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Ligand-Controlled Regiodivergent Thiocarbonylation of Alkynes toward Linear and Branched *α,β*-Unsaturated Thioesters

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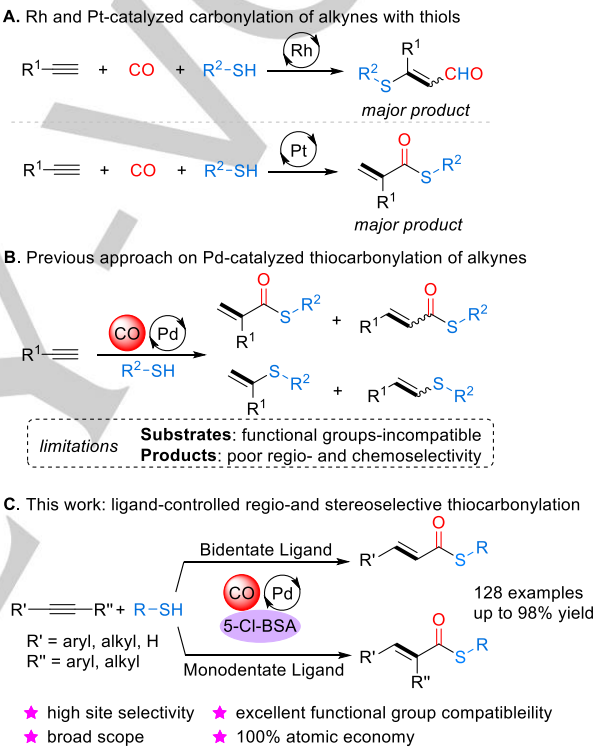
Abstract: Thiocarbonylation of alkynes offers an ideal procedure for the synthesis of unsaturated thioesters. In this report, a robust ligand-controlled regioselective thiocarbonylation of alkynes is developed. Utilizing boronic acid and 5-chlorosalicylic acid as the acid additive to *in-situ* form 5-chloroborosalicylic acid (5-Cl-BSA), and bis(2-diphenylphosphinophenyl)ether (DPEphos) as the ligand, linear *α,β*-unsaturated thioesters were produced in a straightforward manner. Switching the ligand to tri(2-furyl)phosphine can turn the reaction selectivity to give branched products. Remarkably, this approach also represents the first example on thiocarbonylation of internal alkynes.

Introduction

Transition-metal-catalyzed carbonylation reaction is fundamentally important organic transformation by its modularity and the use of carbon monoxide as a cheap and abundant C1 source.[1] Meanwhile, the development of catalytic processes for selective transformations is one of the key goals in organic synthesis. By controlling the regioselectivity, branched and linear products can be obtained selectively from the same substrates. Although recent years have witnessed the successes of regioselective hydroformylation,[2] alkoxycarbonylation,[3] and aminocarbonylation,[4] the development of regioselective thiocarbonylation has been much limited.[5-10] This might be partly due to the strong binding affinities of sulfur-containing compounds to late-transition metals affecting the coordination of ligand with catalyst.[11] And the selectivity of the catalyst system is mainly influenced by the properties of the ligands.[12] Therefore, the pursuit of an alternative catalytic system might constitute, conceptuality aside, a worthwhile endeavor for regiodivergent thiocarbonylation.

Unsaturated thioesters are potent compounds in biosynthetic and organic synthetic chemistry,[13] which usually act as important intermediates to provide the essential chemoselectivity in the synthesis of complexed bioactive molecules and natural products.[14] Besides classic condensation reactions,[13] the thiocarbonylative transformation of alkynes provides an ideal option for producing *α,β*-unsaturated thioesters.[6-9] The first example on transition-metal-catalyzed thioformylation of acetylenes was reported by Ogawa and Sonoda' group in 1990s (Scheme 1A, top), and a small amount of the thiocarbonylation products could be observed when palladium catalyst was used.[6b] Their subsequent work showed that platinum catalysts could improve the selectivity toward the branched product (Scheme 1A, bottom).[6c,d,f]



Scheme 1. Transition-metal-catalyzed thiocarbonylation of alkynes.

The main contributions of palladium-catalyzed thiocarbonylation were accomplished by Xiao, Alper et al.[7] who mainly focused on the transformation of allenes[7b], vinylcyclopropanes[7g], 1,3-dienes[7b,d,e,f]. However, thiocarbonylation reactions of alkynes have been very rarely reported,[8,9] and it is likewise limited by the poor selectivity, more unfortunately, to date, almost no functional groups are compatible within this class of reactions (Scheme 1B). Under this premise, we wondered whether a new catalytic blueprint could be designed to afford high regioselectivity and excellent functional group compatibility for the thiocarbonylation of alkynes. We been able to realize this goal finally after extensive systematic studies. Our protocol is characterized by its ligand-controlled regioselectivity pattern, wide substrate scope and unprecedented functional group compatibility (Scheme 1C).

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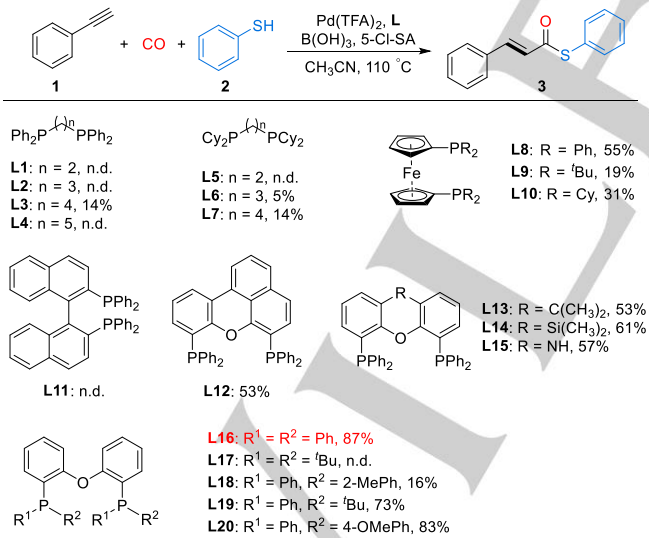
Results and Discussion

Our investigations started with palladium-catalyzed thiocarbonylation of phenylacetylene **1** and thiophenol **2** at 110 ℃ under CO atmosphere (10 bar) in CH_3CN (Table 1). We utilized boric acid ($B(OH)_3$, 10 mol%) and 5-chlorosalicylic acid (5-Cl-SA, 20 mol%) to in-*situ* form 5-chloroborosalicylic acid (5-Cl-BSA).[4f,15] It acted as a mild proton additive to facilitate the reaction and, more importantly, to prevent the deactivation of the ligand under acidic conditions, thus further avoiding the formation of metal plating.[16] Subsequently, a variety of bisphosphine ligands were screened at the first stage. Although conventional ligands (**L1-L7, L11**) barely allowed the reaction to proceed, these observations contributed to our perception that the bite angle of the ligand[17] may have a significant effect on the transformation. The improved yields of the desired product **3** were obtained when ferrocenylphosphines (**L8-L10**) were used as the ligand. Meanwhile, the Xantphos-type ligands such as BenzoXantphos (**L12**), Xantphos (**L13**), SiXantphos (**L14**), and NiXantphos (**L15**) were applied in the reaction, however, still only moderate yields (53%-61%) were available. The direct hydrothiolation products of **1** and **2** were the main byproducts observed in these cases. Encouragingly, an important improvement in the yield of **3** was achieved when employing ligands with more appropriate bite angles (DPEphos-type ligands, **L16-L20**). Finally, 87% yield of the desired product **3** was produced with DPEphos as the ligand (**L16**). Notably, under our best reaction conditions, a control experiment with 30 mol% of 5-chlorosalicylic acid was performed, the desired product **3** was formed in 61% yield with diphenyl disulfide as the major by-product.

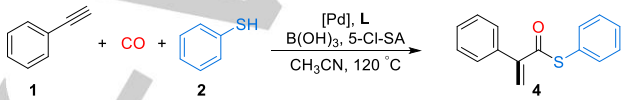
Table 1. Optimization of the thiocarbonylation toward the linear product.[a]



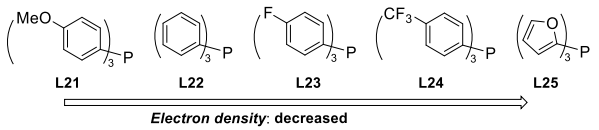
[a] Conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(TFA)_2$ (5 mol%), ligand (5 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), CO (10 bar), CH_3CN (1.0 mL), stirred at 110 ℃ for 14 h. Yields were determined by GC with hexadecane as the internal standard. 5-Cl-SA = 5-chlorosalicylic acid.

When we optimized the linear thioester, trace amount of the branched thioester **4** was detected. According to our knowledge,[18] we believed that the regioselectivity of the branched product can be improved by the choice of proper monodentate ligand. As expected, as shown in Table 2, the yield of **4** significantly increased (form trace to 25%) when replacing DPEphos with triphenylphosphine (**L22**). After experimenting, we found that the yield of **4** increased with decreasing electron cloud density of the ligand (Table 2, entries 1-5). When tri(2-furyl)phosphine (**L25**) was selected as the ligand, the yield up to 50% can be achieved. In the testing of catalyst precursors, $Pd(dba)_2$ and $Pd(CH_3CN)_2Cl_2$ resulted in the best results (Table 2, entries 6-9). Finally, after a judicious choice of the reaction concentration and the ratio of the substrates, an optimal reaction condition was constituted, delivering **4** in 80%yield (Table 2, entries 10-11). Notably, traces of linear product could still be detected. Additionally, the use of equal amount of thiol here is to avoid the further reaction between product **4** and the rest thiol which reduced the yield of **4** in consequence.

Table 2. Optimization of the thiocarbonylation toward the branched product.[a]



Entry	Pd catalyst	Ligand	Yield [%][b]
1	$Pd(TFA)_2$	**L22**	25
2	$Pd(TFA)_2$	**L21**	20
3	$Pd(TFA)_2$	**L23**	33
4	$Pd(TFA)_2$	**L24**	49
5	$Pd(TFA)_2$	**L25**	50
6	$PdCl_2$	**L25**	40
7	$Pd(OAc)_2$	**L25**	46
8	$Pd(dba)_2$	**L25**	62
9	$Pd(CH_3CN)_2Cl_2$	**L25**	62
10	$Pd(dba)_2$	**L25**	74[c]
11	$Pd(dba)_2$	**L25**	80[c,d]



[a] Conditions: **1** (0.2 mmol), **2** (0.24 mmol), Pd catalyst (5 mol%), ligand (10 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), CO (20 bar), CH_3CN (1 mL), stirred at 120 ℃ for 14 h. [b]Yields were determined by GC with hexadecane as the internal standard. [c]CH_3CN (1.5 mL). [d]0.2 mmol of **2** was used. 5-Cl-SA = 5-chlorosalicylic acid.

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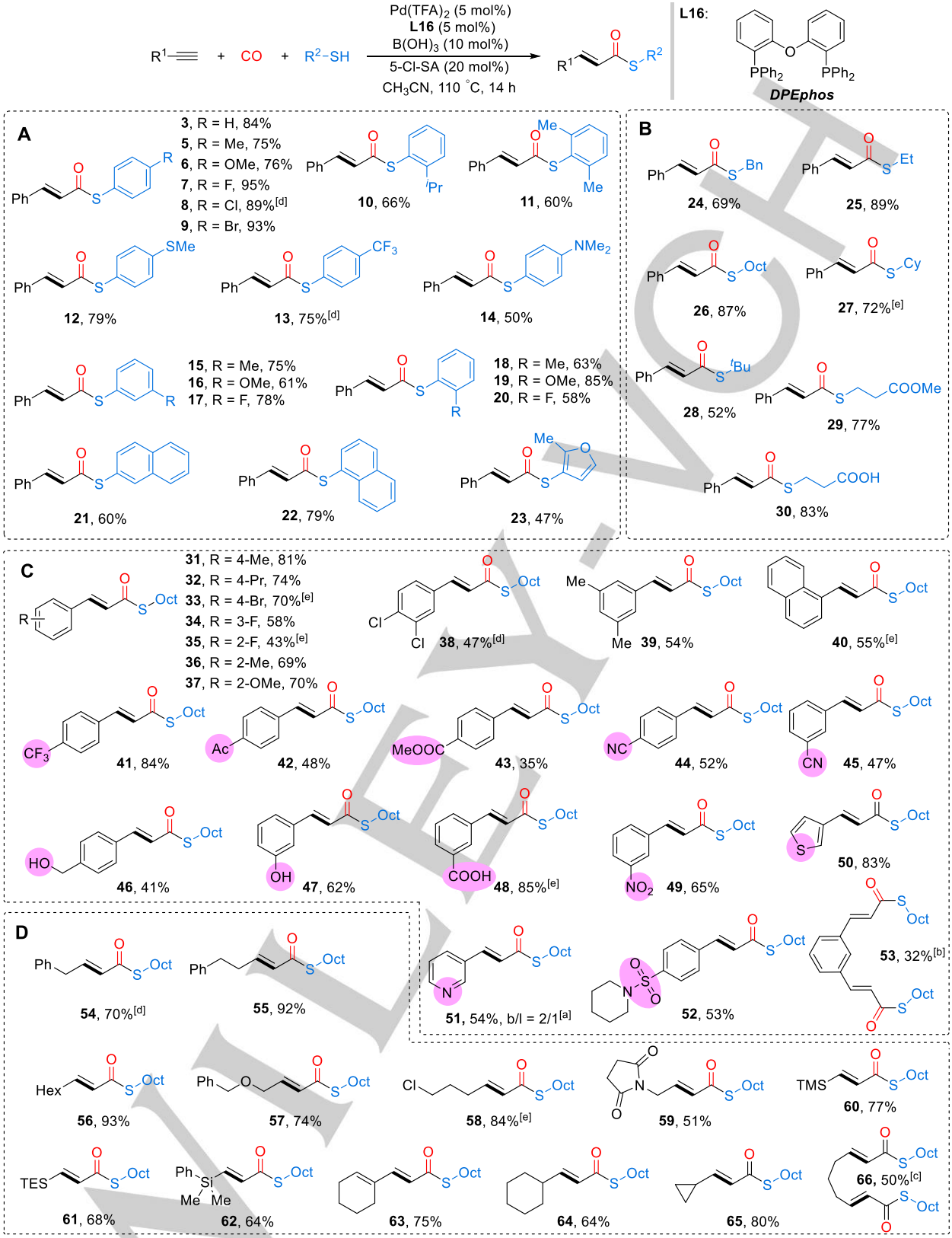

Figure 1. Scope of thiocarbonylation toward linear *α,β*-unsaturated thioesters. Reaction conditions: alkynes (0.2 mmol), thiols (0.24 mmol), $Pd(TFA)_2$ (5 mol%), DPEphos (5 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), in CH_3CN (1.0 mL), stirred under CO (10 bar) at 110 ℃ for 14 h. Unless otherwise noted, the ratio of the product: E/Z > 20/1. Isolated yields. (**A**) Scope of thiophenols. (**B**) Scope of alkyl mercaptan. (**C**) Scope of aryl alkynes. (**D**) Scope of alkyl alkynes. [a]Determined by NMR. [b]1,3-dietnynylbenzene (0.1 mmol) and 1-mercaptooctane (0.2 mmol) were used. [c]1,6-heptadiyne (0.1 mmol) and 1-mercaptooctane (0.24 mmol) were used. [d] 90% purity. [e] 95% purity. Oct = octyl; TMS = trimethylsilyl; TES = Triethylsilyl.

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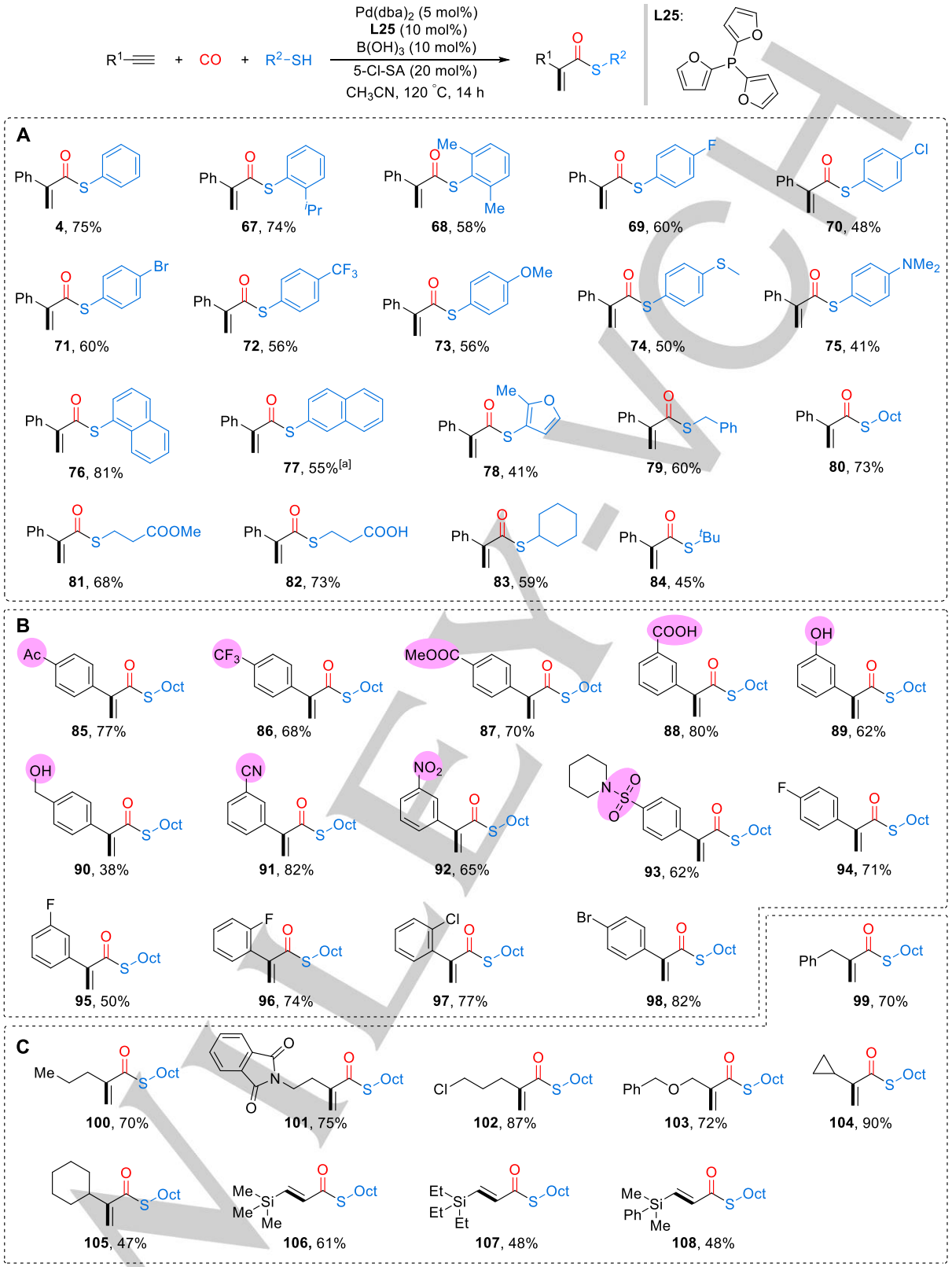

Figure 2. Scope of thiocarbonylation toward branched *α,β*-unsaturated thioesters. Reaction conditions: alkynes (0.2 mmol), thiols (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L25** (10 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), in CH_3CN (1.5 mL), stirred under CO (20 bar) at 120 ℃ for 14 h. Isolated yields. (**A**) Scope of thiols. (**B**) Scope of aryl alkynes. (**C**) Scope of alkyl alkynes. [a] 95% purity.

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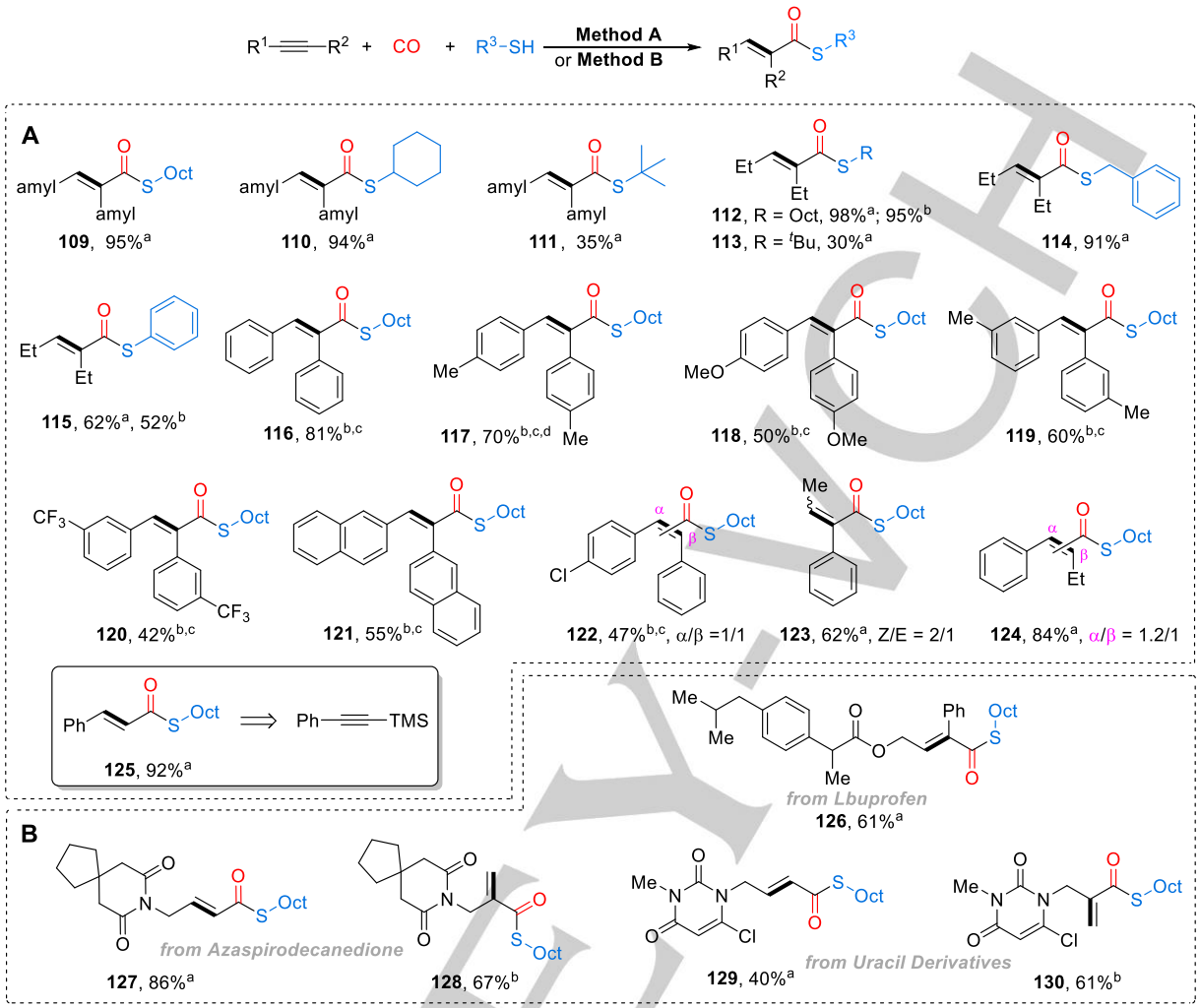

Figure 3. Scope of thiocarbonylation of internal alkynes and bioactive molecules. [a]**Method A**: alkynes (0.2 mmol), thiols (0.24 mmol), $Pd(TFA)_2$ (5 mol%), DPEphos (5 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), in CH_3CN (1.0 mL), stirred under CO (10 bar) at 110 ℃ for 14 h. [b]**Method B**: alkynes (0.2 mmol), thiols (0.2 mmol), $Pd(dba)_2$ (5 mol%), **L25** (10 mol%), $B(OH)_3$ (10 mol%), 5-Cl-SA (20 mol%), in CH_3CN (1.5 mL), stirred under CO (20 bar) at 120 ℃ for 14 h. [c]The reaction proceeded for 24 h. Isolated yields. (**A**) Scope of internal alkynes. (**B**) Modification of bioactive molecules. [d] 95% purity.

With the optimal conditions in hand, the scope of the transformation was carried out immediately. First, the thiocarbonylation of alkynes toward linear *α,β*-unsaturated thioesters was conducted (Figure 1). As evident from the results compiled in Figure 1**A**, both *ortho*-, *meta*-, and *para*-substituted thiophenols can be successfully applied to the reaction and provided the corresponding thioesters in moderate to excellent yields (Figure 1**A**, **3**-**23**). Notably, the steric hindrance (**10**-**11**) or electronic nature (**12**-**13**) of thiophenols hardly effected the transformation. The broad synthetic applicability of the reaction was also reflected in the successful thiocarbonylation of benzyl mercaptan (**24**), primary mercaptans (**25**-**26, 29**-**30**), secondary mercaptan (**27**), and *tert*-butyl mercaptan (**28**). Subsequently, a variety of aryl acetylenes were tested under our standard conditions (Figure 1**C**). Besides alkyl and halogen groups (**31**-**40**), structures containing methoxy (**37**), trifluoromethyl (**41**), acetyl (**42**), ester (**43**), cyano (**44, 45**), hydroxymethyl (**46**), phenol (**47**), carboxyl (**48**), nitro (**49**), thiophene (**50**), pyridine (**51**), or sulfonamide (**52**) can also perfectly be tolerated. The excellent functional groups compatibility demonstrated the robustness of this protocol. Aliphatic alkynes, as an interesting class of unsaturated hydrocarbons, were afterwards tested in this system and transformed into the corresponding linear thioesters in good yields (Figure 1**D**). Even alkyl chloride (**58**) or organosilanes (**60**-**62**) could be accommodated, thus constituting an orthogonal gateway for subsequent manipulation via cross-coupling reactions. Interestingly, diacetylenes could be directly converted to dithioesters, albeit in lower yields (**53**, **66**). Notably, in some cases, the product contains small amount of the other regioisomer and vinyl thioether (noncarbonylation product) as impurities which is very difficult to separate from our target product.

We next turned our attention to study the preparative scope of the branched products (Figure 2). Similarly, both thiophenols and alkyl mercaptans performed well under the conditions (Figure 2**A**). The high regioselectivity of the method is nicely illustrated by the fact that even sterically hindered thiols were successfully converted to branched thioesters in moderate to good yields (**67, 68, 83, 84**). In addition, various aryl acetylenes passed the test

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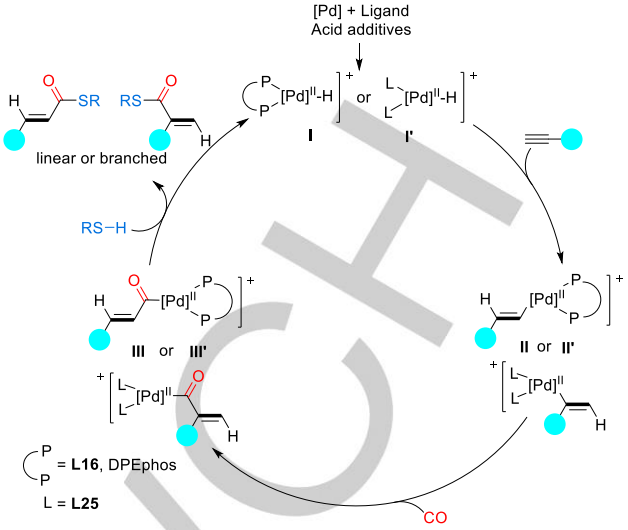
and delivered the corresponding products in satisfactory yields (Figure 2**B**). Likewise, a number of functional groups such as acetyl (**85**), trifluoromethyl (**86**), ester (**87**), carboxyl (**88**), phenol (**89**), hydroxymethyl (**90**), cyano (**91**), nitro (**92**), sulfonamide (**93**), and halides (**94**-**98**) could be accommodated. Furthermore, the alkyl alkynes posed no problems (Figure 2**C**). Notably, the tertiary acetylenes afforded the linear products under the conditions, no corresponding branched thioesters could be detected (**106**-**108**). We speculate that this result is mainly due to the steric hindrance effect from the substrates. It is important to mention that the regioisomers (10-20mol%) can be formed in some cases as well which can not be removed from our target product.

To the best of our knowledge, a catalytic thiocarbonylation reaction of internal alkynes has not been reported yet. Gratifyingly, as shown in Figure 3A, acetylenes end-capped with either arenes or aliphatic motifs were successfully converted to the desired unsaturated thioesters in moderate to excellent yields (**109**-**124**). Importantly, no need to reoptimize the reaction conditions (Method A and B), which is a rather valuable finding that demonstrates the generality of our protocol. The primary (**109, 112**), secondary (**110**), benzylic (**114**), phenyl (**115**), and even *tert*-butyl mercaptans (**111**, **113**) well carbonylative cross-coupled with alkyl internal alkynes and delivered the corresponding products in good yields. Furthermore, our robust Pd-catalyzed thiocarbonylation event could be extended to the use of π-extended system, diarylacetylenes, albeit with prolonged reaction time (**116**-**121**). Asymmetric internal alkynes were tested as well, however, in which the ligands lost their regulatory role. Neither bidentate (Method A) nor monodentate ligands (Method B) could achieve the regioselectivity for them. The reaction site here was based on the nature of the substrates. With increasing steric hinderance (Me- to Et- to Ph-), the selectivity was gradually losted (**122**-**124**). 1-Phenyl-2-(*tert*-butyl)-acetylene could be involved in the reaction, which was proved by GC-MS, however, only trace amount of the thiocarbonylation product was detected, and the structure could be not determined. Interestingly, the TMS group of trimethyl(phenylethynyl)silane was shed in the reaction (**125**). Finally, some examples of bioactive molecule, such as *Lbuprofen*, *Azaspirodecanedione*, and *Uracil* derivatives substituted alkynes were tested and applicable to the reaction (Figure 3**B**). The stereoselectivity in all these tested cases were outstanding, except **123** which might be due to the non-influenceable steric effect of the methyl group.



Scheme 2. Mechanistic proposal.

A possible reaction mechanism is proposed to illustrate the regioselectivity (Scheme 2). We favor an initial generation of Pd-H complex **I** or **I'** in the presence of acid additives and bidentate or monodentate ligand. Then, the anti-Markovnikov or Markovnikov addition of Pd-H complex with alkynes delivers the corresponding linear or branched intermediate **II** or **II'**, which will be transformed into acylpalladium complex **III** or **III'** through the coordination and insertion of CO. Finally, thiol attacks the acylpalladium complex to provide the desired *α,β*-unsaturated thioesters and regenerate the LPd^{II}–H complex for the next catalytic cycle.

Conclusion

In summary, we have discovered a general ligand-controlled regiodivergent thiocarbonylation of alkynes. By employing 5-Cl-BSA as the mild acid additive, various desired linear or branched *α,β*-unsaturated thioesters can be regioselective produced in a straightforward manner. Remarkably, our approach also represents the first example on thiocarbonylation of internal alkynes. The wide substrate scope, high regio- and stereoselectivity, excellent functional group compatibility, robustness, and generality of the protocol suggest that it can be a powerful alternative to known methodologies for preparing *α,β*-unsaturated thioesters.

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Keywords: Ligand-controlled • palladium catalyst • Regioselective • Thiocarbonylation • Thioester

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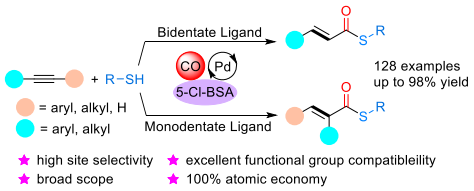

A ligand-controlled regioselective thiocarbonylation of alkynes is reported. Various linear and branched *α,β*-unsaturated thioesters are produced in a straightforward manner. This protocol is characterized by its ligand-controlled regioselectivity pattern, wide substrate scope and unprecedented functional group compatibility. Remarkably, this approach also represents the first example on thiocarbonylation of internal alkynes.