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Addition reactions of heteroatom-COX (X = OR, NR_2, COOR) species with alkynes*

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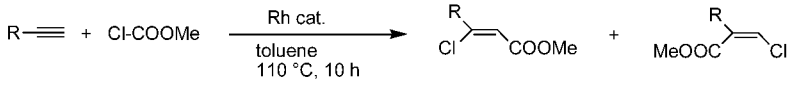
Abstract: Heteroatom-COX species where the heteroatom is Cl, S, or Sn and X is alkoxy, amino, or alkoxycarbonyl group were found to add to the triple bond of alkynes regio- and stereoselectively in the presence of Rh, Pd, or Ni catalyst. Scope and limitation of these synthetic reactions were disclosed. Mechanistic study revealed that oxidative addition of these heteroatom-COX bonds readily took place and the resulting adducts were isolable and characterized by X-ray diffraction analysis. Synthetic applications of the catalytic reactions were also demonstrated.

INTRODUCTION

Development of transition metal complex-catalyzed addition reactions of E–E′ bonds (E ≠ E′, E, E′ = heteroatom or functional group) to alkynes is a research field of considerable interest [1]. These reactions offer simple and efficient synthetic methods for doubly functionalized alkenes, which are useful in organic synthesis. However, the addition reactions of E–C bonds to alkynes are still rare. Among possible variations in this category, the addition of E–COX (X = OR, NR_2) compounds is particularly valuable, when the heteroatom functionality E allows efficient, selective, and functional-group-tolerating transformations. Our study aiming at the creation of a wide spectrum of E–COX bond addition reactions has disclosed four types of these reactions in which the heteroatom functionality is chloro, organostannyl, or organothio. This account describes the state of the art in this category of reactions.

ADDITION OF CHLOROFORMATE

Although hydroesterification of alkynes with carbon monoxide and alcohols or with formate esters has been well documented, the corresponding chloroesterification reaction, which provides a one-step synthesis of β-chloro-α,β-unsaturated esters with high synthetic potential, has never been reported. Exploration for capable catalysts led us to the finding of highly stereo- and regioselective chloroesterification of alkynes with chloroformates (E = Cl, E′ = COOR), catalyzed by rhodium complexes (eq. 1) [2].



(1)

The reaction is generally well catalyzed by $RhCl(CO)(PPh_3)_2$ (87%, 97/3) and $RhCl(cod)(PPh_3)$ (cod = 1,5-cyclooctadiene; 91%, 97/3) and RhBr(cod)(PPh3) (91%, 98/2). Other alkyl and aralkyl chloroformates also react nicely, but phenyl chloroformate displays somewhat low reactivity. As far as ter-

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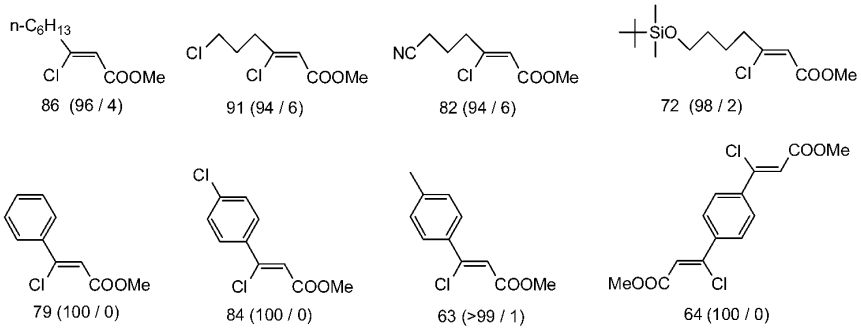
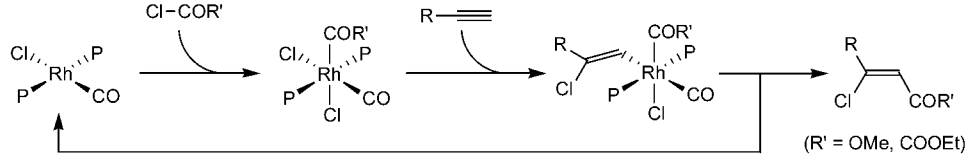
minal alkynes are concerned, the reaction is quite general, and the adducts are formed in high regio- and stereoselectivities in excess of 94% as summarized in Table 1. However, internal alkynes are totally unreactive.

Table 1 Chloroesterification of alkynes.



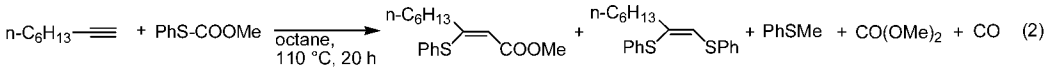
The reaction appears to proceed via the sequence of events illustrated in Scheme 1 (R′ = OMe). The first oxidative addition process readily takes place with methyl chloroformate at 80 °C to generate $RhCl_2(CO)(COOMe)(PR_3)_2$ (PR_3 = PPh_3, PPh_2Me, $PPhMe_2$, PMe_3). These complexes are somewhat thermally unstable in the absence of the chloroformate to regenerate the starting materials. Nevertheless, $RhCl_2$ (CO)(COOMe)$(PPh_2Me)_2$, when heated with 1-hexyne at 110 °C for 3 h, gives the chloroesterification adduct in 28% yield. As to the alkyne insertion process, chloro-rhodation (insertion into Rh–Cl) is more likely than alkoxycarbonyl-rhodation (insertion into Rh–COOR, which must proceed through congested internal attachment of rhodium) in view of the regioselectivity of the catalysis. It is also in agreement with this interpretation that the reductive elimination of organic chlorides from a rhodium(III) center requires much higher temperatures. However, details of the mechanism still await substantiations by experiments.



Scheme 1

ADDITION OF THIOCARBONATE

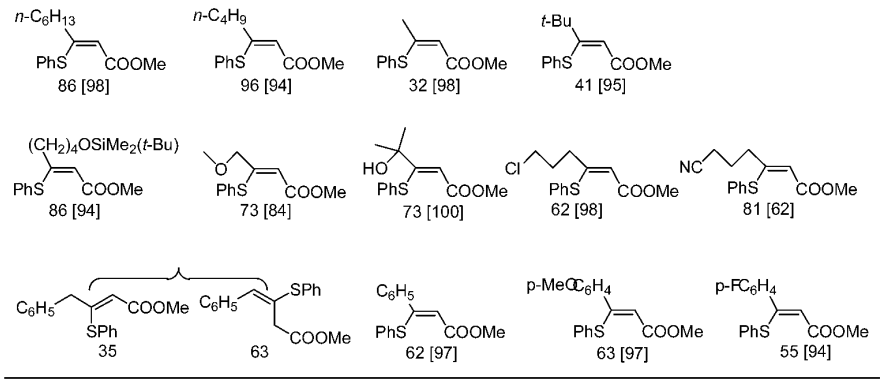
Since the sulfur-to-carbon bond is versatile in transition metal-catalyzed transformations [3], the addition of thioesters is of high synthetic value. $Pd(PCy_3)_2$ has proved to be the right choice to make the addition reactions of *O*-methyl *S*-phenyl thiocarbonate as shown in eq. 2 [4]. The reaction, when effected in the presence of other palladium complex catalysts, is not very clean to afford various by-products; for instance, dithioalkene formation is very extensive when a Pd(dppb) [dppb = 1,4-bis(diphenylphosphino)butane] complex was used in the reaction of 1-octyne.



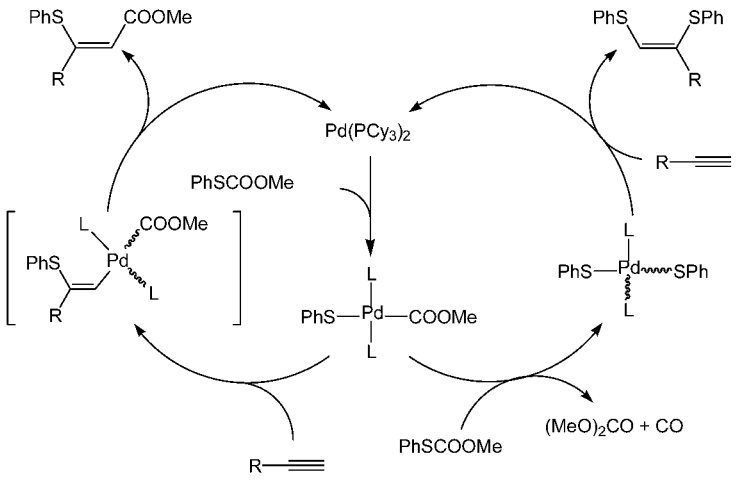
$Pd(PCy_3)_2$	86% (select. 98%)	2%	4%	2%
$PdMe_2(dppb)$	29% (select. 86%)	21%	1%	23%

Another decisive factor affecting the reaction is the nature of solvent; polar solvents such as dimethoxyethane, dioxane, acetonitrile, and dimethylformamide cause extensive decarboxylation of the thiocarbonate to form undesired PhSMe in large quantities (38~69% based on the thiocarbonate used). However, as long as we use $Pd(PCy_3)_2$ and less-polar solvents such as hydrocarbons, the reaction works beautifully to selectively afford β-phenylthio-α,β-unsaturated esters as shown in Table 2.

Table 2 Thioesterification of terminal alkynes.



Thioesterification has been confirmed to be triggered by oxidative addition of the S–C bond of thiocarbonate, and the resulting intermediate reacts with an alkyne molecule to form the corresponding thioesterification product (Scheme 2). However, the intermediate can react with another molecule of thiocarbonate to be converted to dithio palladium species, which we believe is the provenance of the dithioalkene by-product occasionally found in the catalytic reaction.

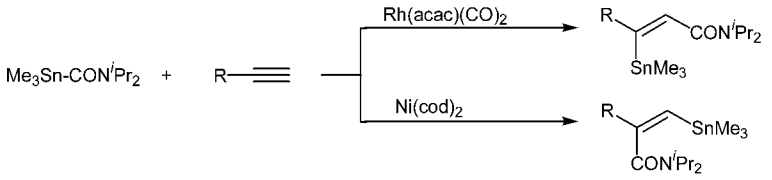


Scheme 2 (L = PCy_3).

ADDITION OF CARBAMOYLSTANNANE

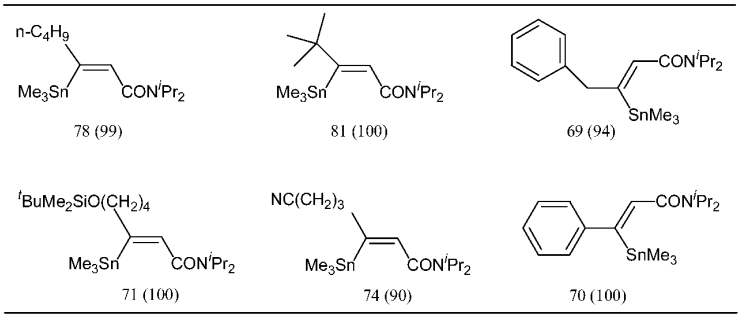
Another direction to explore variations in the category includes the use of amide functionality in place of the ester. $Rh(acac)(CO)_2$ indeed catalyzes the addition of the Sn–$CONR_2$ bond across the C≡C bond, i.e., carbamoylstannation of alkynes with carbamoylstannanes (eq. 3, Table 3) [5]. Although

$Cp^*Rh(CO)_2$ is slightly active, the rhodium phosphine complexes used in chloroesterification and other metal phosphine complexes of Pd, Ni, and Ru do not exhibit catalytic activity at all. However, $Ni(cod)_2$ is active and, very interestingly, displays regiochemical reversal to afford internal attachment of the carbamoyl group. Hiyama and coworkers also have reported the reaction of internal alkynes catalyzed by nickel complexes [6].



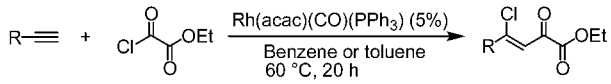
(3)

Table 3 Carbamoylstannation of Alkynes.



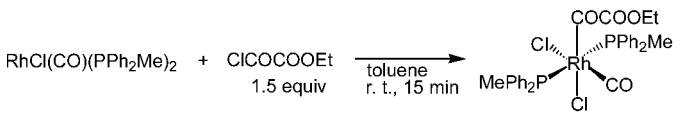
ADDITION OF ALKOXALYL CHLORIDE

A fourth variation came from the use of α-keto ester functionality in place of the simple ester group in the chloroformate. This reaction also proceeds in the presence of Rh(I) mono and bis phosphine complexes. γ-Chloro-β,γ-unsaturated α-keto esters are furnished usually in high yields with high regio- and stereoselectivities (eq. 4) [7].



(4)

The reaction also appears to proceed through the oxidative addition of the ethoxalyl chloride. Different from the reaction with chloroformate, the intermediate adduct is readily formed at room temperature and isolable as stable crystals that allow characterization by X-ray diffraction (eq. 5).

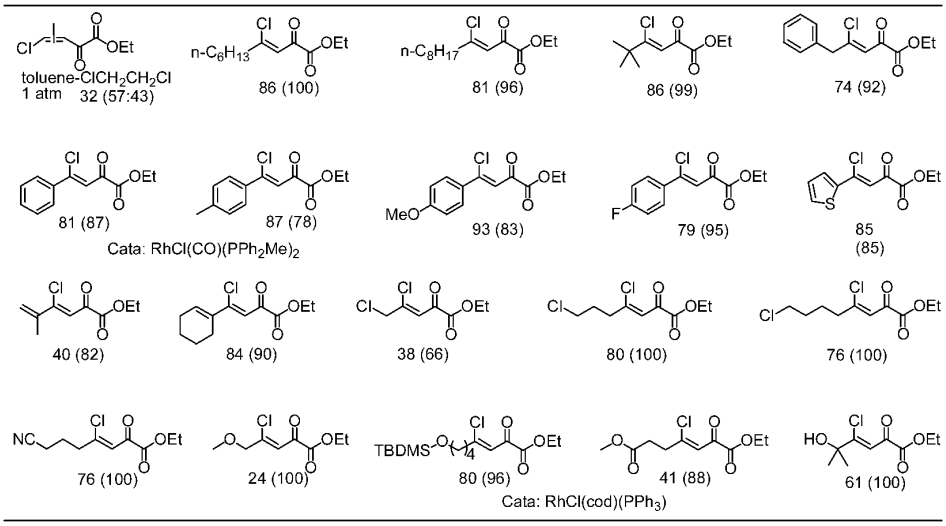


(5)

Some 20 years ago, our and Yamamoto's groups independently found double carbonylation of organic halides that forms α-keto acid derivatives [8]. Mechanistic study related to this reaction has revealed that an α-keto acyl palladium complex very easily undergoes decarbonylation to generate a simple acyl complex. With this past experience in mind, it is rather amazing to learn the easy isolation of the ethoxalyl rhodium complex and the lack or negligible involvement of decarbonylation [9]. The resulting ethoxalyl complex is reactive toward 1-octyne at 60 °C to give the same adduct formed in the catalytic reaction. Accordingly, we tentatively propose the mechanism as illustrated in Scheme 1 (R′ = COOEt).

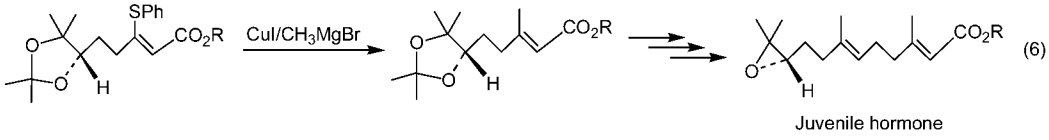
The catalytic reaction also displays a wide applicability as summarized in Table 4, the data in which are obtained by using Rh(acac)(CO)(PPh_3) unless otherwise noted.

Table 4 Chloroketoesterification of alkynes.



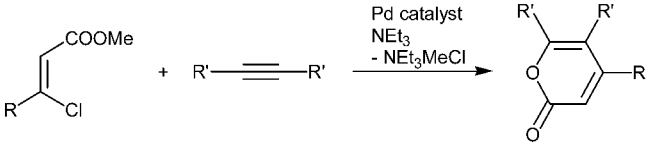
APPLICATIONS OF THESE REACTIONS

The foregoing new reactions provide synthetically useful intermediates, which allow numerous elaborations. For instance, the following synthetic route that involves the use of thioalkenyl ester serves as an example [10].



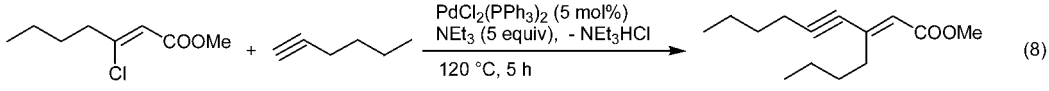
(6)

We have reported on the utility of β-chloro-α,β-unsaturated esters obtained in the chloroesterification. Thus palladium complexes readily catalyze the cyclocondensation of the esters with internal alkynes in the presence of amines to furnish α-pyrones [11].



(7)

The chloroesterification product also readily undergoes the Kosugi–Migita–Stille reaction with organostannanes.



(8)

Much remains to be studied. However, these examples are sufficient to demonstrate the promising use of the products coming from the addition reactions of heteroatom–COX species.

ACKNOWLEDGMENTS

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