] and can be considered as a benchmark ligand for such reactions. In our study, we discovered a peculiar solvent effect, which laid the basis for a new protocol for direct dicarbonylation of 1,3-butadiene and related dienes in the presence of several palladium catalyst systems.

Results and Discussion

At the beginning of this work, we compared the dicarbonylation of 1,3-butadiene with industrially most relevant methanol and *n*-butanol in the presence of Pd(TFA)$_2$ and

HeMaRaPhos **L1** or d*t*bpx **L2** under previously optimized conditions (120°C, 40 bar CO with *p*-toluenesulfonic acid as a co-catalyst; Table 1). As expected in the presence of **L1** both reactions worked well and the desired esters were obtained after 24 h in 86/85% yield and 97% selectivity (Table 1 entries 1–2). Surprisingly, applying **L2** at similar conditions a significantly different performance was observed depending on the alcohol used (Table 1, entries 3–4). In case of methanol, no desired dicarbonylation was detected and no conversion took place at all. A similar behavior was observed using ethanol and *n*-propanol (Figure S4). In contrast, using *n*-butanol the corresponding di-*n*-butyl diester was obtained in 80% yield and 98% selectivity. For the performance of other alcohols see Figure S4. To understand this unusual behavior, the reaction of 1,3-butadiene with methanol was performed in different solvents (Table 1, entries 5–11). All these experiments were completed in the presence of 4 equiv of methanol. We first tested toluene, which is frequently used in carbonylation reactions and were surprised to observe the desired product in substantial amount. In fact, simply the addition of toluene led to 80% of **4aa** with 97% selectivity compared to the originally non-reactive system.

Similarly, in the presence of tetrahydrofuran, heptane, and dichloromethane, product **4aa** is formed, albeit in lower yield. Other co-solvents such as ethyl acetate and acetonitrile only led to traces of **4aa**. As toluene gave the best result among the tested solvents, the influence of the toluene concentration on the mono- and dicarbonylation process was investigated in more detail. As shown in Figure 1, our recently developed palladium catalyst system with **L1** is very robust and not affected by the concentration of methanol. Consequently, product yields between 80 and 85% were obtained. On the other hand, the catalyst with **L2** is very sensitive with respect to the methanol concentration and the product yield of **4aa** is increased with decreasing methanol concentration. Comparing the kinetic behavior of both catalyst systems, some peculiar differences became apparent (Figure 2). The one containing d*t*bpx **L2** shows a prolonged induction period (6–8 h), while in the presence of **L1** in the first two hours **3aa**
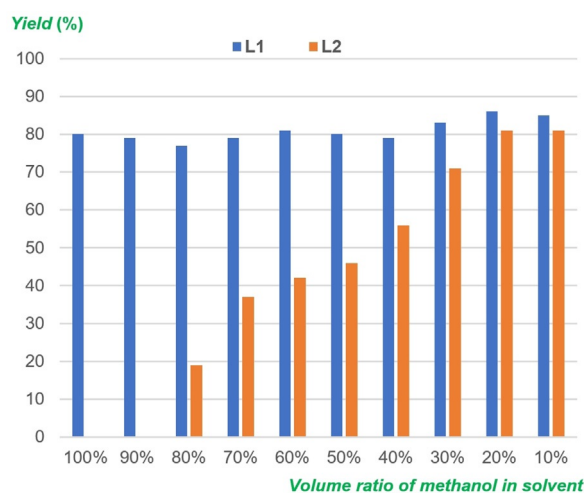
Table 1: Pd-catalyzed alkoxycarbonylation of 1,3-butadiene with methanol and butanol: Variation of solvents.

Entry	Ligand	Solvent	Yield [%]	Selectivity (*n*-/*iso*-)
1	**L1**	MeOH	86	97/3
2	**L1**	*n*BuOH	85	97/3
3	**L2**	MeOH	0	–
4	**L2**	*n*BuOH	80	98/2
5	**L2**	toluene	80	97/3
6	**L2**	THF	62	96/4
7	**L2**	heptane	25	97/3
8	**L2**	MeCN	0	–
9	**L2**	CH$_2$Cl$_2$	31	96/4
10	**L2**	EtOAc	trace	–
11	**L2**	toluene:MeCN (1:1)	18	97/3

For reaction conditions and more details, see Supporting Information, Section 3.8, Table S7.

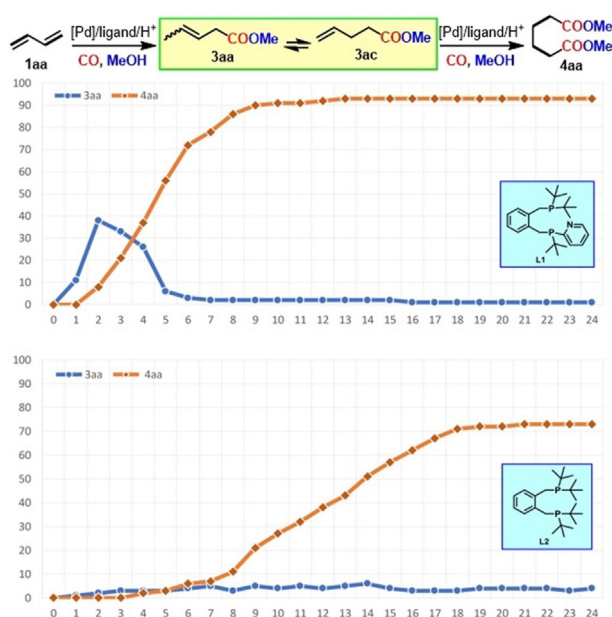***Figure 1.*** Pd-catalyzed alkoxycarbonylation of 1,3-butadiene with methanol in toluene.

Figure 2. Kinetic monitoring experiments. Notes: The X-axis represents time and the Y-axis represents yield. Conditions: Using 100 ml autoclave with sampling function: 1,3-butadiene (gas, 1 g, 18.5 mmol), Pd(TFA)$_2$ (1.0 mol%), HeMaRaPhos or d*t*bpx ligand (2.0 mol%), PTSA·H$_2$O (4.0 mol%), MeOH (4 equiv to 1,3-butadiene), toluene (27 mL), CO (40 atm), 120°C; the yields were determined by GC analysis.

Figure 3. Pd-catalyzed alkoxycarbonylation of 1,3-butadiene with methanol: Variation of ligands.

is mainly formed, which afterwards rapidly is converted to the desired adipate **4aa**.

Next, we were interested to find out if this unexpected solvent effect on 1,3-butadiene dicarbonylation is also observed in the presence of other ligands. Hence, more than 20 standard mono- and bidentate phosphines were tested in this industrially highly relevant process (Scheme S1); however, only using ligands with the 1,2-bis(methyl)benzene backbone gave substantial amounts of the targeted dicarbonylation products. Thus, in case of the adamantly-substituted phosphine **L5** also an increase of the product yield of **4aa** with decreasing methanol concentration is observed (Figure 3).

To understand the origin of this dramatic reactivity difference depending on the methanol concentration a closer look on the reaction mechanism is required. As shown in Scheme 2, the reaction starts with the formation of the active palladium hydride complex **A**,[14] which undergoes coordination and addition to 1,3-butadiene to give the thermodynamically stable π-allyl palladium complex **B**. This complex might be in equilibrium with the corresponding σ-allyl species.[15]

After CO coordination and insertion to give **C**, nucleophilic attack by methanol leads to methyl 3-pentenoate **3**.[16] Preferably, this monocarbonylation product undergoes olefin isomerization and a second carbonylation cycle (complexes **E**,**F**) to give the desired dimethyl adipate.

In general, the polarity and protic nature of the solvent can influence the formation of the active hydride species and each of the individual elementary steps in the two catalytic cycles as well as the isomerization reactions.[16b,c] As an example, Gabriele and co-workers discovered that, for Pd-
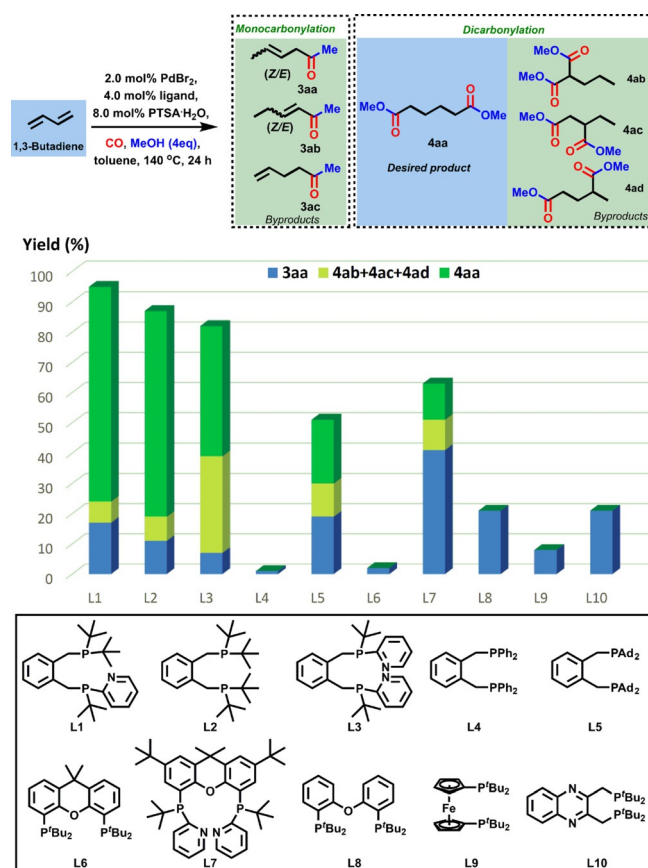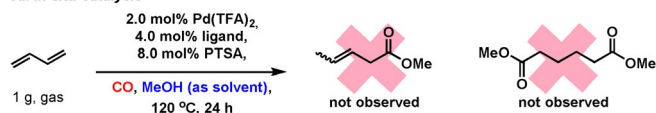
catalyzed oxidative dicarbonylation of alkynes, a large excess of water as co-solvent promoted the formation of maleic acid with unprecedented catalytic efficiencies.[17] To understand the specific influence of the methanol concentration on the activity of certain catalysis in this overall process, several control investigations were performed. As shown in Scheme 3, in methanol as solvent the catalyst system with **L2** shows no conversion at all. This is also true for the preformed palladium complex (Scheme 3a and b). This observation makes clear that either the formation of the palladium hydride or the reaction steps in cycle **I** are prohibited by methanol. In agreement with this assumption using the monocarbonylation product **3aa** gave full conversion in methanol as solvent and **4aa** was obtained in 94% yield (Scheme 3c). In contrast, using toluene as solvent under identical conditions the alkoxycarbonylation of 1,3-butadiene proceeded smoothly and **4aa** was formed in 87% yield (97% selectivity). As shown in Scheme 3d, only trace amounts of the intermediate monocarbonylation product were observed. Apparently, the Pd/d*t*bpx catalyst system allows for the two carbonylation cycles in toluene, while in methanol only the second cycle is working.

Next, we were interested in the generality of the observed effects. Hence, the methoxycarbonylation of other 1,2- and 1,3-dienes to the corresponding diesters, which are of interest for different fine and bulk chemical applications, was inves-
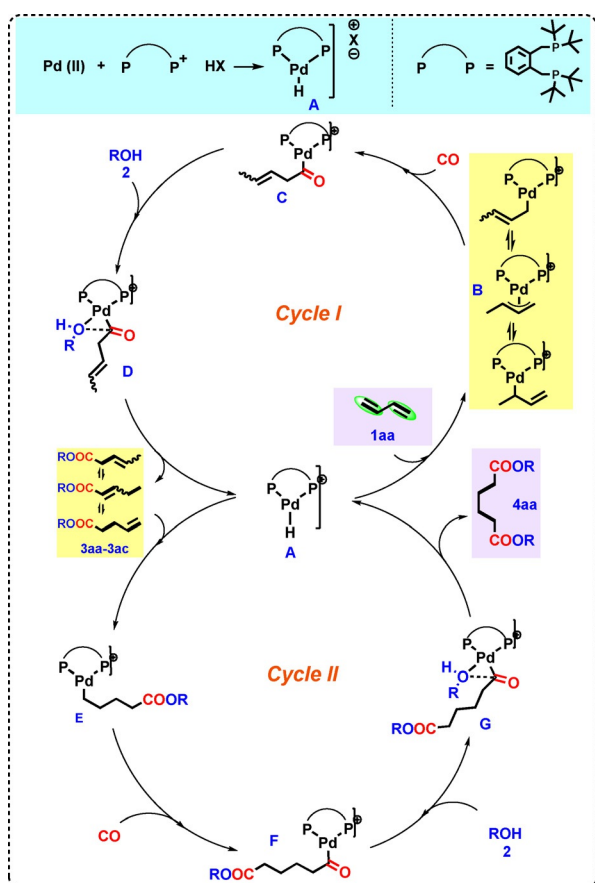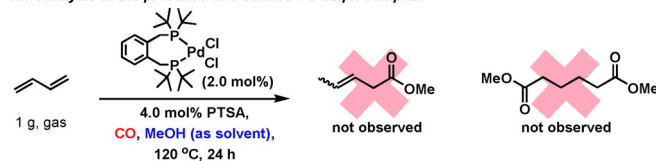
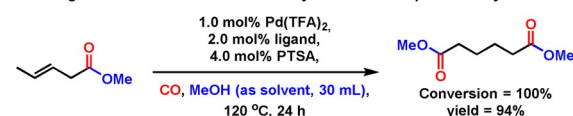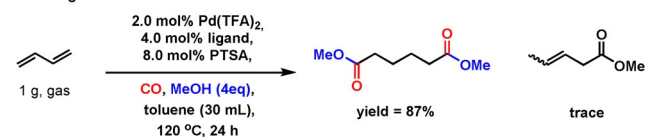**Scheme 2.** Catalytic cycles for the Pd-catalyzed alkoxycarbonylation of 1,3-butadiene with alcohol.

Scheme 3. Selected control experiments.

tigated. More specifically, 37 different dienes and more than 30 alcohols were converted to the corresponding diesters in good to very good yield (Figure 4). For example, linear 1,3-dienes such as 1,3-pentadiene, 1,3-hexadiene, 1,3-heptadiene, 1,3-octadiene showed excellent reactivity and regioselectivity. Notably, the control reactions of 1,3-butadiene or isoprene in pure methanol did not lead to any desired diesters under otherwise identical reaction conditions.

Due to the fast isomerization reactions, substrates with internal conjugated double bonds, for example, **1 ag**, **1 am**, **1 an** also led preferentially to the respective terminal diester. Apart from regular terminal or di-substituted olefins, also tri- (**1 aq**) and even tetra-substituted (**1 an**) dienes with increased steric hindrance on the carbon chain provided the linear diesters **4 aq** and **4 an** in good yields and excellent selectivities. Again, using **1 aq** in pure methanol showed the generalization of the solvent influence and gave no tricarbonylation product **4 aq**. Furthermore, 1-aryl-substituted 1,3-dienes showed similar performance. Here, excellent 1,4-site selectivity was observed (**4 ar**–**4 au**) due to the stabilization of the benzylic metal complex.

Interestingly, in addition to conjugated 1,3-dienes, a selection of seventeen 1,2-dienes including pure aliphatic and aromatic derivatives were smoothly converted to the corresponding linear diesters with similar activity and high regioselectivity. Exemplarily, 1,2-butadiene and 1,2-pentadiene gave the desired products in 73–74% yield (94–95% regioselectivity), while no formation of the diester is observed in methanol as solvent. Notably, this methodology also allows the transformation of substrates with sensitive functional groups such as B(OR)₂.

To assess the potential of the presented catalyst system for practical applications, scale up experiments and a reaction using dienic mixtures were performed (Figure 5). Gratifyingly, using 0.5 mol% of catalyst, dimethyl adipate was obtained in 91% yield and 96% selectivity on >150 g-scale. In addition, a 1:1 mixture of 1,2- and 1,3-butadiene gave dimethyl adipate in similar yield and selectivity.

Conclusion

In summary, we present the first Pd/d*r*bpx-catalyzed direct dimethoxycarbonylation of 1,3-butadiene. Surprisingly, the viability of this industrially relevant process is not only highly dependent on the ligand and catalyst system, but also on the methanol concentration. Using optimal conditions, this straightforward transformation could be realized with excellent yield and selectivity for dimethyl adipate. The generality of the presented catalyst system is demonstrated by the efficient alkoxycarbonylation of 37 different 1,2- and 1,3-dienes. Applying various alcohols provided a general approach to a variety of interesting diesters including functionalized building blocks. The utility of the catalytic system is also showcased by scale up experiments and reactions of mixtures of dienes. We believe these findings will provide motivation to better understand the critical role of solvents and substrate concentration.
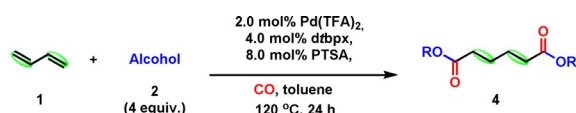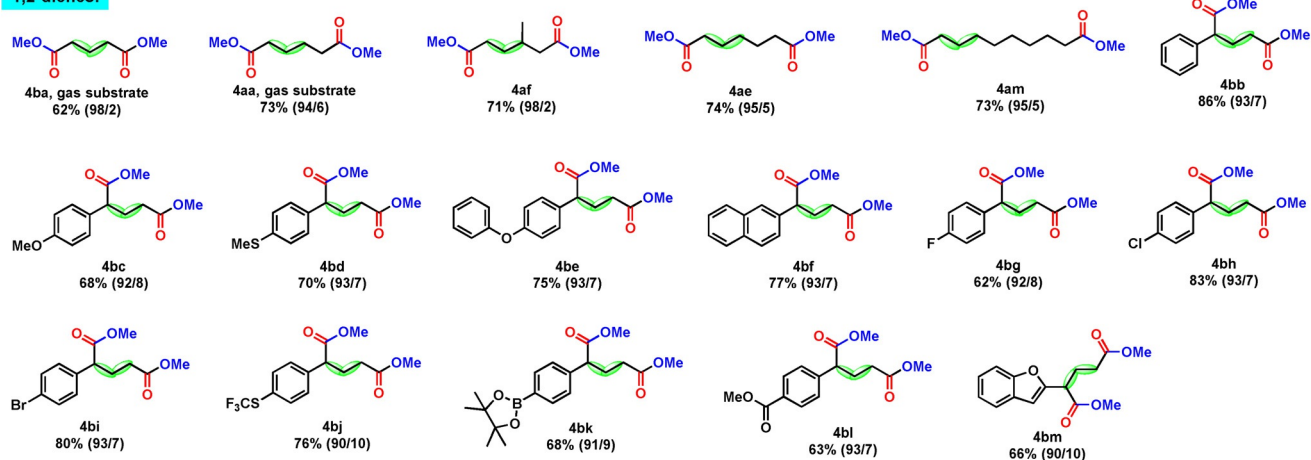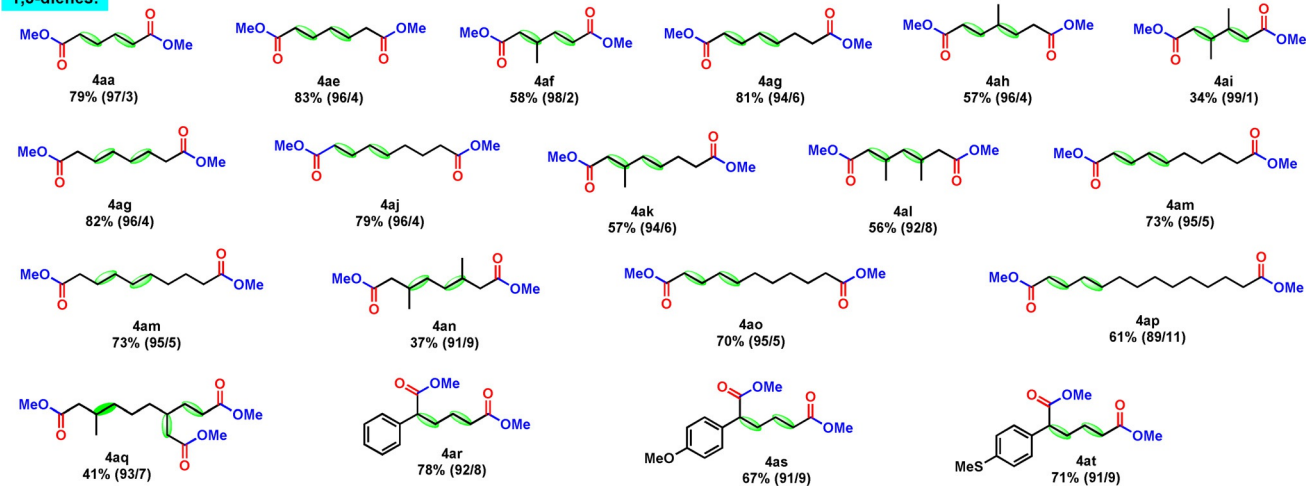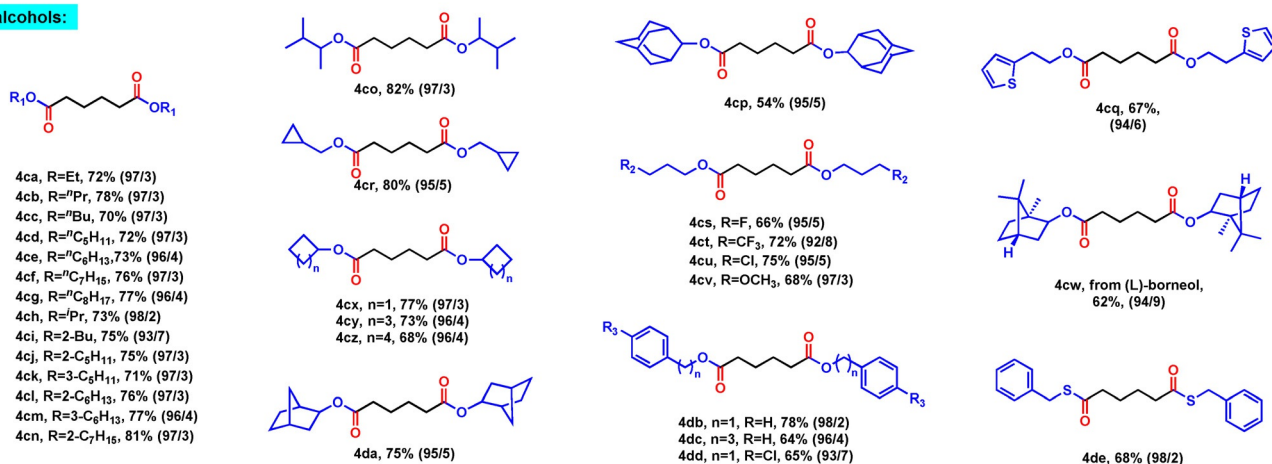
Figure 4. Substrate scope for various dienes and alcohols. Yields are reported as isolated yields; the selectivity is the ratio of the linear diester to branched diesters, which is determined by GC analysis.
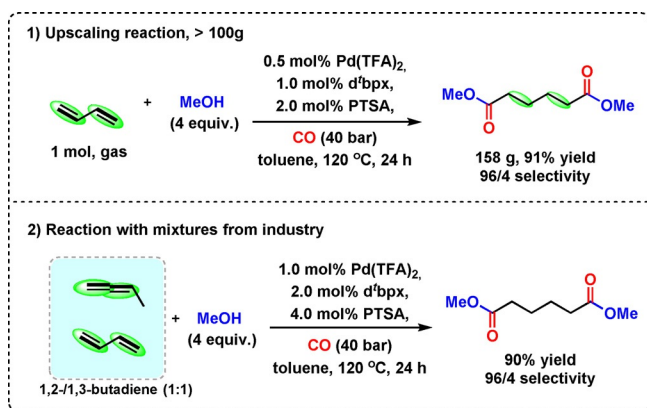
Figure 5. Scale up and dicarbonylation of 1,2-/1,3-diene mixtures.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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