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Palladium-Catalyzed Thiocarbonylation of Alkenes toward Linear Thioesters

Han-Jun Ai, Fengqian Zhao, Hui-Qing Geng, and Xiao-Feng Wu*

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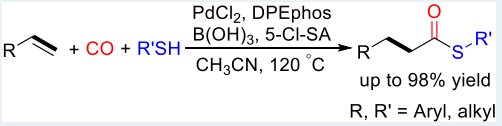
ABSTRACT: Thiocarbonylation of alkenes offers an ideal procedure for the synthesis of thioesters. However, thiocarbonylation of alkenes, especially styrenes, to produce valuable linear thioesters has remained a challenge. In this Letter, a general palladium-catalyzed thiocarbonylation of alkenes to produce linear thioesters has been achieved. Moderate to good yields of desired thioesters can be produced from readily available alkenes in a straightforward manner.



KEYWORDS: *palladium catalyst, carbonylation, thioester, thiocarbonylation, alkene*

Transition-metal-catalyzed carbonylative transformation of alkenes offers an ideal choice for producing aliphatic carboxylic acid derivatives.[1] By using carbon monoxide as an abundant C1 source, depending on the nucleophiles applied, various target products can be obtained straightforwardly through hydroformylation, alkoxycarbonylation, aminocarbonylation, thiocarbonylation, and so on.[2−5] By controlling the regioselectivity, branched or linear products can be obtained as the main product. Studies toward those selectivities have been well established with hydroformylation, alkoxycarbonylation, and aminocarbonylation. Even asymmetric transformations have also been realized with procedures to give branched products. However, thiocarbonylation of alkenes is still rarely reported besides the early efforts from Alper's group and others.[4] In 2016, Fleischer and co-workers reported an attractive and selective palladium-catalyzed thiocarbonylation of alkenes to produce branched products in high yields (Scheme 1, eq 1).[5] The asymmetric version of this reaction was subsequently achieved by Liao and co-workers with their own chiral sulfoxide-(P-dialkyl)-phosphine (SOP) ligands

Scheme 1. Thiocarbonylation of Alkenes

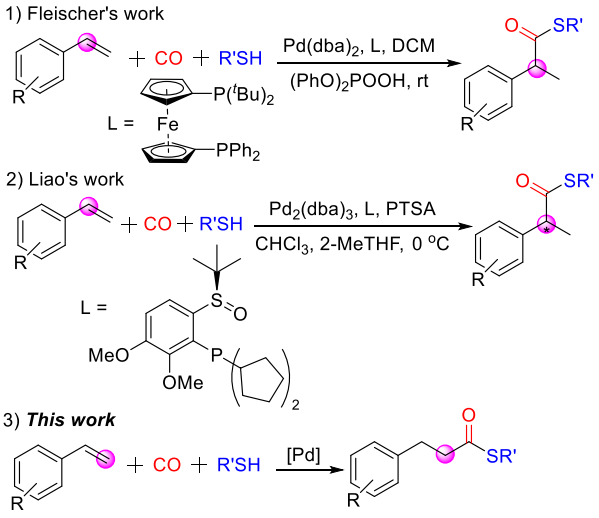
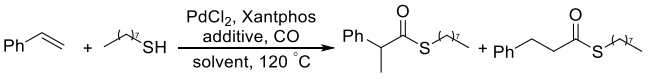


Table 1. Thiocarbonylation of Styrene: Optimization



entry	additive (mol %)	solvent	yield of 3[b]	yield of 4[b]
1	-	CH_3CN	51%	47%
2	*p*-TsOH·H_2O (20)	CH_3CN	23%	75%
3	TFA (20)	CH_3CN	42%	56%
4	5-Cl-SA (20)	CH_3CN	47%	50%
5	$B(OH)_3$ (10)	CH_3CN	52%	46%
6	$B(OH)_3$ (10)/5-Cl-SA (20)	CH_3CN	12%	84%
7	$B(OH)_3$ (10)/5-Cl-SA (20)	DCE	8%	78%
8	$B(OH)_3$ (10)/5-Cl-SA (20)	toluene	28%	68%
9	$B(OH)_3$ (10)/5-Cl-SA (20)	dioxane	44%	50%
10	$B(OH)_3$ (10)/5-Cl-SA (20)	EtOH	40%	44%
11	$B(OH)_3$ (10)/5-Cl-SA (20)	DMSO	trace	trace
12	$B(OH)_3$ (10)/5-Cl-SA (20)	CH_3CN	9%[c]	70%[c]

[a]Conditions: **1** (0.2 mmol), **2** (1.3 equiv), $PdCl_2$ (5 mol %), Xantphos (**L10**) (5 mol %), additive, CO (20 bar), solvent (1 mL), stirred at 120 °C for 22 h. [b]Yield was determined by GC with hexadecane as the internal standard. [c]$PdCl_2$ (1 mol %), Xantphos (**L10**) (1 mol %). 5-Cl-SA = 5-chloro-2-hydroxybenzoic acid.

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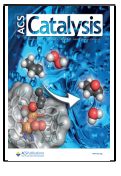

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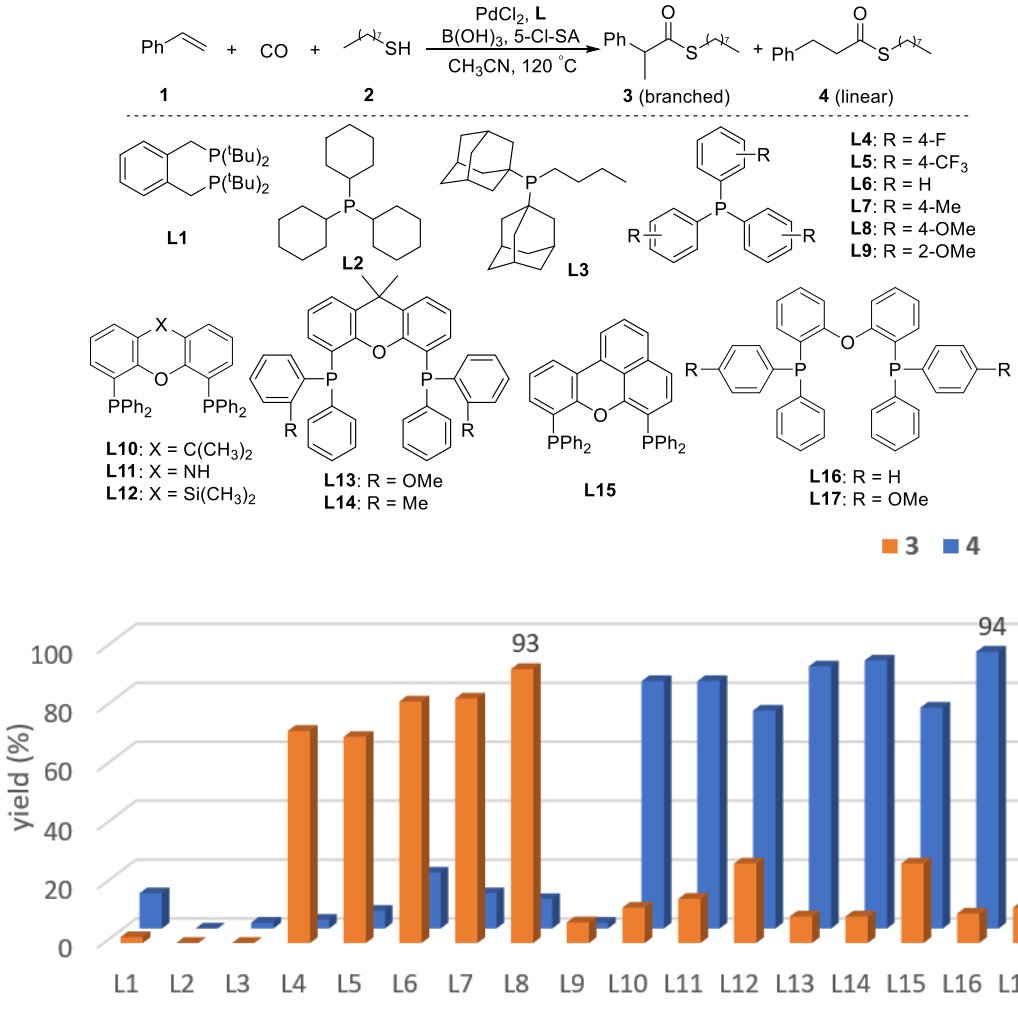
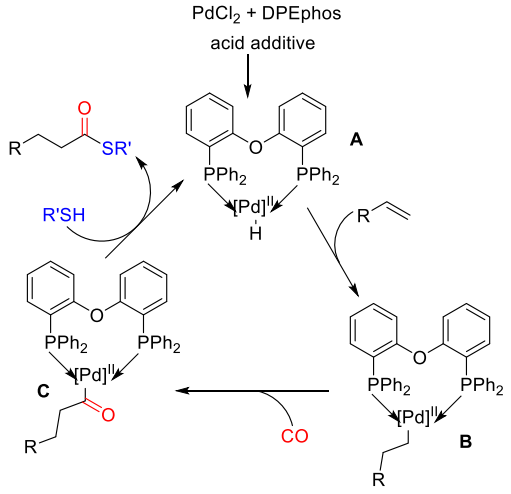
Table 2. Thiocarbonylation of Styrene: Effect of Ligands



[a]Conditions: **1** (0.2 mmol), **2** (1.3 equiv), $PdCl_2$ (5 mol %), ligand (P/Pd = 2/1), $B(OH)_3$ (10 mol %), 5-Cl-SA (20 mol %), CO (20 bar), CH_3CN (1 mL), stirred at 120 °C for 22 h. [b]Yield was determined by GC with hexadecane as the internal standard.

Scheme 2. Proposed Reaction Pathway



(Scheme 1, eq 2).[6] Although linear thioester compounds from thiocarbonylation of alkenes can be detected as side products in the former studies,[4−6] a selective and general procedure for this new transformation, especially for styrenes, has not been achieved yet and stays as a challenge.

Thioesters are a class of chemicals with important applications in various areas.[7] In biosynthetic chemistry, thioesters are common intermediates in fatty acids' generation and degradation and also in many other processes. Because thioesters are mandatory intermediates in several key processes related with ATP usage and regeneration, they are even considered as possible precursors of life.[7d] Consequently, numerous methodologies for their preparation and further synthetic transformation have been developed.[8] However, new and sustainable procedures are still in demand as alternatives. Furthermore, alkenes are readily available in industrial scale by cracking alkanes and naphthalenes. Hence, the use of alkenes as substrates in organic synthesis has attracted considerable attention during the past decades.[9] In order to fill the gap in alkene carbonylation, we herein developed a new procedure on thiocarbonylation of alkenes toward linear thioesters. With palladium as the catalyst, both aromatic and aliphatic alkenes were selectively transformed into the corresponding linear thioesters in good yields (Scheme 1, eq 3).

Our initial studies were started with using styrene **1** and 1-octanthiol **2** as the model substrates. In the presence of $PdCl_2$

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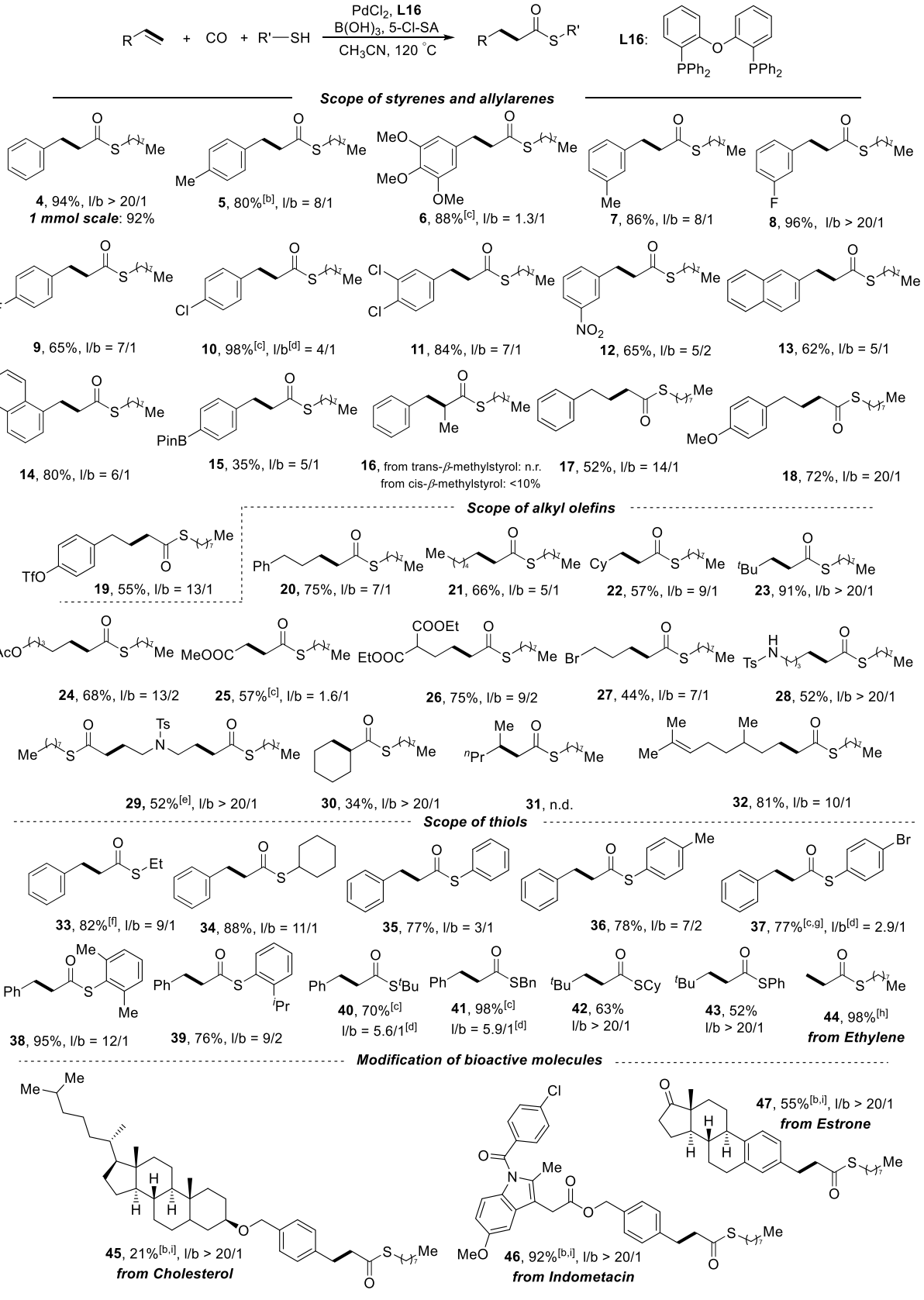
Scheme 3. Synthesis of Linear Thioesters by Thiocarbonylation of Alkenes



[a]Unless otherwise noted, the reaction was performed on a 0.2 mmol scale under the standard conditions. Isolated yields of linear products. [b]4-*tert*-Butylcatechol (5 mol %) was added as additive. [c]Total isolated yield of linear and branched products. [d]Determined by ^{1}H NMR. [e]Diene (0.1 mmol) was used. [f]Three equivalents of ethanethiol was used. [g]One equivalent of 4-bromobenzenethiol was used. [h]Ethylene (3 bar) was used. [i]The reaction was performed on a 0.1 mmol scale.

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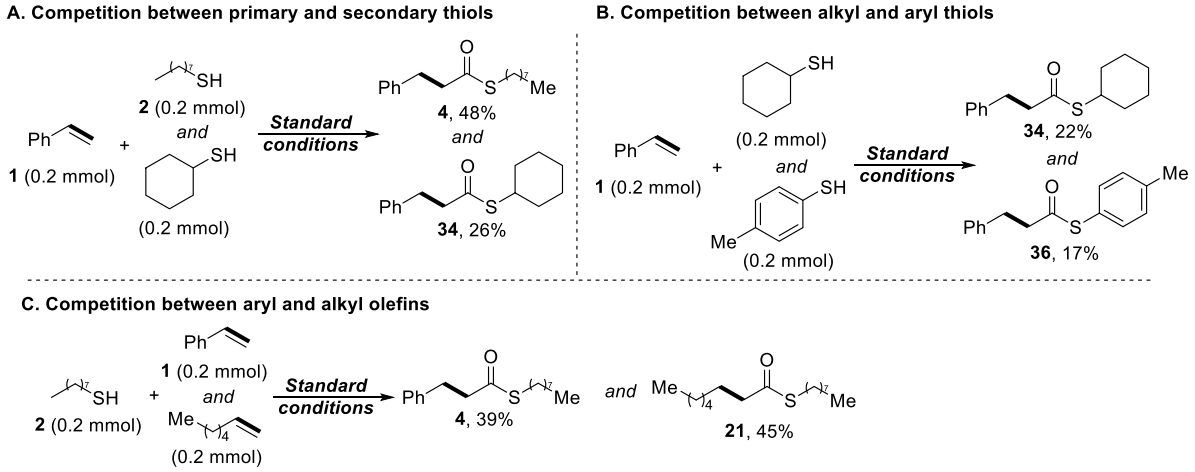
Scheme 4. Competition Reactions



and Xantphos (**L10**) catalyst system under CO pressure, the effects of additives and then solvents were checked (Table 1). Both linear and branched thioesters can be formed in our testing with total conversion of styrene. Interestingly, in the testing of acid additives, 84% yield of **4** together with 12% yield of **3** can be achieved when a combined acid additive was used.[10] The ratio of the two acid additives were checked as well, and the selectivity dropped dramatically when 10 mol % of 5-chloro-2-hydroxybenzoic acid (5-Cl-SA) was used instead of 20 mol %. In the testing of solvents, excellent conversion of styrene can be obtained but with decreased selectivity (Table 1, entries 7−10). However, only a trace amount of thioester was formed when DMSO was used as the solvent, and thioether (none-carbonylation product) can be detected as well (Table 1, entry 11). In our attempts to decrease the reaction temperature, no conversion of substrate could be detected, which might be due to the poison effect of thiol to the palladium catalyst. The selectivity and yield were reduced as well when we performed the reaction under lower CO pressure. However, a 70% yield of linear product **4** can still be formed with 1 mol % of palladium catalyst (Table 1, entry 12).

Subsequently, various phosphine ligands were tested by using $B(OH)_3$/5-Cl-SA as the acidic additive (Table 2). A very low conversion of styrene was obtained when basic and electron-rich phosphine ligands were applied, such as PCy_3 and $BuPAd_2$ (Table 2, **L1**−**L3**). Here, the reaction between basic ligand and acid might be the reason for the loss of activity. Significantly improved yields of branched thioester **3** can be achieved when tris(aryl)phosphine ligands were tested (Table 2, **L4**−**L9**). The best yield of **3** with 93% can be produced when tris(4-methoxyphenyl)phosphine was used as the ligand (Table 2, **L8**). Remarkably, the selectivity between **4** and **3** can be reversed when bidentate phosphine ligands were tested, and **4** became the main product in those cases (Table 2, **L10**−**L17**). Toward the linear selectivity, a 94% yield of **4** was produced with DPEphos as the ligand (Table 2, **L16**).

A possible reaction mechanism is proposed on the basis of our results and previous reports (Scheme 2).[1−6,10] The reaction starts with the generation of the LPd^{II}−H complex **A** from the palladium precursor, ligand, and acid additive. After addition with alkenes, alkylpalladium complex **B** will be formed, which will be transformed into acylpalladium complex **C** after the coordination and insertion of CO. Finally, the desired linear thioesters will be eliminated together with the regeneration of LPd^{II}−H complex for the next catalytic cycle.

With the optimal conditions in our hand, the scope and limitation of this transformation was carried out immediately (Scheme 3). Using 1-octanthiol as the reaction partner, various styrenes were reacted at the first step. In general, moderate to excellent yields of linear thioesters were produced (Scheme 3, **4**−**15**). Both electron-donating and electron-withdrawing groups can be well tolerated. Besides halogen groups, even the nitro group is also compatible here, which is relatively easily reduced under carbon monoxide atmosphere in the presence of a metal catalyst (Scheme 3, **12**). Bpin-substituted styrene can also be transformed to give the desired linear thioester in 35% yield (Scheme 3, **15**). This reaction can also be performed on 1 mmol scale without loss of efficiency and selectivity (Scheme 3, **4**).

However, when β-methylstyrol was tested as an example of internal aromatic substituted alkene, low or no thioester could be formed, which is mainly due to the steric effect raised by the ligand applied (Scheme 3, **16**). Notably, the added trans-β-methylstyrol stays nonreacted, and the conversion of cis-β-methylstyrol was less than 20%. Then three examples of allylarenes were tested under our standard conditions, and moderate to good yields of the desired linear products can be isolated without any problem (Scheme 3, **17**−**19**). Aliphatic alkenes as an interesting class of olefins were tested in this system without exception (Scheme 3, **20**−**32**). Several examples of highly functionalized aliphatic alkenes were transformed into the corresponding linear thioesters in moderate to good yields. However, in the case of tested α-methyl substituted alkene **31**, no target thioester can be obtained, although some thioether was detected. In the testing of thiols, in addition to alkyl thiols, thiophenols can be applied as well. Moderate to excellent yields of the desired thioesters can be produced with styrene or 3,3-dimethyl-1-butene as the reaction partner (Scheme 3, **33**−**43**). Ethylene can be used as starting material as well, 98% yield of the target product can be formed (Scheme 3, **44**). Finally, some examples of bioactive molecule substituted styrene derivatives were tested. In our tested cases, the final products can be isolated without any problem (Scheme 3, **45**−**47**).

Finally, competition reactions between different substrates were carried out under our standard conditions as well (Scheme 4). With styrene as the substrate, primary and

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secondary thiols were tested, and the yield of thioester from primary thiol was much higher than the yield from secondary one (48% vs 26%; Scheme 4, eq A). In the competition reaction of styrene with alkyl thiol and aryl thiol, and thiol with styrene and aliphatic alkene, similar yields of the corresponding thioesters were formed without significant difference (Scheme 4, eqs B and C).

In summary, a general and efficient palladium-catalyzed thiocarbonylation of alkenes has been developed. Moderate to good yields of the desired linear thioesters can be produced from readily available alkenes in a straightforward manner. Remarkably, this also represents the first example on thiocarbonylation of styrenes with linear selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00414.

General comments, general procedure, analytic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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