Transition-Metal Catalysis

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Stereoselective Synthesis of β-Chlorovinyl Ketones and Arenes by the Catalytic Addition of Acid Chlorides to Alkynes

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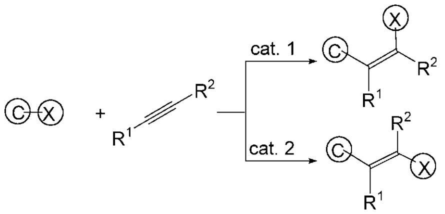
acid chlorides · alkynes · atom economy ·
catalytic addition reactions · iridium

Catalytic addition reactions to C−C multiple bonds can provide access to complex structural units from simple alkene or alkyne building blocks.[1] What sets them apart from more commonly used synthetic transformations, such as cross-coupling or condensation reactions, is their potential to proceed with ideal atom economy.[2] Therefore, the development of new addition reactions could become a key element in the ongoing modernization of the organic chemistry toolkit towards more sustainability. Unfortunately, the design of catalytic reactions in which a substrate X−Y is added across a C−C multiple bond with the formation of carbon–carbon or carbon–heteroatom bonds is extremely challenging: To become true alternatives to intrinsically regiospecific processes involving leaving groups that activate the substrate at one defined position, catalytic addition reactions must be chemoselective in the presence of functionalities that are often more reactive than multiple bonds, regioselective to enable differentiation between the two ends of the C−C bond, and stereoselective for either *syn* or *anti* attack.

A comparably well-studied subset of reactions of this type is the addition of H−X-type substrates, such as alcohols, water, carboxylic acids, or amides, across the C−C triple bond of terminal alkynes.[3] Impressive levels of selectivity for both *E* and *Z* products have been attained, for example, through the use of Ru catalysts with tailored ligands and additives.[3,4] A relatively new and rapidly expanding field of research deals with another subset of this reaction type: the addition of C−X-type substrates, in which C is a carbon residue and X is a functional group, to triple bonds (Scheme 1). Because both groups are integrated into the product, such reactions enable an even higher level of product functionalization within a single reaction step. The carbocyanation reactions developed by Nakao, Hiyama, and co-workers nicely illustrate the synthetic potential of reactions of this type.[5]

Herein, we highlight the catalytic addition of carboxylic acid chlorides to alkynes as a synthetically particularly useful new discovery in this field. This atom-economical transformation provides regio- and stereoselective access to β-chloro α,β-unsaturated ketones from simple and readily available starting materials.



Scheme 1. Catalytic addition to alkynes. The stereoselectivity of the addition depends on the substrates and the catalyst.

Since the products of the addition of acid chlorides to alkynes are versatile intermediates, for example, in the synthesis of heterocycles (see Scheme 5), these reactions have attracted considerable interest in the past. They were found to proceed reasonably well in the presence of several Friedel–Crafts-type catalysts.[6] However, the low stereoselectivity of these methods (the products were usually obtained as mixtures of *E* and *Z* isomers) has limited their synthetic application. Miura and co-workers described the use of a catalyst based on the late-transition-metal rhodium for an oxidative addition–insertion–reductive elimination sequence in which acid chlorides undergo additions to terminal alkynes with a high level of regio- and stereoselectivity.[7] However, the acyl rhodium species intermediately formed eliminated CO so rapidly that, instead of β-chloro α,β-unsaturated ketones, *Z* vinyl chlorides were formed exclusively (Scheme 2, top). Tanaka and co-workers showed that such reactions proceed with the retention of CO in the presence of the same catalyst when chloroformate esters, which are particularly electron-poor substrates, are used.[8] Over the following years, the Tanaka research group developed tailored procedures for the stereoselective, CO-retentive addition of ethoxalyl chloride,[9] perfluorinated acid chlorides,[10] and chloroacetyl chlorides[11] (Scheme 2, bottom).

For the rhodium-based catalyst systems, the degree of CO retention appears to depend solely on the acid chloride substrate. For this reason, the iridium-based protocol recently

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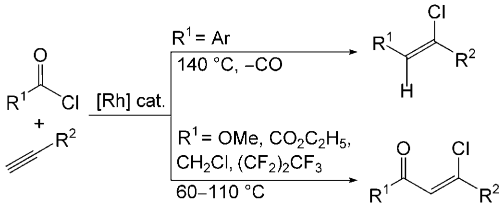
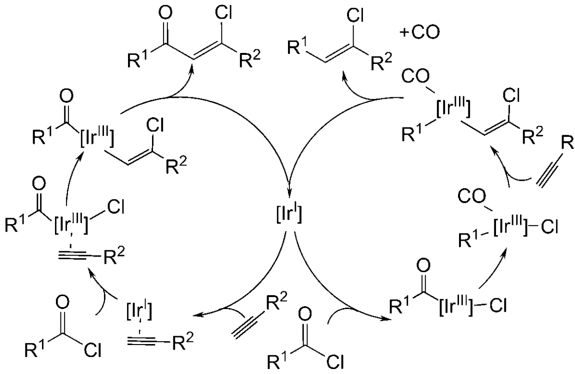


Scheme 2. Catalytic addition of acid chlorides to terminal alkynes with rhodium catalysts: the reactivity observed depends on the type of acid chloride substrate.

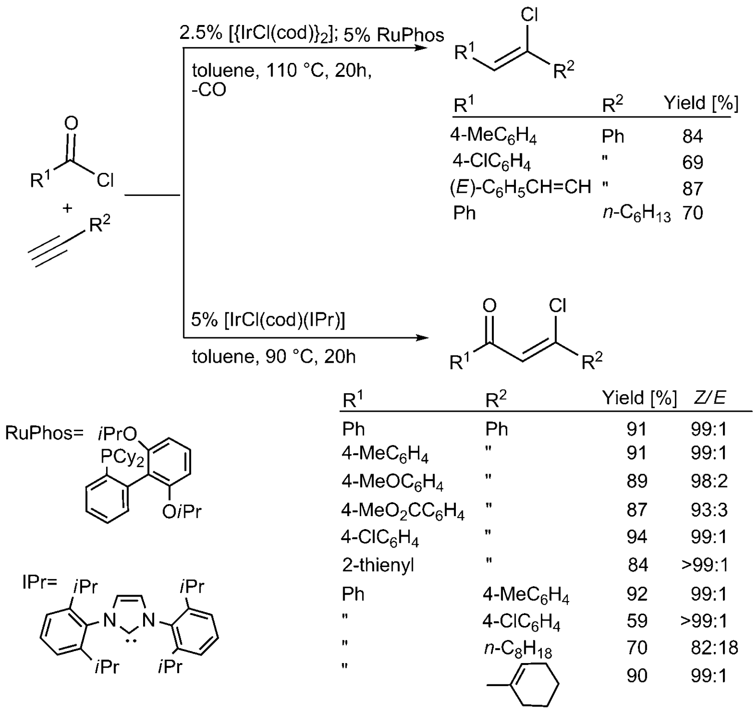
disclosed by Tsuji and co-workers represents a major breakthrough: For the first time, the catalyst composition rather than the substrate defines whether CO is retained in the product or not.[12] In the presence of an Ir^I catalyst with a sterically crowded N-heterocyclic carbene ligand,[13] the addition of simple aromatic acid chlorides to terminal alkynes leads selectively to *Z* β-chloro α,β-unsaturated ketones regardless of the electronic properties of the acid chloride. In contrast, when the carbene ligand is replaced with the electron-rich, bulky, monodentate phosphine "RuPhos",[14] the decarbonylation step is promoted to the extent that the corresponding *Z* vinyl chlorides are obtained exclusively (Scheme 3).

Through the use of these two complementary protocols, the addition of aroyl chlorides with various electronic properties to a range of aliphatic and aromatic terminal alkynes is possible. Depending on the catalyst system employed, the reaction proceeds with CO extrusion or retention. In both cases, the *Z*-configured products are obtained with high selectivity. The reaction still has some limitations: α,β-unsaturated or aliphatic acid chlorides are not suitable substrates, and no reaction is observed for internal alkynes. Furthermore, a reversal of the stereoselectivity by ligand tuning, as reported for other catalytic addition reactions of alkynes,[4] has not yet been successful; thus, opportunities exist for follow-up research.

Tsuji and co-workers proposed two competing catalytic cycles (Scheme 4) based on the established reactivity of acid chlorides with low-valent transition-metal complexes, as well as spectroscopic investigations, stoichiometric studies, and the crystallization of intermediates. The initiating step of the catalytic cycle already determines whether the reaction proceeds with or without decarbonylation. If the oxidative addition of the acid chloride occurs first, as observed for Ir/



Scheme 4. Plausible reaction mechanism.



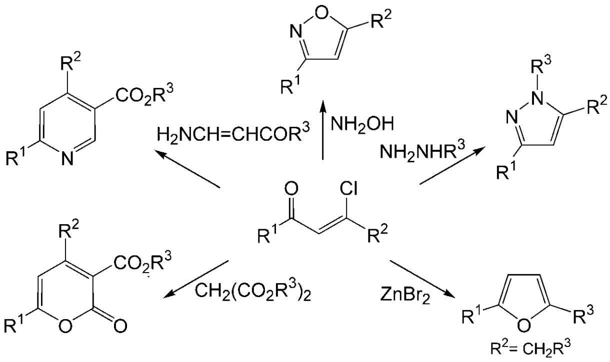
R^1	R^2	Yield [%]
4-MeC_6H_4	Ph	84
4-ClC_6H_4	"	69
(*E*)-$C_6H_5CH{=}CH$	"	87
Ph	*n*-C_6H_{13}	70

R^1	R^2	Yield [%]	*Z*/*E*
Ph	Ph	91	99:1
4-MeC_6H_4	"	91	99:1
4-$MeOC_6H_4$	"	89	98:2
4-$MeO_2CC_6H_4$	"	87	93:3
4-ClC_6H_4	"	94	99:1
2-thienyl	"	84	>99:1
Ph	4-MeC_6H_4	92	99:1
"	4-ClC_6H_4	59	>99:1
"	*n*-C_8H_{18}	70	82:18
"		90	99:1

Scheme 3. Iridium-catalyzed addition of acid chlorides to terminal alkynes. cod = cyclooctadiene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), RuPhos = 2-dicyclohexylphosphanyl-2′,6′-diisopropoxy-1,1′-biphenyl.

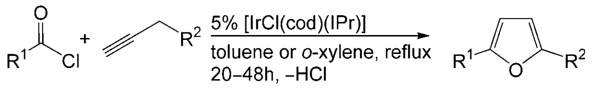
RuPhos complexes, decarbonylation takes place before the alkyne can insert into the iridium–chloride bond (or iridium–carbon bond). A reductive elimination releases the *Z* vinyl chloride product, and the active Ir/RuPhos catalyst is regenerated by the release of carbon monoxide. If the iridium atom is instead ligated by the carbene ligand, the alkyne substrate is the first to coordinate to the metal center. Thus, the alkyne can insert into the iridium–chloride bond (or iridium–acyl carbon bond) immediately after oxidative addition of the acid chloride, before decarbonylation can occur. The *Z* β-chloro α,β-unsaturated ketone product is liberated by reductive elimination to regenerate the original Ir^I species.

Both product types, accessible selectively through the two complementary iridium-based procedures, are of considerable preparative value. A few representative examples for further synthetic elaboration of the *Z* β-chloro α,β-unsaturated ketones are summarized in Scheme 5. Thus, these compounds are immediate precursors of pyridines, isoxazoles, pyrazoles, furans, and pyranones.[15]



Scheme 5. Synthetic uses of *Z* β-chloro α,β-unsaturated ketones.

Tsuji and co-workers have already demonstrated that one of these follow-up reactions can be carried out in the same reaction mixture without isolation of the *Z* β-chlorovinyl ketone intermediate:[12] When terminal alkynes with a methylene unit adjacent to the triple bond were used, 2,5-disubstituted furans were obtained directly (Scheme 6).[16]



Scheme 6. Iridium-catalyzed synthesis of furans.

In view of the rich chemistry outlined herein, it will be interesting to see whether the new synthetic strategy will be made applicable to an even broader range of substrates and spark innovation in the design of new heterocycle syntheses.

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