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Phosphine-Catalyzed Annulation Reactions of 2-Butynoate and α-Keto Esters: Synthesis of Cyclopentene Derivatives

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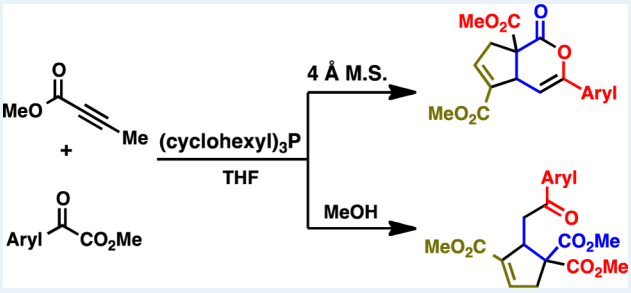
Supporting Information

ABSTRACT: We have developed phosphine-catalyzed annulation reactions for the synthesis of highly substituted cyclopentene derivatives from 2-alkynoate and α-keto esters. These transformations involve carbon−carbon bond cleavage of α-keto esters. Preliminary mechanistic studies suggest that, in addition to facilitating carbon−carbon bond formation, the phosphine catalyst plays a role in promoting methanolysis.



KEYWORDS: *alkynoates, α-keto esters, phosphines, organocatalysis, annulation reactions, fused rings, C−C bond cleavage*

INTRODUCTION

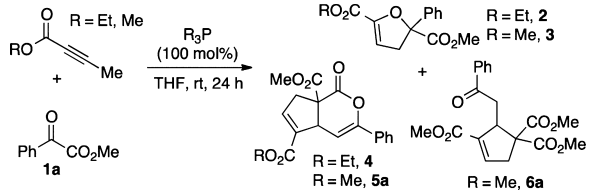
Activation of carbon−carbon multiple bonds with nucleophilic phosphine catalysts offers a robust strategy for the assembly of structurally complex cycloaddition products from relatively simple precursors.[1−5] Of note, since the pioneering work of Lu and co-workers,[6,7] allenic esters have been employed extensively in cycloaddition transformations.[8,9] Similarly, 2-alkynoate esters are known to act as three-carbon synthons and undergo analogous cycloaddition reactions.[6,7,10−14] However, such transformations have been relatively less explored.

Our lab has explored the use of nitrogen- and phosphine-based catalysts for the synthesis of novel products derived from allenoates.[15−19] In these studies, we reported divergent reactions of allenoates and electron-deficient ketones that led to either 2,3-dihydrofurans or oxetanes, under phosphine- and nitrogen-based catalysts, respectively.[20] While working to expand the substrate scope for 2,3-dihydrofuran synthesis, we discovered yet another atypical phosphine-catalyzed reaction between 2-butynoate esters and electron-deficient ketones (in this case, benzoylformate).

RESULTS AND DISCUSSION

In early studies, we discovered that ethyl 2-butynoate and methyl benzoylformate (**1a**), in the presence of 1 equiv of tributylphosphine, delivered dihydrofuran **2** in a modest 30% yield, accompanied by substantial substrate decomposition (Table 1, entry 1). In an attempt to improve the efficiency of the reaction, we explored less nucleophilic trialkylphosphine catalysts.[21] No reaction was observed with tris(2-cyanoethyl)-phosphine (Table 1, entry 2), but use of tricyclopentylphosphine led not only to dihydrofuran **2** (29% yield) but also to a new and unexpected product, bicyclo **4** in 43% yield (Table 1, entry 3). Examination of tricyclohexylphosphine led to only 11% of dihydrofuran **2** and an improved yield for bicyclo **4** (64%).

Table 1. Trialkylphosphine-Catalyzed Reactions of 2-Butynoate and α-Keto Esters[a]



entry	catalyst	alkynoate R	yield (%),[b] 2/3:4/5a:6a
1	*n*-Bu_3P	Et (1.5 equiv)	30:−:−
2	$(NCCH_2CH_2)_3P$	Et (1.5 equiv)	no reaction
3	$(cyclopentyl)_3P$	Et (1.5 equiv)	29:43:−
4	$(cyclohexyl)_3P$	Et (1.5 equiv)	11:64:−
5	$(cyclohexyl)_3P$	Me (3.0 equiv)	1:39:32
6	*tert*-butyl$(cyclohexyl)_2P$	Me (3.0 equiv)	7:31:1
7	$(tert\text{-butyl})_3P$	Me (3.0 equiv)	no reaction

[a]Reactions were conducted with 1.0 equiv of benzoylformate ester and 1.5 or 3.0 equiv of methyl 2-butynoate. [b]Yield of products as determined by ^1H NMR using 2,3-dimethylnaphthalene as an internal standard.

Moreover, we discovered that with 3 equiv of methyl 2-butynoate the reaction gave only a trace amount of dihydrofuran **3**, a 39% yield of bicyclo **5a**, and a 32% yield of yet a third product, monocyclic cyclopentene **6a** (Table 1, entry 5). The structural assignment of **5a** was ascertained by spectroscopic methods and X-ray crystallography and was found to be the *cis*-fused bicyclic compound shown in Figure 1. Compared to entry 5,

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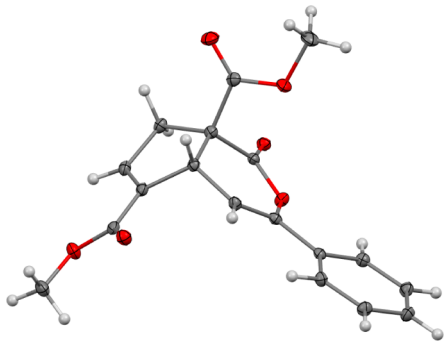
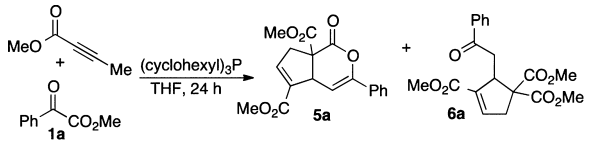


Figure 1. ORTEP diagram of the X-ray crystal structure of bicyclo **5a**.

Table 2. Optimization of Tricyclohexylphosphine-Catalyzed Reactions[a]



entry	catalyst loading (mol %)	temp	additive	% yield, **5a**:**6a** (total)[b]
1	100	rt	4 Å MS	76:–
2	100	rt	MeOH[d]	–:74
3	50	rt	–	44:16 (60)
4	25	rt	–	30:1 (31)[c]
5	50	60 °C	–	51:24 (75)
6	20	60 °C	–	– (37)[c]
7	50	60 °C	4 Å MS	55:–
8	50	60 °C	MeOH[d]	–:75

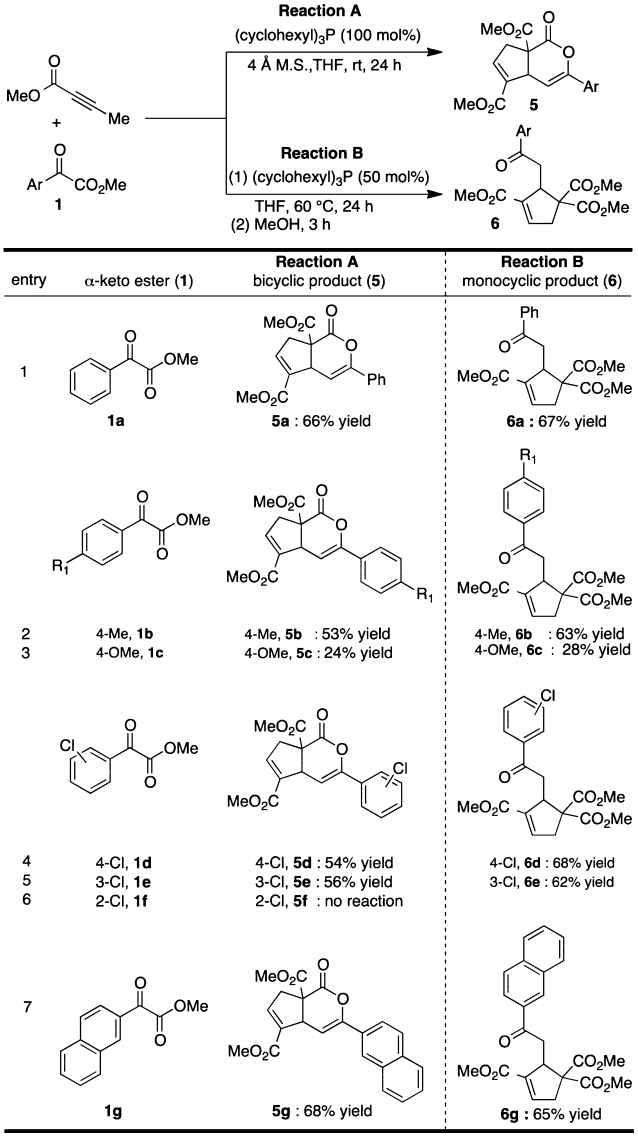
[a]Reactions were conducted with 1.0 equiv of methyl benzoylformate and 3.0 equiv of methyl 2-butynoate. [b]Yield as determined by ^{1}H NMR using 2,3-dimethylnaphthalene as an internal standard. Yield of **3** <5% in all reactions. [c]The total yield did not improve after an additional 24 h of reaction time. [d]MeOH added after 24 h and reaction mixture stirred for 3 h.

use of the bulkier *tert*-butyldicyclohexylphosphine gave lower yields (Table 1, entry 6), while tri-*tert*-butylphosphine gave no reaction (Table 1, entry 7).

Reaction optimization studies using tricyclohexylphosphine as the hit catalyst revealed that addition of 4 Å MS (molecular sieves) to the reaction mixture (hypothesized to remove the methanol byproduct) afforded bicyclo **5a** exclusively in 76% yield (Table 2, entry 1). On the other hand, addition of methanol to the reaction mixture after 24 h, followed by stirring for an additional 3 h, afforded monocyclo **6a** exclusively in 74% yield (Table 2, entry 2). It is worth noting that replacing THF with MeOH as the reaction solvent does not result in product formation. The addition of MeOH after 24 h is thought to facilitate the conversion of **5a** to **6a**, and our preliminary data suggest that the methanolysis reaction is phosphine-mediated (*vide infra*).

As shown in entries 3 and 4 of Table 2, use of a substoichiometric amount of catalyst at room temperature (rt) led to reduced yields. In entry 4 of Table 2, the yield did not improve with an extended reaction time of 24 h.[22] On the other hand, at an elevated temperature of 60 °C, use of 50 mol % tricyclohexylphosphine led to a 75% combined yield of **5a** and **6a** (Table 2, entry 5). Running the reaction at 20 mol % catalyst at 60 °C led to only 37% combined yield, which did not improve with an additional 24 h of reaction time

Table 3. Substrate Scope for the Annulation Reaction of Methyl Butynoate and Aroylformate Esters[a]



[a]Reactions were conducted with 1.0 equiv of α-keto ester and 3.0 equiv of methyl 2-butynoate. The yield is the average isolated yield for two runs.

(Table 2, entry 6). When the reaction was performed with 50 mol % catalyst at 60 °C with the addition of 4 Å MS, a slightly decreased 55% yield of bicyclo **5a** was observed (Table 2, entry 7). Under similar conditions but with the MeOH additive instead, the reaction gave a 75% yield of monocyclo **6a** (Table 2, entry 8). Therefore, the reaction conditions in entry 1 of Table 2 were found to be optimal for the formation of the bicyclic product, while the conditions shown in entry 8 of Table 2 were optimal for monocyclic product formation.

Using the optimized conditions for the synthesis of monocyclic and bicyclic products, we explored the substrate scope with respect to the α-keto ester (Table 3, reactions A and B). Benzoylformate ester **1a** gave an isolated yield of 66% for **5a** and 67% for **6a** (Table 3, entry 1). Electron-rich 4-Me-ester **1b** resulted in 53% yield of **5b** and 63% yield of **6b** (Table 3, entry 2). Interestingly, the more electron-rich 4-OMe-ester **1c** performed poorly in both instances, resulting in a 24% yield of **5c** and a 28% yield of **6c** (Table 3, entry 3). 4-Cl-ester **1d** yielded **5d** in 54% yield and **6d** in 68% yield, while 3-Cl-ester

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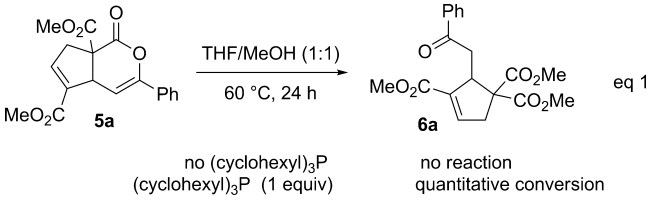
1e gave 56% of **5e** and 62% of **6e** (Table 3, entries 4 and 5, respectively). Curiously, in entry 6 of Table 3, 2-Cl-ester **1f** gave no reaction. With naphthyl ester **1g**, products **5g** and **6g** were obtained in 68% and 65% yield, respectively (Table 3, entry 7).

MECHANISM-DRIVEN EXPERIMENTS

Qualitative analysis of the rates of formation of **5** and **6** at different catalyst loadings (for instance, entry 5 of Table 1 vs entry 3 of Table 2) led us to suspect that the rate of methanolysis might be phosphine-dependent. Consequently, analytically pure bicyclo **5a** was allowed to stir in a THF/MeOH (1:1) solvent mixture at 60 °C. Interestingly, after 24 h, cyclopentene **6a** was not observed (eq 1). However, in the presence of

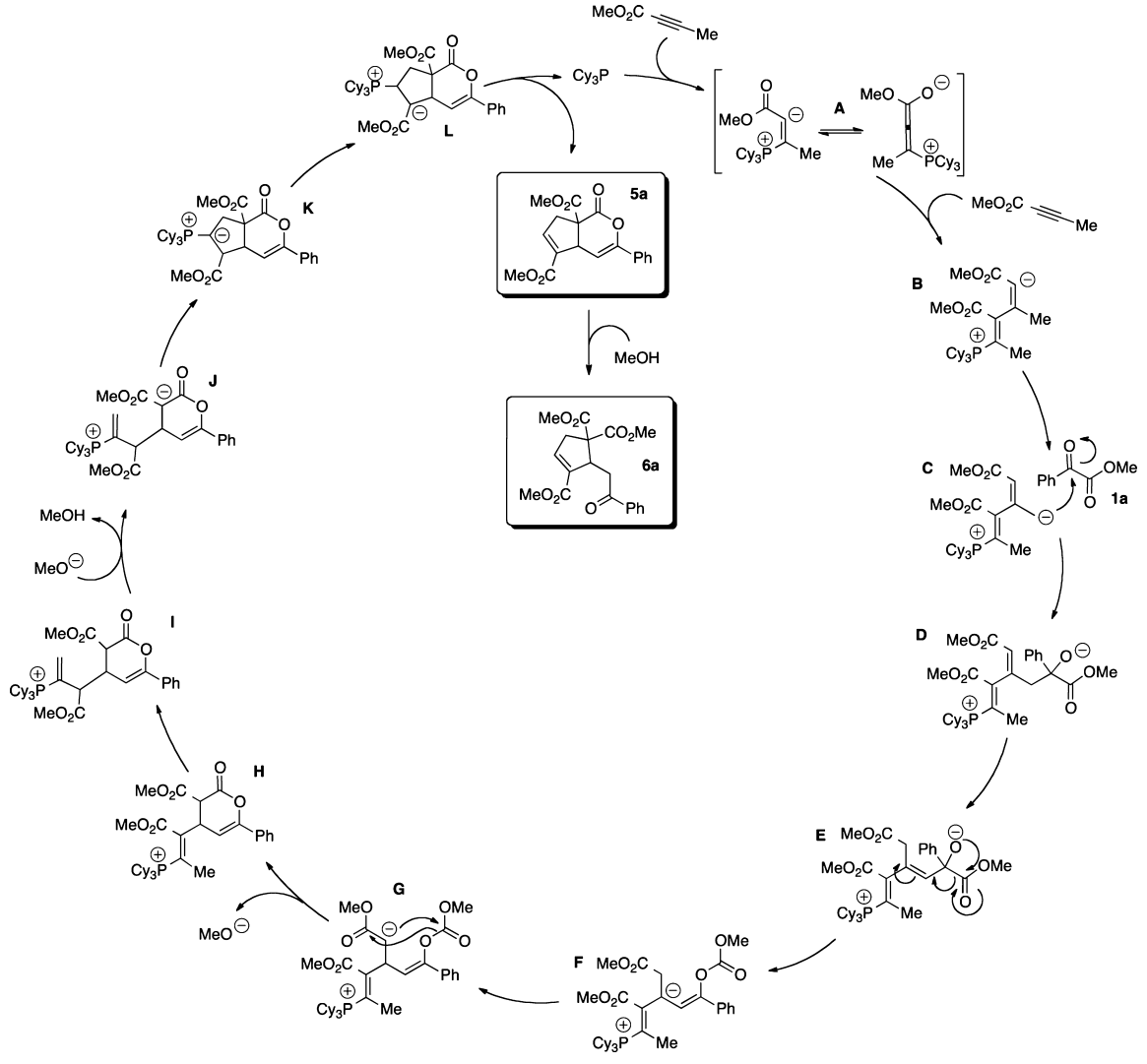


tricyclohexylphosphine, cyclopentene **6a** was observed in quantitative yield after 24 h. These results are consistent with a methanolysis reaction that is phosphine-mediated.

Tributylphosphine is known to facilitate acylation reactions via formation of an acyl phosphonium intermediate.[23,24] While an analogous activation of the lactone moiety in **5a** is plausible, it remains unproven in this system. It is also plausible that the catalyst is assisting in a base-catalyzed pathway that is not fully understood at this time. Perhaps anionic/basic intermediates resulting from phosphonium salt or ylide formation could facilitate methoxide formation, allowing methanolysis.[25]

In all reactions employing tricyclohexylphosphine, dihydrofuran **3** is always formed, albeit in trace amounts (as observed by ^{1}H NMR analysis of unpurified reaction mixtures). We have speculated about the existence of a dihydrofuran (e.g., **2**) as an intermediate en route to the bicyclic product (e.g., **4**). For this reason, dihydrofuran **2** (1 equiv) and methyl 2-butynoate (1 equiv) were subjected to similar reaction conditions as employed throughout reaction A in Table 3. However, the corresponding bicyclic product was not observed, suggesting

Scheme 1. Plausible Mechanism for Phosphine-Catalyzed Annulation Reactions[a]



[a]Cy_3P is tricyclohexylphosphine. For the sake of simplicity, all steps are drawn as irreversible, although reversibility is likely for some, and only a single *E*/*Z* stereoisomer is shown.

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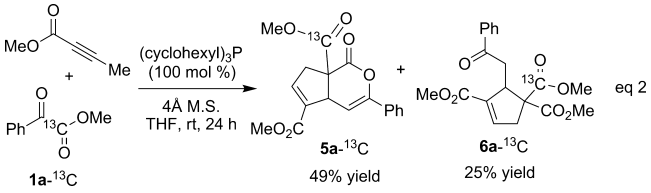
dihydrofuran and the bicyclic product are formed via divergent pathways.

An isotope labeling experiment was also conducted to track the respective carbonyl groups in the annulation products. Use of ^{13}C-labeled benzoylformate **1a** resulted in a 49% NMR yield of **5a**-^{13}C and a 25% NMR yield of **6a**-^{13}C, and both products contained a ^{13}C-labeled ester group (eq 2). In both cases, no ^{13}C scrambling was observed.



The mechanistic details of this transformation have not been fully established, yet our results as well as analogies to related phosphine-catalyzed transformations[6,26−29] allow the delineation of a plausible pathway, shown in Scheme 1.

The reaction is triggered by the addition of the catalyst to methyl 2-butynoate, resulting in zwitterionic intermediate **A**, which adds to another molecule of methyl 2-butynoate resulting in intermediate **B**.[30] The transfer of a proton to give intermediate **C** followed by an addition reaction to **1a** results in intermediate **D**, which undergoes isomerization to intermediate **E**. A rearrangement reaction involving C−C bond cleavage leads to intermediate **F**.[31−33] The transfer of a proton to intermediate **G** followed by a concerted ester group transfer and cyclization reaction results in intermediate **H**.[34] Isomerization to **I** and subsequent deprotonation gives intermediate **J**, which is primed for a second annulation reaction leading to intermediate **K**. Proton transfer gives intermediate **L** set for catalyst elimination, resulting in product **5a** and simultaneously regenerating the catalyst. Methanolysis of **5a** results in product **6a**.

CONCLUSION

We have discovered an unprecedented annulation reaction of 2-butynoate and α-keto esters to give highly substituted cyclopentene derivatives. In this transformation, the tricyclohexylphosphine catalyst exhibits different modes of reactivity, promoting cyclization and methanolysis. The bicyclic product skeleton, containing a cyclopentene ring fused to a dihydropyrone heterocycle, is a scaffold that can map onto certain natural products.[35,36] The presence of multiple carbonyl and alkene functionalities in these synthesized products provides ample opportunity for further functionalization to natural products or other elaborate molecules of interest.

ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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