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Rhodium-Catalyzed Intermolecular Carbonylative [2 + 2 + 1] Cycloaddition of Alkynes Using Alcohol as the Carbon Monoxide Source for the Formation of Cyclopentenones

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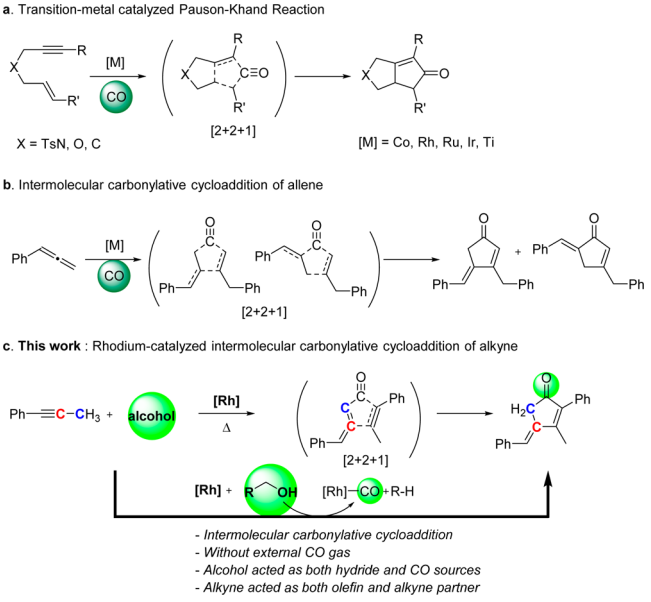
Supporting Information

ABSTRACT: A highly regioselective rhodium-catalyzed intermolecular carbonylative [2 + 2 + 1] cycloaddition of alkynes using alcohol as a CO surrogate to access 4-methylene-2-cyclopenten-1-ones has been developed. In this transformation, the alcohol performs multiple roles, including generating the Rh−H intermediate, functioning as the CO source, and assisting in the isomerization of the alkyne. Alkynes can act as both the olefin and the alkyne partner in the cyclopentenone core.

The cyclopentenone motif is a very powerful synthon for the synthesis of various biologically active molecules.[1] Among the available synthetic methods,[2−4] the Pauson−Khand reaction (PKR) has been developed as a powerful tool in the synthesis of cyclopentenone cores (Scheme 1a).[5] In 1994, an important catalytic conversion, using $Co_2(CO)_8$, $P(OPh)_3$, and 3 bar of CO as reagents, was reported.[6] Since then, other metals, including ruthenium,[7] rhodium,[8] iridium,[9] and titanium,[10] have been established as suitable catalysts of the PKR. Moreover, synthetic utility has been significantly expanded by the incorporation of more reactive allenes in place of alkenes.[11]

Scheme 1. Transition Metal-Catalyzed Formal [2 + 2 + 1] Cycloaddition



Rhodium-catalyzed carbonylative cycloaddition reactions of unsaturated hydrocarbons have been studied extensively.[11,12] Although considerable progress has been made in this area, the intermolecular version may suffer from regioselectivity, reactivity of substrates, or feasibility of the required catalyst. Thus, development of an efficient synthetic method with regiocontrolled, readily available substrates and a proper catalyst is still required. Toward this end, we and other groups reported[13] the carbonylative cycloaddition of allenes with CO in the presence of a catalyst (Scheme 1b). Although the inclusion of allenes within the scope of useful substrates has widened the utility of the rhodium-catalyzed carbonylative cycloaddition, their use[14] leads to regioselectivity problems and undesirable side reactions, such as dimerization and hydrodimerization.[15]

In general, carbonylation reactions, including PK-type reactions, are carried out in the presence of carbon monoxide (Schemes 1a,b). However, the use of CO gas is not desirable due to its toxicity and difficulty to control. Thus, in some studies, CO was replaced by other organic and inorganic carbonyl compounds.[16] Several years ago, we reported the use of alcohols as a CO and hydride in a rhodium-catalyzed intramolecular Pauson−Khand reaction without the requirement for external CO gas and reductive cyclization.[17,18]

With this in mind, we designed a new, one-pot synthesis including alkyne isomerization followed by intermolecular [2 + 2 + 1] carbonylative cycloaddition[19] using an alcohol as a CO surrogate. We hypothesized that the alkyne could act as an allene replacement due to the feasibility of its isomerization with a transition-metal hydride, such as rhodium or iridium.[20] Thus, 1-aryl-1-propynes were expected to serve both as an alkene and alkyne-like moiety in the construction of a cyclopentenone skeleton (Scheme 1c). We envisioned that it would be a straightforward and efficient process for assembling cyclopentenones from readily available 1-aryl-1-propynes[21,22]

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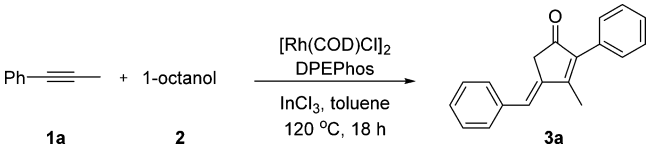
Org. Lett. XXXX, XXX, XXX−XXX

and alcohols. To the best of our knowledge, this is the first report of rhodium-catalyzed intermolecular carbonylative cycloaddition of alkynes with alcohols for constructing cyclopentenones.

The Rh-catalyzed synthesis of 4-alkylidene-2-cyclopenten-1-ones was discovered from the reaction of 1-phenyl-1-propyne in the presence of 1-octanol, bis[2-(diphenylphosphino)-phenyl]ether (DPEPhos), $InCl_3$, and $[Rh(COD)Cl]_2$ in toluene at 120 °C. A yield of 76% was achieved (Table 1).[23]

Table 1. Screening the Reaction Conditions[a]



entry	variation from standard conditions	yield[b] (%)
1	none	76
2	Xantphos instead of DPEPhos	NR
3	$RhCl_3$ instead of $[Rh(COD)Cl]_2$	NR
4	benzyl alcohol instead of 1-octanol	dec
5	4-chlorobenzaldehyde instead of 1-octanol	NR
6	without $InCl_3$	15
7	diphenylacetylene instead of 1-phenyl-1-propyne	NR
8	with 2,6-dichlorobenzoquinone	trace
9	without $[Rh(COD)Cl]_2$	NR
10	without alcohol	NR

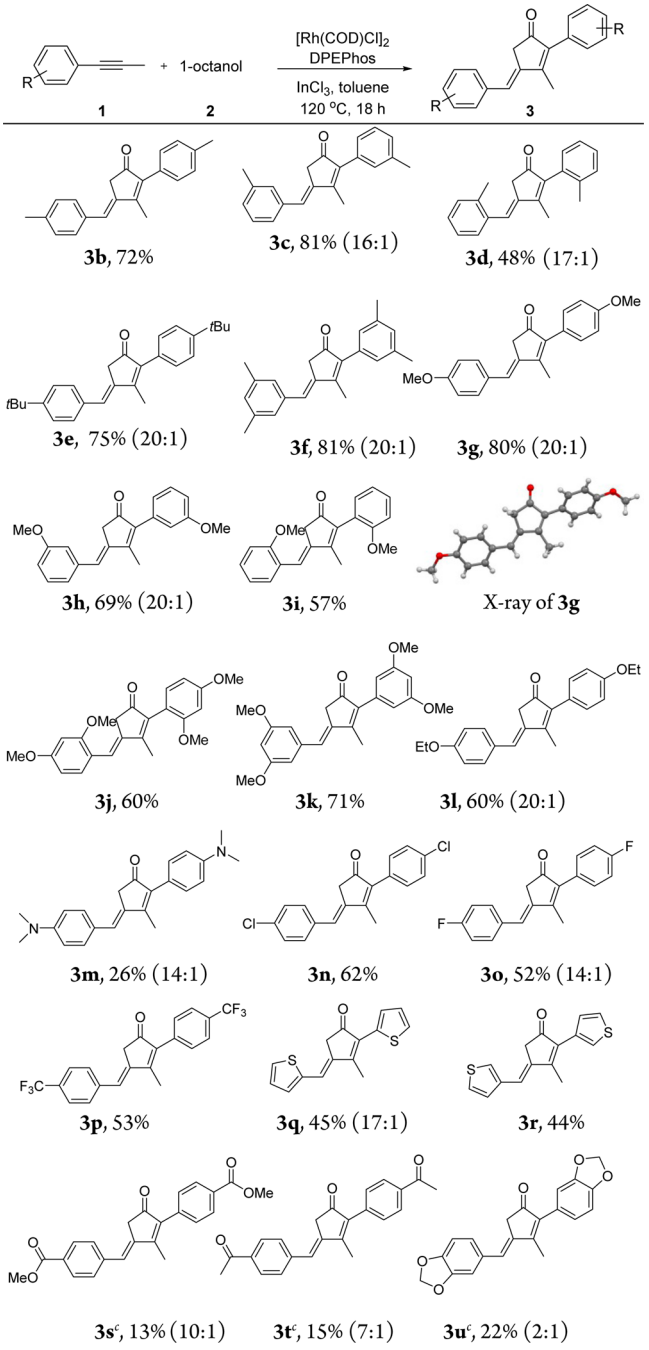
[a]Reaction conditions: 0.3 mmol of **2**, 3 equiv of **1a**, 6 mol % of $Rh(COD)Cl]_2$, 12 mol % of DPEPhos, 15 mol % of $InCl_3$, and 2 mL of toluene. [b]Isolated yield. NR: no reaction.

Next, we screened various reaction conditions (Table 1 and Supporting Information, SI). Ligand exchange from DPEphos to Xantphos[19b] and other bidentate phosphines was ineffective (entry 2 and SI). Other rhodium compounds like $RhCl_3$ were also examined as catalysts (entry 3 and SI). When 1-octanol was replaced with benzyl alcohol, the decomposed product was formed due to the reactivity of benzyl alcohol (entry 4). Interestingly, the use of a CO surrogate, 4-chlorobenzaldehyde,[16] resulted in no desired product (entry 5). Using 1-octanol as a CO surrogate, different additives, varying amounts of catalyst, and different reaction temperatures were explored. Among the additives used, the carbonylative [2 + 2 + 1] cycloaddition was most favorable in the case of $InCl_3$ (see the SI). Without $InCl_3$, the reaction was sluggish (entry 6), suggesting that $InCl_3$ was a key additive in this reaction.[24] Other alkynes such as diphenylacetylene showed no activity (entry 7), which implies that the [2 + 2 + 1] cycloaddition was specific to 1-phenyl-1-propyne.[22] Addition of hydride acceptors gave no product (entry 8). As expected, no product was formed in the absence of the alcohol, the ligand, or the rhodium catalyst (entries 9 and 10 and SI).

With the optimum reaction conditions established, the substrate scope was studied next (Scheme 2).

Arylmethylacetylenes with an electron-donating group (Me, OMe, OEt, and *t*-Bu) on the aryl group were found to be good substrates (**3b–l**). However, a poor yield (26%) was observed for *N*,*N*-dimethyl-4-(1-propynyl)aniline (**3m**). Arylmethylacetylenes with an electron-accepting group (F, Cl, CF_3) on the aryl group were also studied (**3n–p**). For substrates bearing F, Cl, or CF_3 groups, reasonable yields (52%, 62%, and 53%, respectively) were observed. In the cases of 2- and 3-(1-propynyl)thiophene (**3q,r**), reasonable yields (44% and 45%, respectively) were observed. Substrates bearing an ester, a ketone, or an acetal group gave poor yields (13%, 15%, and 22% yields for **3s**, **3t**, and **3u**, respectively) with low selectivity (2:1–10:1). Steric effects were observed in some cases; when a methoxy group was located at the *para* or *meta* positions, the corresponding cyclic enones were isolated in yields of 80% and 69%, respectively. However, in the cases of 1-methoxy-2-(prop-1-yn-1-yl)benzene and 2,4-dimethoxy-1-prop-1-yn-1-yl)-

Scheme 2. Scope with Various Alkyne Substrate and 1-Octanol[a,b]



[a]Reaction conditions: 0.3 mmol of **2**, 3 equiv of **1**, 6 mol % of $Rh(COD)Cl]_2$, 12 mol % of DPEPhos, 15 mol % of $InCl_3$, and 2 mL of toluene. [b]Isolated yield. [c]Regioselectivity (*E*/*Z* isomer) of products shown in parentheses.

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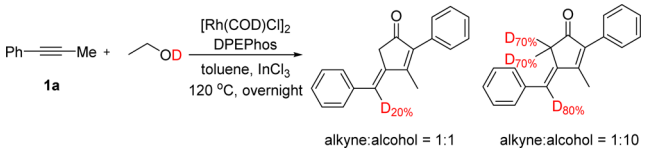
benzene, reasonable yields (57% and 60%, respectively) were observed. The regioselectivity was highly dependent upon the substrate. In some cases, a single isomer was isolated, and most of the products except **3s**, **3t**, and **3u** were isolated with high regioselectivity (generally >14:1).

To gain some insight into the possible reaction mechanism, the following reactions were studied (Scheme 3).

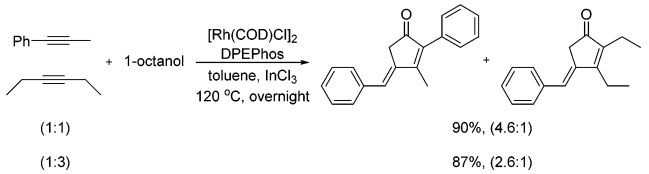
Scheme 3. Carbonylative Cycloaddition Reaction with Ethanol-d_1



Reactions of 1-phenyl-1-propyne (**1a**) with ethanol-d_1 and ethanol-d_6 were studied under the optimized reaction conditions, and the corresponding deuterated product was isolated (Scheme 3 and SI). The degree and position(s) of deuteration were highly dependent upon the ratio of **1a** to ethanol-d_1. When the ratio was 1:1, the percentage of deuterium incorporated at the benzylidene was 20%. When the ratio was 1:10, 80% of the hydrogens at the benzylidene and 70% of the hydrogens at the C-5 position were replaced by deuterium. These observations suggested the involvement of an Rh−H intermediate and a facile scrambling of the three hydrogens at the benzylic and C-5 positions. Moreover, as the amount of ethanol-d_1 increased, the concentration of metal−deuteride species increased, resulting in high contents of deuterium in various positions in the product.

We also performed a competition experiment with various substrates (Scheme 4 and SI). When a 1:1 mixture of

Scheme 4. Intercrossing Experiment of Different Alkyne Systems

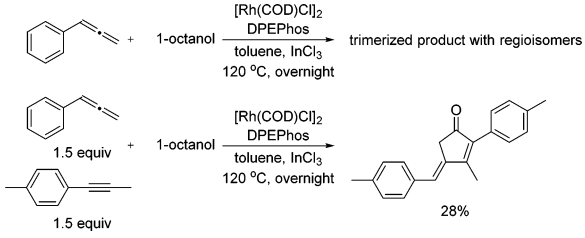


methylphenylethyne and 3-hexyne was used as the substrates, two cyclic enones were isolated in a 4.6:1 ratio with overall 90% yield. In the case of a 1:3 substrate mixture of methylphenylethyne and hept-3-yne, two cyclic enones were isolated in a 2.6:1 ratio with an overall yield of 87%. These observations suggested that an arylmethylethyne, in any combination with other alkynes, could react as both an alkyne and an alkene partner under our conditions, eventually generating cyclic enones.

Phenylallene has often been suggested as a reaction intermediate in Rh-catalyzed catalytic reactions with 1-phenyl-1-alkyne.[21,22a] Thus, phenylallene was included as a substrate in our reaction (Scheme 5).

When phenylallene was reacted with 1-octanol, no cyclopentenone was observed. Instead, a trimer of allene with several regioisomers was detected in the GC analysis with 100% conversion (see the SI). When a 1:1 mixture of phenylallene and methyl-*p*-tolylethyne was reacted with 1-octanol, a cyclic

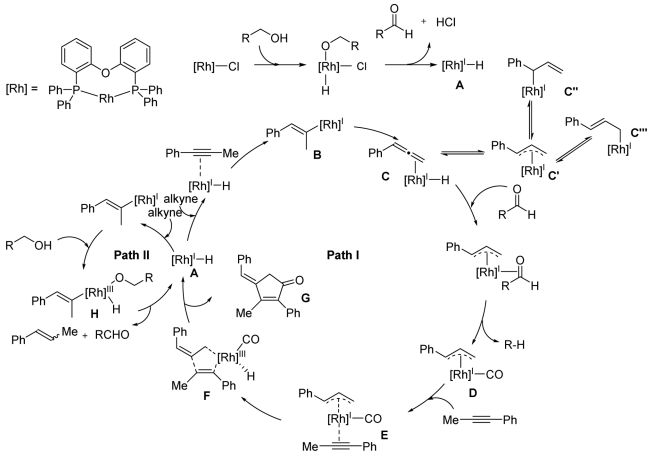
Scheme 5. Reaction of Allene and Allene/Alkyne



enone derived from methyl-*p*-tolylethyne was isolated in 28% yield. Thus, phenylallene did not participate in the carbonylative cycloaddition reaction under our reaction conditions.[15c,21] Moreover, this observation suggested that isomerization of methyl-*p*-tolylethyne to 1-methyl-4-(propa-1,2-dien-1-yl)benzene occurred within the coordination sphere of rhodium through the formation of a π-methyl-*p*-tolylethyne rhodium hydride intermediate resulting from methyl-*p*-tolylethyne and a rhodium hydride. The rhodium hydride might come from a reaction between the rhodium catalyst and 1-octanol.

On the basis of these experimental results, together with observations from previous studies,[17,20−22] a plausible reaction mechanism is proposed for the carbonylative [2 + 2 + 1] cycloaddition of methylphenylethyne in the presence of a rhodium catalyst with an alcohol as a CO surrogate (Scheme 6). The reaction begins with the formation of an Rh−H

Scheme 6. Proposed Reaction Mechanism



intermediate via a sequential reaction of the rhodium compound with an alkyne and alcohol in path I.[25] The alkyne is hydrogenated to 1-phenyl-1-propene during the formation of the Rh−H intermediate **B**. Intermediate **B** then isomerizes to form another intermediate π-allene rhodium complex **C**. The intermediate **C** could form an equilibrium mixture with the π-allyl rhodium intermediate **C′** and Rh−alkene complexes (**C″** and **C‴**). The π-allyl rhodium intermediate then reacts with an aldehyde to form **D**. This intermediate **D** reacts with another alkyne to form the π-allylalkyne rhodium intermediate **E**. The allyl group acts as an olefin partner in the ring formation of the metallacyclic intermediate **F**, which then generates products **G** and **A** by a reductive elimination. The intermediate **A** can then enter the catalytic cycle path II. In one example, the generation of the alkene in path II, 1-phenyl-1-propene, was confirmed by GC analysis. Thus, 3 equiv of alkyne was needed to accomplish

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both cycles: 2 equiv of alkyne was used to build a cyclopentenone backbone and 1 equiv of alkyne was for the reaction of regeneration of rhodium hydride **A** via path II.[23]

In conclusion, we have developed an intermolecular [2 + 2 + 1] carbonylative cycloaddition of simple alkynes in the presence of an alcohol, $InCl_3$, and an $[Rh(COD)Cl]_2$/DPEPhos catalytic system. The alcohol plays an important role in the formation of cyclopentenones by acting as the source of CO and facilitating the Rh−hydride intermediate. In these transformations, alkynes act as both the olefin and the alkyne partner in the Pauson−Khand-type reaction. It is likely that the reaction proceeds via a π-allylalkyne rhodium intermediate. A deeper understanding of these reactions and their application toward organic synthesis, as well as a comprehensive theoretical study on the mechanistic details, are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00458.

Experimental procedure, characterization and NMR spectral data (PDF)

Single-crystal X-ray diffraction data for compound **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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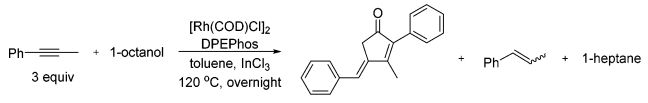
(23) When the reaction was carried out using 1-dodecanol instead of octanol, the formation of 4-methylene-2-cyclopenten-1-one, 1-propenylbenzene, and undecane was confirmed by GC−MS (see the SI) and the cyclopentenone was isolated.



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(25) Neither the addition of allyl-Rh(I) across the C═O bond of the in situ generated aldehyde motif nor the reduction of the allene backbone upon the reductive elimination of the in situ generated Rh hydride formation was observed.

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