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Regioselective Thiocarbonylation of Vinyl Arenes

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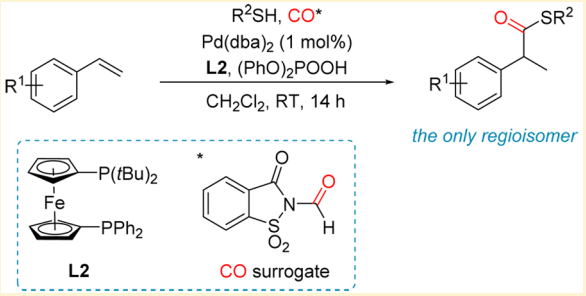
Supporting Information

ABSTRACT: A palladium-catalyzed thiocarbonylation of styrene derivatives is reported for the first time. The combination of thiols as nucleophiles and a bidentate ligand ensures a unique reaction outcome with high regioselectivity toward the more valuable branched isomer and new reactivity. The ambient reaction conditions (temperature, catalyst loading) and the use of a CO surrogate render this transformation a useful method for the synthesis of thioesters from available feedstock. Various functional groups on arene and thiol substituents are tolerated by the system. Notably, challenging *ortho*-substituted styrenes are converted with unprecedentedly high regioselectivity.



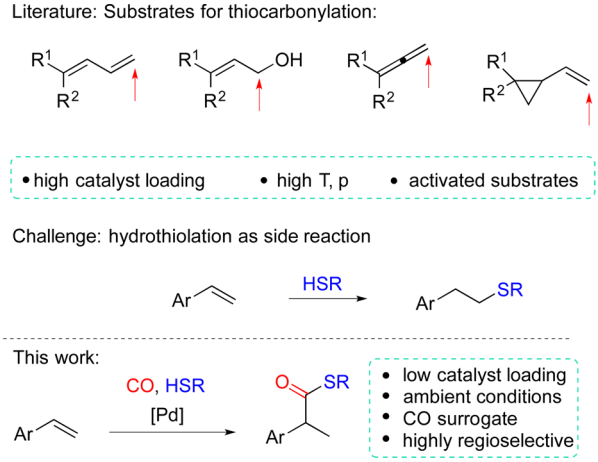
INTRODUCTION

Thioesters constitute a compound class with immense biological importance, and they are also of considerable interest for synthetic organic chemists. They are less stabilized by mesomeric effects than alcohol-derived esters due to poorer orbital overlap and are therefore often found as intermediates in biochemical processes, when an activated acyl functionality is needed, e.g., in transfer reactions assisted by coenzyme A.[1] Their properties also render them expedient intermediates in numerous synthetic applications, such as the formation of esters,[2] amides,[3] and aldehydes[4] as well as the synthesis of ketones via transition-metal-catalyzed cross-coupling reactions.[4,5]

Many different methods are available to synthesize thioesters, but the most common one is acylation of thiols by using a carboxylic acid, acid anhydride, or chloride as the acyl source in the presence of an activating reagent.[6] Another approach was reported by Lee and co-workers,[7] who described a copper-catalyzed reaction between aldehydes and thiols using a peroxide as an oxidant. Furthermore, the thiocarbonylation of aryl halides was intensively investigated.[3,8] However, some of these reactions often proceed under harsh reaction conditions or suffer from low atom economy, and the substrates are not readily available or already possess functional groups with a high oxidation state at the carbon atom.

In comparison, the thiocarbonylation of alkenes—also referred to as hydrothioesterification—represents a highly atom- and waste-economic method for accessing thioesters. Moreover, it allows for the synthesis of complex and reactive molecules from easily available starting materials in a single step. The investigations of this transformation, conducted mainly by Alper and co-workers, focused predominantly on the thiocarbonylation of conjugated dienes,[9] allylic alcohols,[10] allenes,[11] and vinylcyclopropanes[12] (Scheme 1). All of these reactions proceed with high catalyst loading (3−5 mol%) and elevated temperatures (100−110 °C) and pressures (27 bar)

Scheme 1. Thiocarbonylation of Double Bonds: Previously Reported Substrates and Our New Development



and cannot be applied to other types of double-bond-containing compounds. To the best of our knowledge, simple alkenes were used as substrates only in few examples in patents from Drent[13] and Foley.[14]

Thiols are prone to oxidation, readily forming the corresponding disulfides, and they are also widely regarded as catalyst poisons for late transition metals, with their strong M−S bonding rationalized through a hard/soft acid/base (HSAB) soft−soft interaction.[15] Possibly, these preconceptions and the competing hydrothiolation reaction might have hindered progress in this area, although metal-catalyzed cross-couplings with thiols are known.[16] Herein, we report the first chemoselective palladium-catalyzed thiocarbonylation of styrenes, which is carried out under mild reaction conditions (room

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temperature, low pressure, or CO surrogate) and in a highly regioselective fashion (Scheme 1). Careful adjustment of the catalyst system and reaction conditions led to a successful suppression of the side reaction.

RESULTS AND DISCUSSION

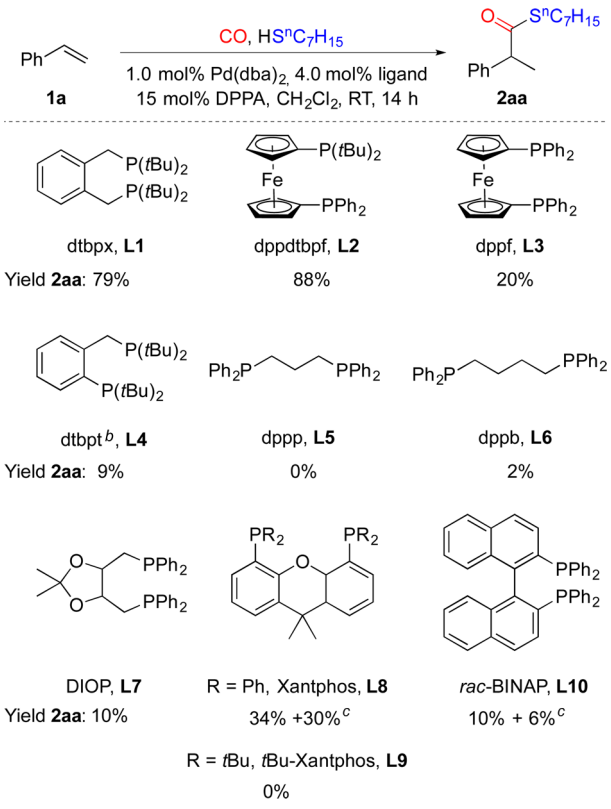
Recently, we developed a method[17] for the alkoxycarbonylation of olefins[18] under mild conditions using a Pd(0) precatalyst, a bidentate phosphine ligand, and a recyclable CO surrogate (*N*-formylsaccharin), which enables a convenient and safe reaction setup in two-chamber pressure tubes developed by Skrydstrup.[19] The originally envisioned direct transfer of the methodology to thiocarbonylation was not possible. Initially, we struggled with problems of reproducibility and low yields. Additionally, we observed the formation of linear thioethers from styrenes, which were found to stem from the oxygen-mediated thiol−ene (or hydrothiolation) reaction.[20] Fortunately, by thoroughly purifying all of the reaction components prior to use, we were able to prevent this side reaction. The initial screening of the ligands was performed using styrene (**1a**) and *n*-heptanethiol as model substrates and $Pd(dba)_2$ (dba = dibenzylideneacetone) and diphenylphosphoric acid (DPPA) as the catalyst system (Scheme 2). The screening was carried out in an autoclave under 2.5 bar CO atmosphere in order to ensure equal reaction conditions for all ligands.

The known successful carbonylation ligand **L1** also showed a promising result in the thiocarbonylation, affording exclusively the branched thioester **2aa** in 79% yield (NMR). However, an improved yield was obtained using ligand **L2**, which was known from a detailed study by Holzapfel and Bredenkamp on ligand effects in the methoxycarbonylation of medium-chain alkenes, where the electronically differentiated **L2** was shown to outperform **L1**.[21] Those authors reasoned that such ligands might accelerate the final alcoholysis step in alkoxycarbonylation, which also emerges from several studies concerning ethene methoxycarbonylation by Pringle.[22] Another advantage of **L2** is its straightforward synthesis[23] and lower price per mole.

To examine the effects of steric and electronic differentiation of **L2** on catalytic activity, we also tested the symmetrical ferrocene derivative **L3**, which showed a significantly reduced activity. We speculated that electronic differentiation might be the key to activate catalysts; however, the desmethylene analogue of **L1**, the known carbonylation ligand **L4**,[22a,24] provided the product in low yield. Additionally, also the comparatively electron-poor bidentate ligands **L5**−**L7** exhibited no or low activity. The typical carbonylation ligands **L8** and **L10** were active but not in a regioselective fashion. Interestingly, no product was obtained employing the sterically more demanding *t*Bu-Xantphos (**L9**).[25]

Using the same model substrates and ligand **L2**, the influence of Pd source and acid co-catalyst was investigated (Table 1). First, several palladium precursors were tested. Among the Pd(II) sources, only $Pd(acac)_2$ (Table 1, entry 4; acac = acetylacetonate) was able to catalyze the reaction, albeit in moderate yield. The best yield was achieved with $Pd(dba)_2$ as a catalyst precursor (Table 1, entry 5), affording **2aa** in 88% yield. In contrast to our previous studies on the alkoxycarbonylation, the acid screening showed no difference in activity between diphenylphosphoric, 1,1′-diphenylphosphoric, *p*-toluenesulfonic, and methanesulfonic acids, with yields around 90% (Table 1, entries 5−7 and 9), whereas trifluoroacetic acid (TFA) and benzoic acid showed poor yields (Table 1, entries 8 and 10). The moderately acidic DPPA was chosen as additive for substrate screening, in order to be able to employ substrates containing labile functional groups.

Scheme 2. Ligand Screening for the Thiocarbonylation of Styrene[a]



[a]The reaction was carried out in the autoclave (2.5 bar of CO). Reaction vessel: styrene (115 μL, 1.0 mmol, 1 M solution), 1 mol% $Pd(dba)_2$ (5.8 mg, 10 μmol), 4 mol% ligand (40 μmol), 15 mol% DPPA (38 mg, 150 μmol), HeptSH (210 μL, 177 mg, 1.3 mmol), 790 μL CH_2Cl_2, RT, 14 h. Yields were determined by quant. NMR spectroscopy. [b]0.5 mmol. [c]Linear thioester, determined by quant. GC-FID. Ligand abbreviations: dtpbx, **L1** = 1,2-bis(di-*tert*-butylphosphinomethyl)benzene; dppdtbpf, **L2** = 1-diphenylphosphino-1′-(di-*tert*-butylphosphino)ferrocene; dppf, **L3** = 1,1′-bis(diphenylphosphino)-ferrocene; dtbpt, **L4** = di-*tert*-butyl(2-(di-*tert*-butylphosphanyl)-benzyl)phosphane; dppp, **L5** = 1,3-bis(diphenylphosphino)propane; dppb, **L6** = 1,4-bis(diphenylphosphino)butane; *rac*-DIOP, **L7** = (±)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane; Xantphos, **L8** = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; *t*Bu-Xantphos, **L9** = 4,5-bis(di-*tert*-butylphosphino)-9,9-dimethylxanthene; and *rac*-BINAP, **L10** = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

The substrate scope was evaluated under the optimized conditions in glass pressure tubes by using *N*-formylsaccharin (**3**) as a CO surrogate, in order to liberate 2.5 bar CO by treatment with a base in DMF at room temperature (Table 2).[26] First, different thiols were tested using $Pd(dba)_2$, DPPA and **L2** as the catalyst system in the carbonylation of styrene. All linear aliphatic thiols furnished high yields of the branched products **2aa**−**2ac** (>90%, Table 2, entries 1−3). Notably, we repeated the reaction of styrene and *n*-heptylthiol at 5 mmol scale and obtained the product **2aa** in quantitative yield and with excellent regioselectivity. The use of benzylthiol also resulted in product formation in a good yield of 82% (Table 2, entry 4). A good yield of product **2ae** was obtained when

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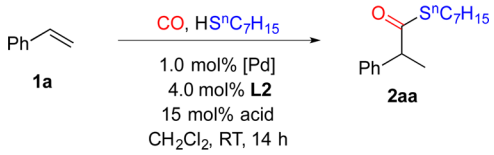
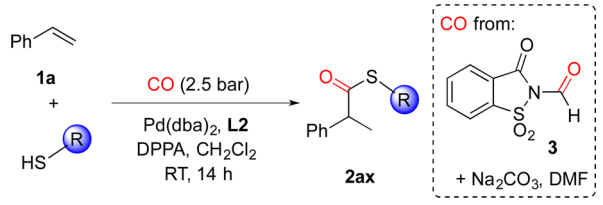
Table 1. Catalyst and Acid Screening for the Thiocarbonylation of Styrene[a]



entry	[Pd]	acid	pK_a (DMSO)	conv (%)[b]	yield **2aa** (%)[b]
1	$PdCl_2$	DPPA	3.9	21	0
2	$Pd(OAc)_2$	DPPA	3.9	18	0
3	$Pd(PPh_3)_4$	DPPA	3.9	32	24
4	$Pd(acac)_2$	DPPA	3.9	74	53
5	$Pd(dba)_2$	DPPA	3.9	94	88
6	$Pd(dba)_2$	MsOH	1.6	100	91
7	$Pd(dba)_2$	BNPA	3.4	81	81
8	$Pd(dba)_2$	TFA	3.5	55	11
9	$Pd(dba)_2$	*p*TsOH	7.1	100	89
10	$Pd(dba)_2$	PhCOOH	11.1	23	4

[a]The reaction was carried out in the autoclave (2.5 bar of CO). Reaction vessel: styrene (115 μL, 1.0 mmol, 1 M solution), 1 mol% [Pd] (10 μmol), **L2** (21 mg, 40 μmol), 15 mol% acid (150 μmol), HeptSH (210 μL, 177 mg, 1.3 mmol), 790 μL CH_2Cl_2, RT, 14 h. [b]Determined by quant. NMR spectroscopy. Acid abbreviations: DPPA = diphenylphosphoric acid; MsOH = methanesulfonic acid; BNPA = 1,1′-bi-2-naphthol phosphoric acid; TFA = trifluoroacetic acid; and *p*TsOH = *p*-toluenesulfonic acid.

Table 2. Thiol Screening in the Carbonylation of Styrene[a]



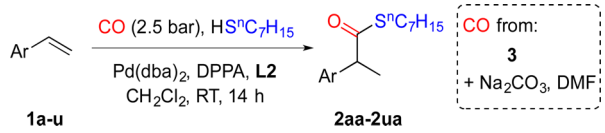
entry	product	R	yield (%)[b]
1	**2aa**	^{n}C$_7$H$_{15}$	95
2	**2ab**	^{n}Pr	92
3	**2ac**	Et	96
4	**2ad**	Bn	82
5	**2ae**	*N*-Boc-cysteine methyl ester	62
7	**2af**	Cy	28
8	**2ag**	Ph	33 + 26[c]

[a]Reaction conditions: Chamber A: CO generation (max. 2.5 bar): **3** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: styrene (115 μL, 1.0 mmol, 1 M solution), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L2** (21 mg, 40 μmol), DPPA (38 mg, 150 μmol), RSH (1.3 mmol), 790 μL CH_2Cl_2, RT, 14 h. [b]Isolated yields. [c]Linear thioether.

protected cysteine was employed as a substrate (Table 2, entry 5). As expected, a significantly reduced activity of the catalyst system was observed when a secondary thiol was used (Table 2, entry 6). Interestingly, thiophenol led to the formation of the desired thioester product **2ag**, but also the linear ether was observed (Table 2, entry 8). In general, arylthiols have a lower bond dissociation energy (S−H) than alkanethiols, resulting in more facile formation of thiyl radicals and the hydrothiolation side reaction. This side reaction could be initiated by molecule-assisted electron transfer.[27] However, this result contradicts our previously described system for the alkoxycarbonylation of olefins, since in this case the ester was not formed when phenol was employed. We previously reasoned that a β-hydride elimination of a coordinated alcohol molecule is necessary to form the catalytically active palladium hydride species.[28] This disparity leads us to the assumption that the catalyst activation mechanism of thiocarbonylation differs from the alkoxycarbonylation, or that more than one pathway for the activation exists.

Furthermore, the reactivity of various alkenes was investigated, starting with the examination of styrene derivatives employing heptanethiol as the nucleophile (Table 3). In

Table 3. Thiocarbonylation of Substituted Styrenes[a]



entry	educt	product	Ar	yield (%)[b]
1	**1a**	**2aa**	C_6H_5	95
2	**1b**	**2ba**	2-Me-C_6H_4	89
3	**1c**	**2ca**	2-OMe-C_6H_4	97
4	**1d**	**2da**	2-OH-C_6H_4	55[c]
5	**1e**	**2ea**	2-OAc-C_6H_4	49
6	**1f**	**2fa**	2-CF_3-C_6H_4	0
7	**1g**	**2ga**	3-Me-C_6H_4	99
8	**1h**	**2ha**	3-OMe-C_6H_4	90
9	**1i**	**2ia**	4-Me-C_6H_4	99
10	**1j**	**2ja**	4-OMe-C_6H_4	99
11	**1k**	**2ka**	4-OAc-C_6H_4	93
12	**1l**	**2la**	4-CF_3−C_6H_4	50
13	**1m**	**2ma**	4-Ph−C_6H_4	86
14	**1n**	**2na**	4-^{t}Bu-C_6H_4	95
15	**1o**	**2oa**	4-OH-C_6H_4	49
16	**1p**	**2pa**	4-NH_2−C_6H_4	0
17	**1q**	**2qa**	4-NO_2−C_6H_4	0
18	**1r**	**2ra**	4−F-C_6H_4	91
19	**1s**	**2sa**	4−Cl-C_6H_4	81
20	**1t**	**2ta**	4−Br-C_6H_4	72
21	**1u**	**2ua**	6-OMe-naphth-2-yl	90

[a]Reaction conditions: Chamber A: CO generation (max. 2.5 bar): **3** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: vinyl arenes (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L2** (21 mg, 40 μmol), DPPA (38 mg, 150 μmol), HeptSH (210 μL, 177 mg, 1.3 mmol), 790 μL CH_2Cl_2, RT, 14 h. [b]Isolated yields. [c]The lactone was obtained.

general, *ortho*-substituted styrenes (Table 3, entries 2−6) provided lower yields than the corresponding *meta*- and *para*-substituted derivatives (Table 3, entries 7−12), but most impressively with no breakdown in regioselectivity as was observed in the alkoxycarbonylation. Notably, thiocarbonylation of **1d** did not furnish the thioester, but rather the five-membered lactone **2da**, which was already observed in the alkoxycarbonylation reaction.[17] We were able to increase the yield with the new catalytic system for the desired lactone from 16% to 55%.

Sterically more demanding groups, such as phenyl or *t*Bu groups (Table 3, entries 13 and 14), were tolerated in the *para*-position, showing excellent yields. An electronic effect on the reactivity was observed with the electron-withdrawing CF_3 group in the *para*-position, which decreased the yield to 50% (Table 3, entry 12), whereas no activity was observed with the

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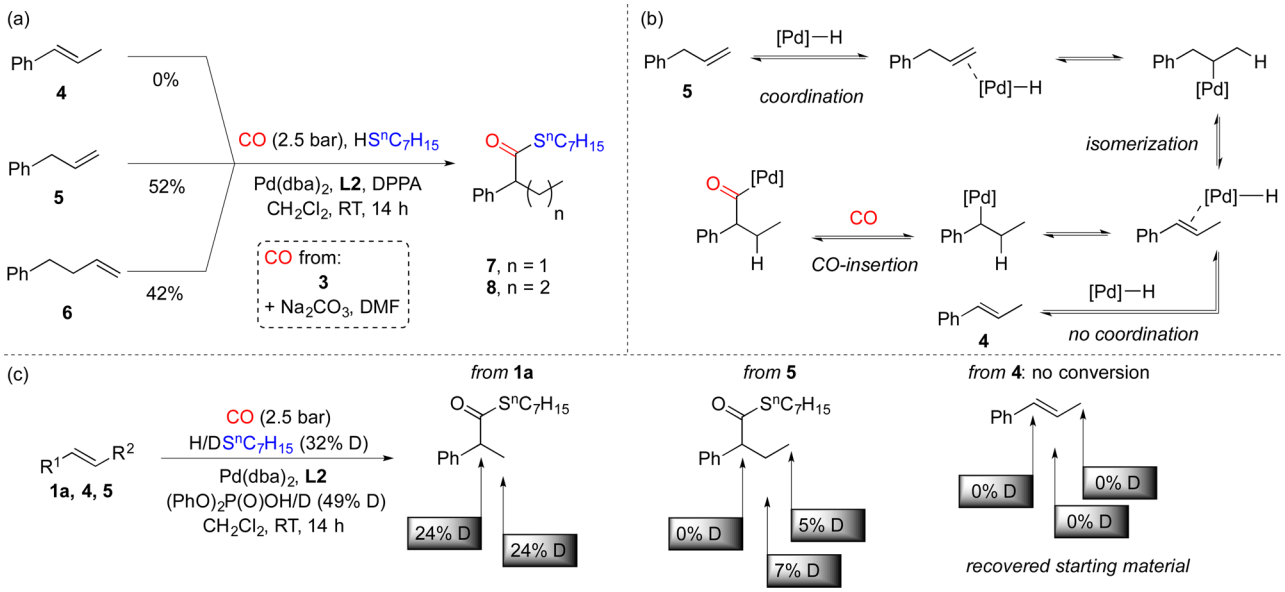
Scheme 3. Thiocarbonylation of Various Olefins and Rationalization of the Results[a]



[a](a) Thiocarbonylations of **4**–**6**. Reaction conditions: Chamber A: CO generation (max. 2.5 bar): **3** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L2** (21 mg, 40 μmol), DPPA (38 mg, 150 μmol), HeptSH (210 μL, 177 mg, 1.3 mmol), 790 μL CH_2Cl_2, RT, 14 h. Isolated yields. (b) Plausible explanation of the results. (c) Deuteration experiments.

CF_3 group in the *ortho*-position (Table 3, entry 6) and in the presence of a nitro group (Table 3, entry 17). Basic substituents, such as the amino group, were not tolerated by the catalytic system (Table 3, entry 16). Moreover, an interesting trend for halides in the *para*-position was established (Table 3, entries 18–20). The yields decreased significantly from fluoro to chloro to bromo substitution, which might be explained by the fact that competitive oxidative addition to palladium becomes more likely along this row. The vinylnaphthalene **1u** delivered the corresponding branched ester **2ua**, which could be transformed to *rac*-Naproxen in an additional simple hydrolysis.

Afterward, further alkenes were tested (Scheme 3a). Surprisingly, the internal alkene **4** did not undergo any carbonylation reaction, whereas the terminal nonconjugated alkenes **5** and **6** generated exclusively the branched products **7** and **8** in moderate yields. A possible explanation might be that a direct carbonylation in the benzylic position of **4** is not possible due to steric hindrance, but a terminal insertion of substrates **5** and **6**, followed by an isomerization, is conceivable (Scheme 3b). A deuteration experiment using partially deuterated thiol and acid revealed that the insertion of the Pd catalyst is already the limiting factor for the carbonylation of **4**, as no deuterium was incorporated in the recovered starting material (Scheme 3c and Supporting Information). On the other hand, deuterium was found in β- and γ-positions of product **7**. In comparison, when using styrene, 24% deuterium was determined on both carbon atoms. In summary, a limitation of the catalytic system seems to be substitution in the α- or β-position of styrene (see Supporting Information for more examples).

In addition, a comparison between alkoxy- and thiocarbonylation was conducted, since several results suggested different behaviors of the two systems (Figure 1). Therefore, selected substrates were tested under either typical alkoxy (C.1.x) or thio conditions (C.2.x), and the nucleophile was varied (C.x.1 = HeptOH; C.x.2 = HeptSH), as well. In summary, the best yields were observed under thio conditions using HeptSH as a

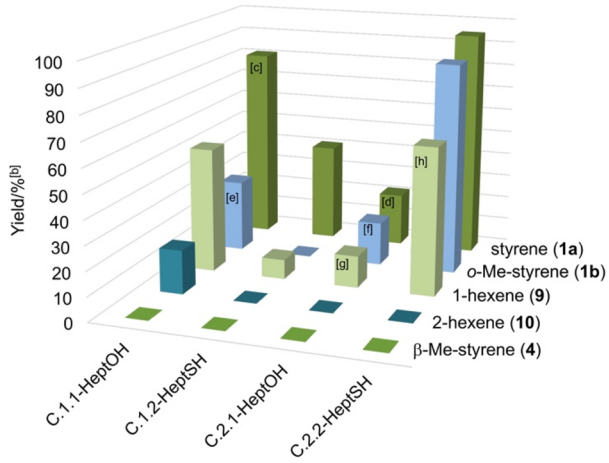


Figure 1. Comparison between alkoxy- and thiocarbonylation. [a]Reaction conditions: Chamber A: CO generation (max. 2.5 bar): **3** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: C.1.1 and C.1.2 (alkoxy conditions), olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L1** (16 mg, 40 μmol), BNPA (52 mg, 150 μmol,), *x* μL HeptOH (280 μL, 232 mg, 2.0 mmol)/*x* μL HeptSH (315 μL, 265 mg, 2.0 mmol), 1000 − *x* μL CH_2Cl_2, RT, 14 h; C.2.1 and C.2.2 (thio conditions), olefin (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L2** (21 mg, 40 μmol), DPPA (38 mg, 150 μmol), *x* μL HeptSH (210 μL, 177 mg, 1.3 mmol)/*x* μL HeptOH (190 μL,156 mg, 1.3 mmol), 1000 − *x* μL CH_2Cl_2, RT, 14 h. [b]Isolated yields. [c]b/l = 94/6. [d]b/l = 94/6. [e]b/l = 25/75. [f]b/l = 69/31. [g]b1/b2/l = 17/44/39. [h]b1/b2/l = 22/43/35 (see Supporting Information).

nucleophile. One can conclude that the two different reaction conditions are closely related to the corresponding nucleophile. Whereas, for the carbonylation of **1a** under alkoxy conditions with HeptOH (C.1.1) as well as under thio conditions with HeptSH (C.2.2), high to excellent yields were generated, there was a significant breakdown in reactivity when using alkoxy conditions with HeptSH (C.1.2) or thio conditions with

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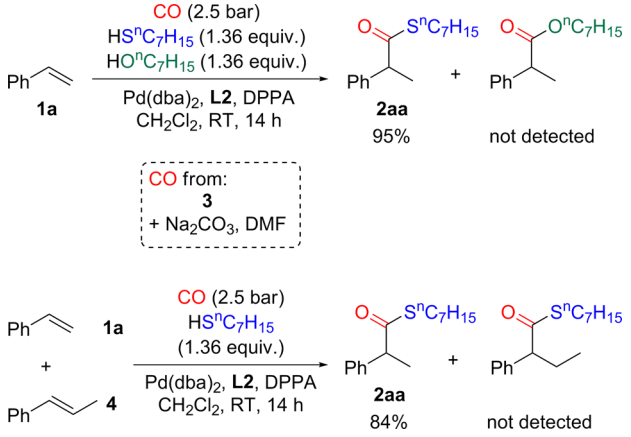
HeptOH (C.2.1). A similar situation was observed when using the sterically demanding **1b** as a substrate. Nevertheless, in all different combinations of nucleophile and reaction conditions, no product formation was observed for **4**. Additionally, all reactions using HeptSH and a styrene derivative proceeded in a completely regioselective fashion, whereas also the linear product was observed for all reactions with HeptOH. In order to figure out if this concept can also be transferred to aliphatic olefins, 1-hexene (**9**) and 2-hexene (**10**) were investigated. Whereas **10** can only be carbonylated under alkoxy conditions (C.1.1), generating exclusively the linear product, **9** showed moderate yields for C.1.1 and C.2.2 and low yields for C.1.2 and C.2.1. In the carbonylation of **9** under thiocarbonylation conditions, an isomerization took place, followed by unselective carbonylation of each carbon atom. Under alkoxy conditions, only the terminal position was functionalized, which is a known regioselectivity for the ligand **L1**.

Finally, two competition experiments were performed (Scheme 4). Interestingly, the carbonylation of styrene under

Scheme 4. Competition Experiments[a]

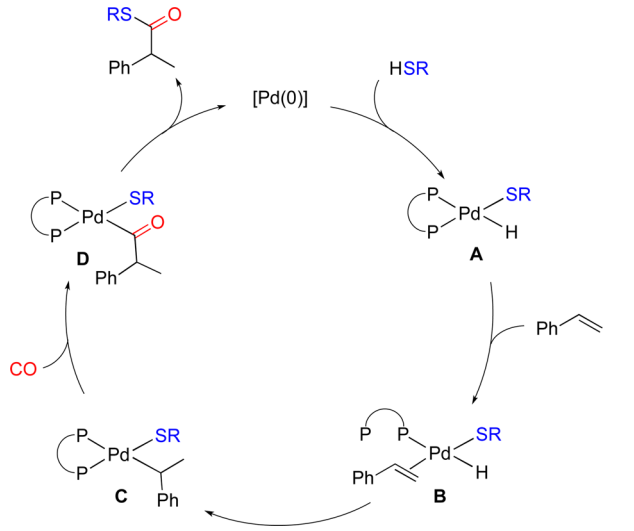


[a]Reaction conditions: Chamber A: CO generation (max. 2.5 bar): **3** (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: styrene (115 μL, 1.0 mmol, 1 M solution), $Pd(dba)_2$ (5.8 mg, 10 μmol), **L2** (21 mg, 40 μmol), DPPA (38 mg, 150 μmol), HeptSH (210 μL, 177 mg, 1.3 mmol), HeptOH (190 μL, 156 mg, 1.3 mmol) or alkene **4** (130 μL, 1.0 mmol), 790 μL CH_2Cl_2, RT, 14 h. Yields were determined by quant. NMR spectroscopy.

thiocarbonylation conditions by adding both O- and S-nucleophiles generated exclusively thioester **2aa**, with no loss in activity (95%). In a thiocarbonylation of a 1:1 mixture of styrene (**1a**) and the unreactive β-methylstyrene (**4**), only a slight decrease in the yield of the carbonylation product of styrene was observed. This shows that the catalyst is not inhibited by alkene **4**.

The obtained results, especially the excellent regioselectivity and reactivity of sterically hindered *ortho*-substituted styrenes, suggest a different mechanism compared to the known alkoxycarbonylation reaction using ligand **L1**. The main difference might arise from the better coordinating ability of the thiol, which would influence the reactivity of the complex by its donor properties. Our postulated catalytic cycle is based on the accepted hydride mechanism for the carbonylation reaction, with the difference that the thiol acts as a ligand (Scheme 5). The catalytically active species **A** is formed from the Pd(0) precursor by oxidative addition of the thiol and a

Scheme 5. Postulated Reaction Mechanism



ligand exchange. Coordination of the alkene is enabled by a transitory de-coordination of one phosphorus atom to give **B**. Insertion of the alkene into the Pd–H bond furnishes complex **C**, which undergoes a CO coordination and insertion. The resulting acyl complex **D** is converted to the product and hydride **A** in reductive elimination/oxidative addition steps. The Brønsted acid additive might play a role in the oxidative addition of the thiol and in the activation of the acyl species.

CONCLUSION

In summary, we developed the first chemoselective thiocarbonylation of vinyl arenes, which proceeds under mild reaction conditions and in a highly regioselective fashion. The devised catalytic system tolerates a wide variety of functional groups for the thiocarbonylation of substituted styrenes, generating exclusively the branched products, even for sterically demanding groups in the *ortho*-position. Interestingly, the system is also selective for terminal double bonds, whereas internal ones are not carbonylated. This property could be used in the transformation of compounds containing several double bonds. Comparative investigations of the thio- and the alkoxycarbonylations show that a different mechanism might be operating in the thiocarbonylation, which can result in new applications. A more detailed study is ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11020.

Detailed experimental procedures, along with spectroscopic and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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