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Carbocyclization of unsaturated thioesters under palladium catalysis†

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An intramolecular thioester–olefin cross-coupling reaction for the preparation of cyclic ketone structures from unsaturated thioesters is described. This method capitalizes on the unique reactivity of thioesters with low-valent palladium catalysts and copper(I) salts to form acyl-metal species. Trapping of such intermediates with alkene functional groups generates the corresponding *exo*-methylene cycloalkanone products. Unsaturated thioester substrates, which can be accessed using a suite of modern synthetic methods, can now be regarded as precursors to complex carbocyclic derivatives.

The modern synthetic chemist, while empowered with an impressive arsenal of reaction technologies that enable rapid assembly of acyclic molecules, is confronted with the rich challenges posed by architecturally complex cyclic structural motifs. In principle, stereodefined linear molecules can function as precursors to carbocyclic derivatives. Yet few methods, among which alkene metathesis[1] is arguably foremost, make possible the conjoining of two ends of a chain to form ring products, a limitation that has frustrated our own efforts in synthesis. Motivated by the difficulties of preparing in convergent fashion a number of heteroatom-rich polycyclic targets, we have sought to identify new types of carbocyclization processes from functionalized acyclic molecules bearing common 'end' groups. Our efforts in this area have resulted in the development of an intramolecular coupling reaction of unsaturated thioesters (Fig. 1A). This method operates under the action of a catalytic palladium source, copper thiophene-2-carboxylate, and zinc formate, the latter of which is critical for achieving efficient turnover numbers. We expect this process to be of general utility in synthesis and hope that our findings embolden future studies to identify new catalytic processes that transform complex linear molecules into carbocyclic ring products.

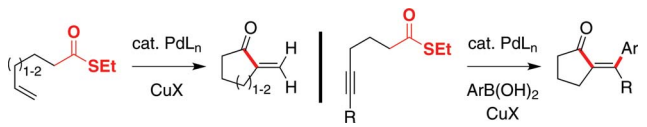
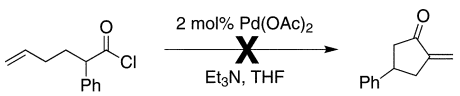


Fig. 1 A palladium-catalyzed thioester carbocylization reaction.

Although intramolecular olefin hydroacylation of unsaturated aldehydes has been studied extensively, the preparation of cycloalkanone products through analogous coupling reactions of carboxylic acid derivatives and alkenes (or alkynes) finds considerably less precedent.[2,3] In our hands, attempts to promote cyclization of δ,ε-unsaturated acid chlorides under palladium catalysis afforded none of the desired cyclic products (eqn (1)).[4,5] These results prompted us to consider alternative starting materials, which included thioester derivatives. The decision to investigate such substrates (*i.e.*, **1**, Table 1) was based on the growing body of literature highlighting the facility of thioesters to engage in metal-catalyzed transformations.[6] Pioneering work by Fukuyama *et al.*[7] and Liebeskind *et al.*[8] has demonstrated that thioesters may be directly converted to the corresponding aldehydes and ketones under palladium catalysis. These conditions often take advantage of thiophilic metal co-factors both to activate the thioester C–S bond for oxidative addition and to sequester the liberated thiolate anion. Privileged among the many available thiophilic metal additives available are the copper(I) salts made prominent by Liebeskind. In a series of reports, Liebeskind has demonstrated the superior ability of select copper(I) carboxylates, in particular copper(I) thiophene-2-carboxylate (CuTC), in concert with palladium salts to facilitate acyl-palladium formation.[7] These studies provided the backdrop for our own investigations.



(1)

Thioester **1** (Table 1) was selected as a convenient starting material for exploratory reaction development. Initial attempts to promote cyclization of this material successfully afforded enone **2**, albeit at low conversion. Extensive screening of palladium sources,[9] ligands, solvents, and temperature had little

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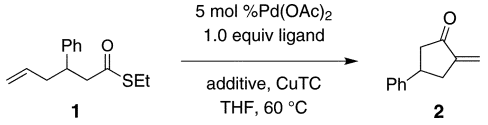
Table 1 Evaluation of reaction conditions for catalytic thioester carbocyclization



Entry[a]	Ligand	Additive	CuTC equiv.	Conversion[b]
1	$P(2\text{-furyl})_3$	—	3.2	25[c]
2	$P(OMe)_3$	—	3.2	30
3	$P(OMe)_3$	—	1.6	30
4	$P(OEt)_3$	—	1.6	30
5	$P(O^iPr)_3$	—	1.6	10
6	$P(OMe)_3$	Et_3N	1.6	20
7	$P(OMe)_3$	$^iPr_2NEt$	1.6	15
8	$P(OMe)_3$	$Zn(OAc)_2$	1.6	30
9	$P(OMe)_3$	$Zn(CO_3)$	1.6	10
10	$P(OMe)_3$	$Zn(OTf)_2$	1.6	—
11	$P(OMe)_3$	$Zn(O_2CH)_2$	1.6	80
12	$P(OMe)_3$	$Zn(O_2CH)_2$	0	0
13	$P(OMe)_3$	NaO_2CH	1.6	35[d]
14	$P(OMe)_3$	Cu_2O/HCO_2H	1.6	5[e]

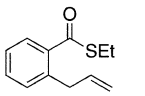
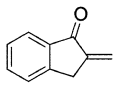
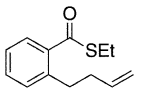
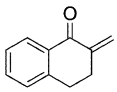
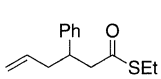
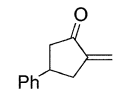
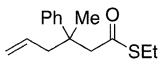
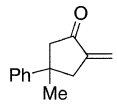
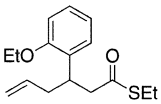
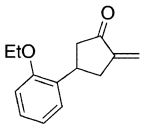
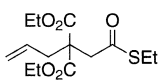
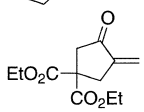
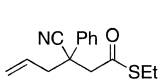
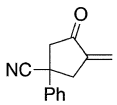
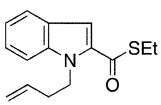
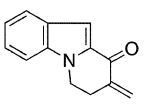
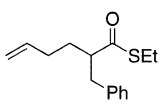
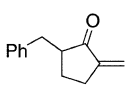
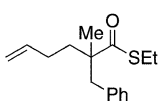
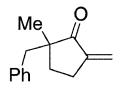
[a] Reactions were performed with 5 mol% $Pd(OAc)_2$, 1.6 equiv. CuTC, 1.0 equiv. ligand, and 1.0 equiv. additive unless otherwise noted. [b] Percent conversion estimated by integration of the unpurified ^1H NMR spectrum. [c] 10 mol% P(2-furyl)$_3$. [d] Reaction performed with 2.0 equiv. NaO_2CH. [e] Reaction performed with 1.0 equiv. Cu_2O and 2.0 equiv. HCO_2H.

effect on improving the reaction. Use of phosphine ligands, such as P(2-furyl)$_3$, in catalytic amounts necessitated that a large excess of CuTC also be employed (entry 1). Increasing ligand loading did not provide for a compensatory reduction in CuTC equivalents. The overall amount of CuTC, however, could be lowered with no evident loss in product conversion by replacing the triarylphosphine ligand with a trialkylphosphite, specifically P(OMe)$_3$ (entries 2 and 3). The effectiveness of P(OMe)$_3$ in this process may be due, in part, to its influence on the partial dissolution of CuTC, which appears to be largely insoluble in THF. It is also possible that the phosphite ligand creates a more sterically accessible and electrophilic coordination environment for alkene binding.[8d] In this regard, use of other phosphite ligands such as P(O^iPr)$_3$ shows a pronounced diminution in product formation (entry 5, Table 1).

Having selected P(OMe)$_3$ as the optimal ligand/additive, we were challenged with making additional modifications to the protocol that would substantially improve catalyst turnover numbers. The influence of tertiary amine additives on reaction performance was examined with the expectation that a nitrogen base would facilitate Pd(0) regeneration (entries 6 and 7); these conditions gave disappointing results. In considering that both Liebeskind[10] and Fukuyama[7b] have utilized zinc compounds to effect cross-coupling reactions with thioorganic substrates, we questioned whether a zinc additive would promote turnover (entries 8–11). Of the zinc(II) salts tested, the formate complex (entry 11) was unique, with production of **2** increasing by over 40% as compared to all other reaction conditions examined. Zinc formate, however, cannot be used in place of CuTC, underscoring the importance of a copper additive for thioester activation (entry 12). Other formate sources do not afford similar enhancements in turnover number (entries 13 and 14). At this time, we speculate that zinc formate may retard the rate of Pd aggregate and/or Pd black formation.

Examination of our optimized protocol with thioester derivatives appearing in Table 2 serves to illustrate the scope and utility of the cyclization reaction. The critical role of zinc formate in this cyclization process is evident from entries 2, 3, 5, 6, 9 and 10; reactions conducted in the absence of zinc formate furnish <30% of the desired product (product % conversion in parentheses). By contrast, our optimized conditions perform with a range of disparate examples, affording both five and six-membered carbocycles in moderate to excellent yield. As noted in related

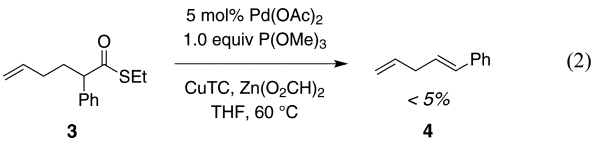
Table 2 Carbocycle synthesis *via* thioester–olefin cross-coupling

Entry[a]	Substrate	Product	Yield[b,c]
1			**90**
2			**46** (0)
3			**76** (25)
4			**83**
5			**80** (20)
6			**89** (30)
7			**94**
8			**30**
9			**50** (0)
10			**33** (0)

[a] Reactions performed with 5 mol% $Pd(OAc)_2$, 1.0 equiv. $P(OMe)_3$, 1.6 equiv. CuTC, 1.0 equiv. $Zn(O_2CH)_2$, THF, 60 °C for 18 h. [b] Isolated yields following chromatography on silica gel. [c] Values in parentheses represent estimated percent product formation (based on ^1H NMR integration) in reactions performed without $Zn(O_2CH)_2$.

processes involving acyl-metal intermediates (*e.g.* intramolecular hydroacylation),[2] formation of 5-membered ring structures is generally more efficient when compared to reactions that furnish cyclohexyl products (entries 1 and 2, Table 2). Not surprisingly, substrates possessing a geminally disubstituted center and that are predisposed towards cyclization are particularly well-suited to this process (*cf.* entries 3 and 4). Carbocyclization reactions also perform efficiently with unsaturated thioesters bearing a range of common functional groups, including ethers, nitriles, and oxy-esters. The tricarbonyl derivative shown in entry 6 highlights the uniqueness of the thioester to undergo selective activation and subsequent cyclization.

Substitution at the α-carbon of the thioester delivers cyclic ketone products in modest yields (entries 9 and 10, Table 2). In these substrates, competitive decarbonylation and β-hydride elimination appears to arrest catalyst turnover.[11] We have found that subjecting α-phenyl thioester **3** to the reaction conditions returns almost entirely starting material and trace amounts of the skipped diene (eqn (2)). Formation of this minor product is the result of decarbonylation of the acyl-Pd intermediate and subsequent β-hydride elimination. The stability of the acyl-Pd species and the rate of CO loss are arguably the principle competing factors that lower catalyst turnover numbers. Future modifications to our protocol that can extend the lifetime of the acyl-metal adduct should lead to increased reaction scope and may allow for the preparation of larger-membered carbocyclic rings.

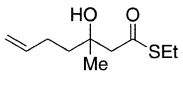
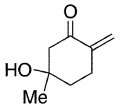
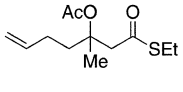
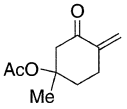
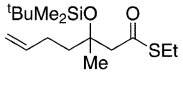
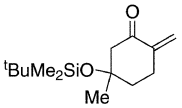
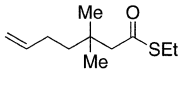
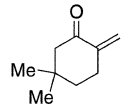
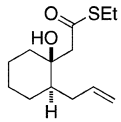
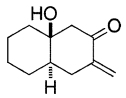
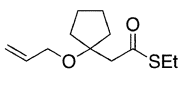
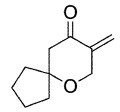


3 **4** (2)

Consistent with our hypothesis that successful cyclization necessitates the acyl-Pd intermediate be rapidly intercepted by the pendant nucleophile, internal alkenes do not engage as coupling partners in this reaction. We conclude that the additional steric hindrance of such olefins adversely influences coordination to the acyl-Pd species. Spent reaction mixtures from tests with internal alkenes consist primarily of starting material, along with trace amounts of decarbonylated decomposition products.

Suppositions based on the instability of the putative acyl-Pd intermediate have guided substrate design. Following the work of Willis and Dong,[12] we have found that appropriate placement of a weakly coordinating group such as an alcohol or ether helps promote cyclization of ε,ζ-unsaturated thioesters to give cyclohexanone products (Table 3).[13] Comparison of entries 1–3 show demonstrable differences in reaction performance based on the choice of the β-substituent group. The highest product yield is obtained for entry 1, in which the tertiary alcohol is positioned appropriately to chelate the acyl-Pd species. Thioesters bearing weakly coordinating β-groups (*e.g.*, acetate, silyl ether) are considerably less effective as substrates (entries 2 and 3), and the *gem*-dimethyl derivative shown in entry 4 gives no detectable amount of the desired cyclohexenone. Other β-alcohol and ether derivatives (entries 5 and 6) can be successfully employed in this cyclization process, giving the desired 6-membered ring structures

Table 3 Internal coordination facilitates ring formation

Entry[a]	Substrate	Product	Yield[b]
1			73
2			37
3			< 10[c]
4			0
5			81
6			61

[a] Reactions performed with 5 mol% $Pd(OAc)_2$, 1.0 equiv. $P(OMe)_3$, 1.6 equiv. CuTC, 1.0 equiv. $Zn(O_2CH)_2$, THF, 60 °C for 18 h. [b] Isolated yields following chromatography on silica gel. [c] Estimated conversion to product based on ^1H NMR integration.

in yields exceeding 60%. Entry 5 highlights the utility of the thioester coupling method for the preparation of fused bicyclic structures, a common motif in natural and synthetic materials. Collectively, these results are consistent with a role for internal coordination of the acyl-Pd intermediate and offer a practical solution for expanding the substrate scope of this method.

We have initiated studies with alkyne-substituted thioesters with the goal of identifying coupling partners other than terminal alkenes that can engage in facile acyl-palladation. In these reactions and as an added feature of this coupling technology, the vinyl-Pd intermediate may be intercepted with a nucleophile to afford β-substituted enone products.[14] We have found that treatment of methyl-substituted alkyne **5** with 10 mol % $Pd(OAc)_2$ and 3.2 equivalents of CuTC in the presence of phenyl boronic acid affords ketone **6** in 56% yield (Fig. 2). Despite the similarity of these conditions to known methods for thioester–boronic acid cross-coupling, none of the phenyl ketone product is detected in this reaction.[8a] Although terminal alkynes fail to cyclize,[15] other internal alkynes such as **7** are efficiently and stereospecifically converted to the β,β-disubstituted enone products. Such compounds are difficult to prepare in isomerically pure form using alternative tactics,[16] a fact that serves to further underscore the utility of our method.

We have developed an intramolecular thioester–olefin cross-coupling reaction as a technology for generating cycloalkanones from simple acyclic precursors. Under the action of catalytic $Pd(OAc)_2$, starting thioesters decorated with a number of

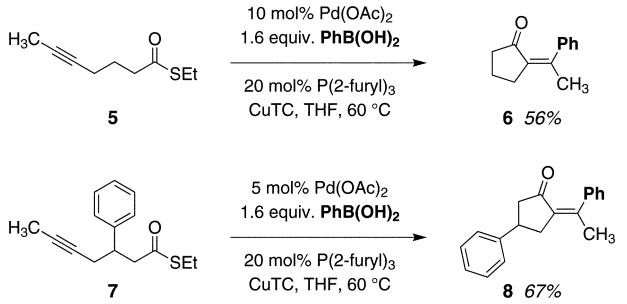


Fig. 2 Alkyne substrates afford tetra-substituted olefin products.

common functional groups can be efficiently processed to the corresponding enones. Our findings offer a distinct approach for carbocycle synthesis and give impetus for further investigations to identify methods that enable ring formation from polysubstituted acyclic starting materials.

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