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Controlled Rh-Catalyzed Mono- and Double-decarbonylation of Alkynyl α-Diones To Form Conjugated Ynones and Disubstituted Alkynes

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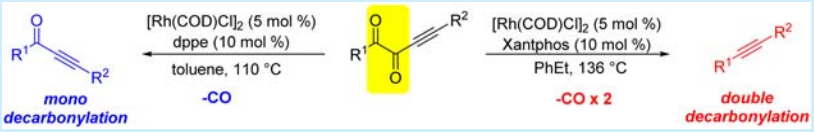
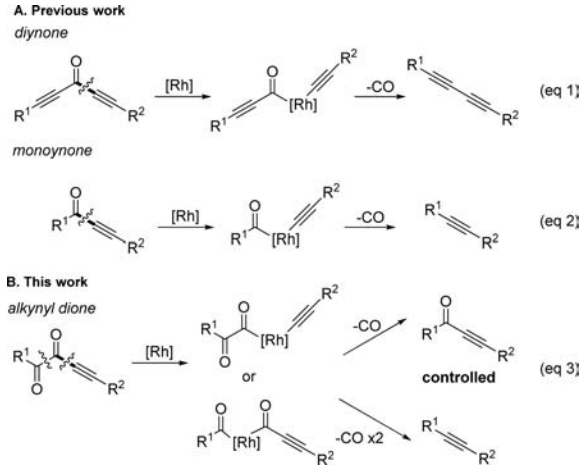
Supporting Information



ABSTRACT: A Rh-catalyzed controlled decarbonylation of alkynyl α-diones is described. By using different ligand and solvent combinations, mono- and double-decarbonylation can be selectively achieved to give conjugated ynones and disubstituted alkynes, respectively. A fundamental study on catalytic activation of unstrained C−C bonds under nonoxidative conditions is presented.

Transition-metal-catalyzed C−C activation has emerged as a useful tool to carry out transformations that can be difficult or impossible under traditional methods.[1] While novel transformations and synthetic applications have been elegantly demonstrated in strained systems or using a permanent/temporary directing group, far fewer examples are available for catalytic activation and subsequent functionalization of non-strained C−C bonds without the aid of chelation.[2,1j,o] Inspired by the broad applicability of the C−C≡N bond activation,[3] our laboratory has been interested in the activation of analogous C−C≡C bonds.[4] Recently, we reported the Rh-catalyzed decarbonylation of diynones and monoynones enabled by using bidentate phosphine ligands with a large bite angle (Scheme 1, eqs 1 and 2).[5] DFT calculations supported an initial cleavage of the alkynyl acyl bond for these transformations. Given the unique nature of this bond cleavage, it is natural to wonder if such a mode of activation can be extended to other systems, such as 1,2-diketones. Perhaps a more intriguing question is whether a controlled activation of the vicinal dicarbonyls, e.g., mono- vs double-decarbonylation, can be realized in a catalytic fashion. As an exploratory study, here we describe the development of a controlled Rh-catalyzed mono- and double-decarbonylation of alkynyl α-diketones to form conjugated ynones and disubstituted alkynes (Scheme 1, eq 3).

Scheme 1. Decarbonylation of Alkynyl Ketones



In 1974, Kaneda and co-workers reported the first examples of Rh-catalyzed decarbonylations of 1,3- and 1,2-diketones; however, low yields and only single decarbonylation were observed.[2d] We have recently shown that mono-decarbonylation of isatins (cyclic 1,2-diones) followed by alkyne insertion can be catalyzed by a Rh(I) catalyst, albeit requiring the use of a directing group.[6] To the best of our knowledge, double-decarbonylation of 1,2-diketones remains an elusive transformation;[7] moreover, C−C activation of an yne-α-dione system has not been studied previously. Hence, these reasons motivated us to investigate a controlled catalytic decarbonylation of alkynyl α-diketones. The challenges are 2-fold: (1) compared to other ketones, yne-α-diones exhibit significantly higher electrophilicity and can undergo facile cycloaddition[8] and intramolecular cyclization;[9] thus, substrate stability and chemoselectivity are not trivial issues; (2) conjugated ynones, the product of monodecarbonylation of yne-α-diones, were previously demonstrated to undergo facile decarbonylation to give 1,2-disubstituted alkynes,[5b] thus discovering a new catalytic system that can selectively halt at the monodecarbonylation stage can be another concern.

To investigate the reactivity of alkynyl diones, 1,4-diphenylbut-3-yne-1,2-dione (**1a**) was employed as the model

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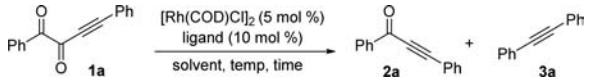
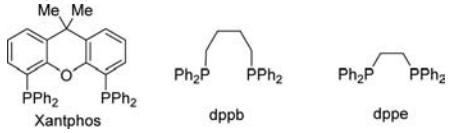
Table 1. Selected Optimization Studies[a]



entry	ligand	solvent (M)	temp (°C)	time (h)	2a, yield[b] (%)	3a, yield[b] (%)
1	Xantphos	ethylbenzene (0.1)	136	48	trace	58
2	Xantphos	chlorobenzene (0.1)	131	48	64	21
3	Xantphos	toluene (0.1)[c]	130	48	33 (40)	
4	dppb	toluene (0.1)[c]	130	48	66 (70)	
5	dppe	toluene (0.1)[c]	130	2.5	63	
6	dppe	toluene (0.05)[c]	130	2.5	69	
7	dppe	toluene (0.01)[c]	130	18	77	
8	**dppe**	**toluene (0.02)**[d]	**110**	**8**	**92**	
9	Xantphos	ethylbenzene (0.02)[d]	136	48	20	75
10	**Xantphos**	**ethylbenzene (0.05)**	**136**	**40**	-	**89**



[a]The reactions were run with alkynyl dione **1a** (0.10 mmol) under a positive pressure of argon. [b]Isolated yields number in parentheses is percent conversion of starting material. [c]Reaction run in a sealed vial. The heating bath temperature is 130 °C. [d]Substrate added via syringe pump over 5 h in the dark.

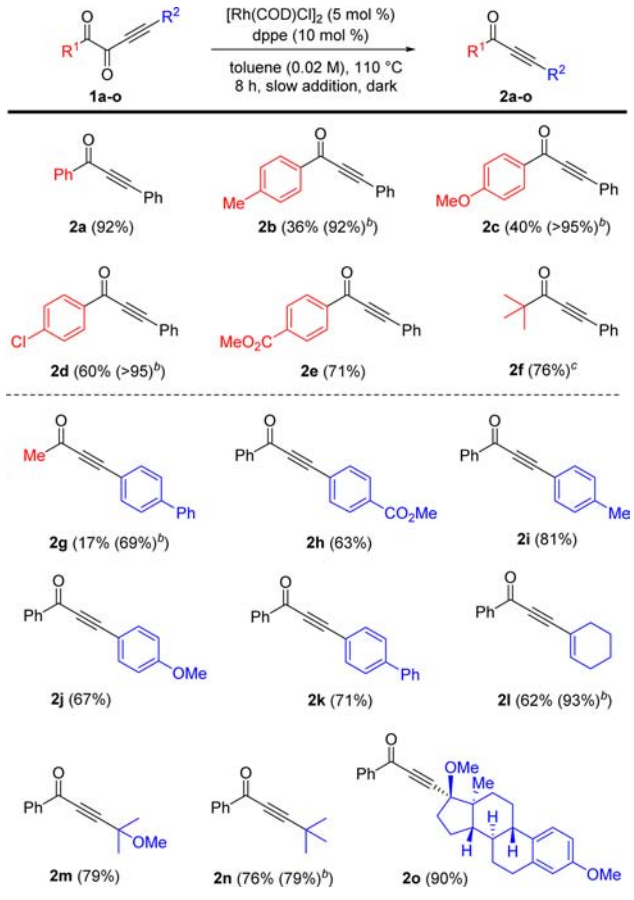
substrate and was first subjected to the previous decarbonylation conditions with 5 mol % of $[Rh(COD)Cl]_2$ and 12 mol % of Xantphos in ethylbenzene (Table 1, entry 1). While the doubly decarbonylated product **3a** can be isolated in 58% yield, the monodecarbonylated ynone **2a** can only be observed in a trace amount. Nevertheless, this preliminary result was encouraging regarding the reactivity of the ynedione functional group; next, we sought to control the selectivity for the formation of **2a** over **3a**.

Lowering the temperature to 131 °C (reflux under PhCl) yielded a mixture of **2a** and **3a** (Table 1, entry 2). Running the reaction in a sealed vial (versus an open system under a positive pressure of argon) in toluene effectively shut down production of alkyne **3a**; however, conversion to ynone **2a** remained low (Table 1, entry 3). A screen of ligands revealed that ligands with a smaller bite angle accelerated the reaction rate, with dppe giving the 63% yield in only 2.5 h (Table 1, entry 5), although the exact reason remains unclear. The major byproducts from this reaction were found to be a mixture of structurally unidentifiable dimeric compounds, which was likely caused by undesired intermolecular reactions. Consequently, the reaction concentration was adjusted to avoid dimerizations. Ultimately, it was found that running the reaction at 0.02 M in toluene, with slow addition of the substrate, provided conjugated ynone **2a** in 92% yield after 8 h (Table 1, entry 8).[10,11]

With the optimal conditions for single decarbonylation in hand, we next optimized the process for double decarbonylation. When slow addition and diluted conditions were applied with the Xantphos and ethylbenzene system, the yield of **3a** was increased, albeit with formation of 20% of **2a** (Table 1, entry 9). Increasing the concentration to 0.05 M ultimately furnished **3a** exclusively in 89% yield (Table 1, entry 10).[12]

With the optimized conditions in hand, the scope of monodecarbonylation was investigated (Scheme 2). A variety of aryl groups containing electron-donating or -withdrawing groups are compatible for this transformation. Lower yields were obtained when an electron-donating group is present on the arene (e.g., **2b** and **2c**), which is largely attributed to the light

Scheme 2. Mono-decarbonylation of Alkynyl Diones[a]



[a]Reactions were run on a 0.10 mmol scale; all yields are isolated yields. [b]Number in parentheses is percent conversion of starting material. [c]The reaction was run with Xantphos as the ligand in refluxing PhEt.

sensitivity of the substrates. In general, the reactions were run in the dark to minimize such an issue. Alkyl groups were also tolerated. While it gave a low yield (24%) under the dppe

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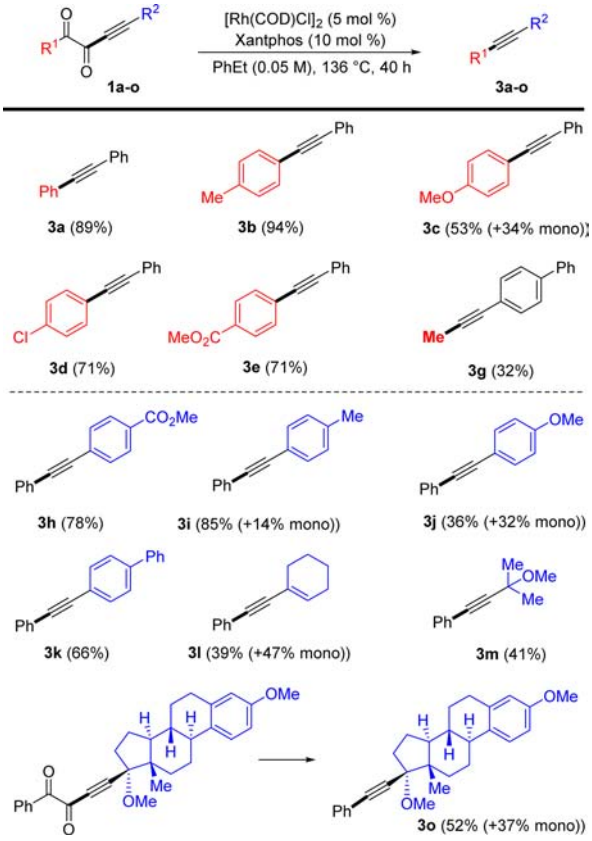
conditions, the *tert*-butyl ketone **1f** gave 76% yield with the Xantphos ligand and under PhEt reflux (vide infra). Methyl ketone **1g** proceeded with a much lower yield (**2g**, 17%), which was likely due to the poor stability of the starting material. A range of substituents on the alkyne part, including alkyl, aryl, and alkenyl groups, were well tolerated, giving the corresponding ynones in good yields without significant electronic bias (**2h**–**n**). Gratifyingly, a complex ethynyl estradiol-derived substrate **1n** furnished the mono-decarbonylation in 90% yield.

The scope of double-decarbonylation was also explored (Scheme 3). A variety of aryl substituents were tolerated, giving

Scheme 3. Double-decarbonylation of Alkynyl Diones[a]

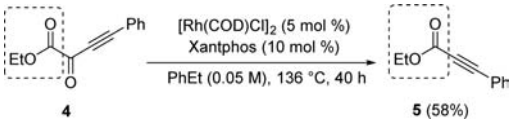


[a]Reactions were run on a 0.10 mmol scale; all yields are isolated yields. **1f** and **1n** gave monodecarbonylated products only.

good to excellent yields (**3a**–**e**, 53–94%).[13] While the methyl-substituted ketone is certainly more challenging due to the aforementioned stability issue, 32% yield of the corresponding alkyne **3g** was nevertheless isolated. Not surprisingly, the bulky *t*-Bu ketone substrate **1f** only gave mono-decarbonylation under the standard double-decarbonylation conditions (vide supra). The alkyne substituents were also examined. Aryl, alkenyl, and alkyl groups were all found to be suitable for this transformation. While the *tert*-butyl-substituted alkyne **1n** only offered the mono-decarbonylation, the analogous OMe-substituted substrate **1m** and the estradiol derivative **1o** smoothly provided the double-decarbonylation products, suggesting an interesting electronic or coordination effect.

Finally, encouraged by the success of C–C activation of α-diketones, we wondered whether this transformation could be generalized to α-keto esters. To our delight, subjecting the alkynyl α-keto ester **4** to our standard Xantphos conditions indeed gave the decarbonylated product, ynoate **5**, in 58% yield (Scheme 4). To the best of our knowledge, this represents the first example of catalytic C–C activation of α-keto esters. Further investigation of this topic is ongoing.

Scheme 4. Decarbonylation of an α-Keto Ester



In summary, an unusual reactivity of alkynyl α-diones is disclosed. Utilizing different rhodium-catalysis conditions, mono- and double-decarbonylative C–C bond formation can be realized in a controlled fashion. These reactions were operated under pH and redox neutral conditions. Both alkyl and aryl groups were tolerated, suggesting a promising substrate scope. In addition, an α-keto ester substrate also successfully underwent decarbonylation to give an ynoate. The new and fundamental reactivity discovered in this work should help to advance our understanding of the transition-metal-mediated activation of unstrained C–C bonds, which is expected to open the door to new avenues for developing alkynyl-transfer reactions.[5b] Mechanistic studies and further expansion of the reaction scope are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02911.

Experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF)

Spectra of unknown compounds and all products (PDF)

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Notes

The authors declare no competing financial interest.

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(10) It was found that exposing the substrate to light for extended periods of time (such as during the slow addition process) led to lowered yields for several examples. For this reason, the reaction was run in the dark.

(11) While the exact reaction mechanism remains to be disclosed, a control experiment showed that subjecting benzil (PhCOCOPh) to the standard reaction conditions gave no observable decarbonylation product. This result suggested that the alkynyl group facilitated the C−C activation.

(12) For additional reaction condition optimizations, see the Supporting Information (Table S1).

(13) Substrate stability is less of an issue under Xantphos/PhEt conditions as this catalyst system is much more active than the dppe one. In less than 1 h, most diones were converted to a mixture of mono- and double-decarbonylation products. The prolonged reaction time allows for conversion of mono to double products.

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