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Iridium-Catalyzed Addition of Acid Chlorides to Terminal Alkynes

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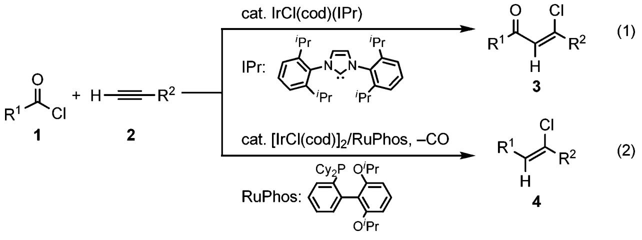
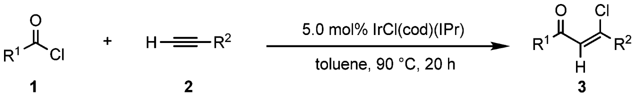
Acid chlorides[1] are valuable substrates in transition-metal-catalyzed reactions because of their facile oxidative addition to metal centers.[2] The addition of acid chlorides to alkynes should be very useful, since both the carbonyl and chloro functionalities can be introduced simultaneously and atom-economically. However, the carbonyl functionality is often lost during the catalysis[1a−c] via facile decarbonylation steps. Miura, Nomura and co-workers[3] have reported a pioneering rhodium-catalyzed addition of acid chlorides to terminal alkynes. In this case, the carbonyl functionality was also lost completely. Recently, Tanaka and co-workers adapted the reaction by employing perfluorinated acid chlorides[4a] or chloroacetyl chlorides[4b] as restricted substrates and achieved the reaction without the decarbonylation. Thus, to date, use of acid chlorides as the substrate[5] has severe limitations in realizing the CO-retentive addition. The Friedel−Crafts addition of acid chlorides to alkynes using a stoichiometric[6a−c] or catalytic (20 mol %)[6d] amount of a Lewis acid is known but suffers from low stereoselectivity of products. Therefore, a capable catalyst system must be developed for the reaction. Herein we report that an iridium N-heterocyclic carbene (NHC)[7] complex successfully catalyzes the addition of common aromatic acid chlorides (**1**) to terminal alkynes (**2**) without decarbonylation (eq 1):

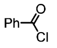
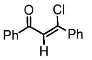
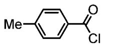
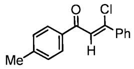
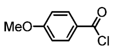
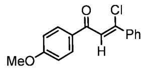
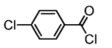
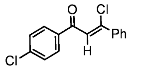
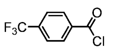
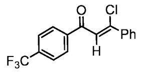
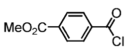
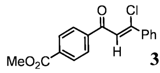
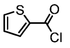
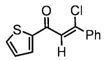
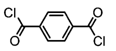
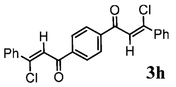
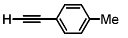
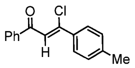
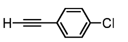
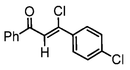
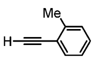
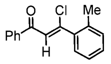
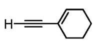
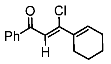
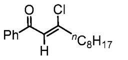


On the other hand, when the NHC ligand is changed to a phosphine, the addition reaction proceeds via decarbonylation (eq 2). Furthermore, the former reaction (eq 1) can be applied to a catalytic synthesis of 2,5-disubstituted furans.

First, the reaction in eq 1 was optimized with benzoyl chloride (**1a**) and phenylacetylene (**2a**).[8] As a result, IrCl(cod)(IPr)[9] was found to be the best catalyst, affording **3a** in 91% yield with high *Z*-selectivity (Table 1, entry 1).[10] Various *β*-chloro-α,*β*-unsaturated ketones (**3**) were obtained regio- and stereoselectively from **1** and **2** (Table 1). Electron-rich (**1b**, **1c**) and electron-poor (**1d**−**f**) aroyl chlorides were smoothly converted to **3b**−**f** in high yields without decarbonylation (entries 2−6). The regio- and stereochemistry of all products were unambiguously determined with the aid of 2D NMR spectroscopy.[8] The *Z* configuration of **3e** and **3f** was further confirmed by a single-crystal X-ray diffraction study.[8] 2-Thenoyl chloride (**1g**) afforded the corresponding ketone **3g** in high yield (entry 7). The reaction of a terephthaloyl chloride (**1h**) with 2 equiv of **2a** gave pure **3h** in good yield (entry 8). Various terminal alkynes, including enyne **2e** and 1-decyne (**2f**), afforded the corresponding **3i**−**m** regioselectively (entries 9−13). Neither α,*β*-unsaturated acid chlorides, aliphatic acid chlorides, nor internal alkynes provided **3**.

Table 1. Addition of Acid Chlorides **1** to Terminal Alkynes **2**[a]



entry	1		2		3		% yield[b] (*Z*/*E*)[c]
1		**1a**	$\mathrm{H{-}C{\equiv}C{-}Ph}$	**2a**		**3a**	91 (99/1)
2		**1b**		**2a**		**3b**	91 (99/1)
3		**1c**		**2a**		**3c**	89 (98/2)
4		**1d**		**2a**		**3d**	94 (99/1)
5[d]		**1e**		**2a**		**3e**	92 (99/1)
6[d]		**1f**		**2a**		**3f**	87 (93/3)
7		**1g**		**2a**		**3g**	84 (>99/1)
8[e]		**1h**		**2a**		**3h**	79 (100/0)
9		**1a**		**2b**		**3i**	92 (99/1)
10		**1a**		**2c**		**3j**	59 (>99/1)
11[f]		**1a**		**2d**		**3k**	85 (>99/1)
12		**1a**		**2e**		**3l**	90 (99/1)
13[f]		**1a**	$\mathrm{H{-}C{\equiv}C{-}{}^{n}C_8H_{17}}$	**2f**		**3m**	70 (82/18)

[a] Conditions: acid chloride (0.50 mmol), alkyne (0.75 mmol), IrCl(cod)(IPr) (0.025 mmol, 5.0 mol %), toluene (1.0 mL), 90 °C, 20 h. [b] Isolated yield. [c] Determined by GC analysis. [d] Using a reaction time of 36 h. [e] Using 1.5 mmol of **2a**. [f] Using a reaction time of 48 h.

When the reaction of **2f** (Table 1, entry 13) was carried out at higher temperature (in refluxing toluene) under otherwise identical reaction conditions, **3m** was not obtained; instead, 2-heptyl-5-phenylfuran (**5a**) was produced in good yield (Table 2). Employing

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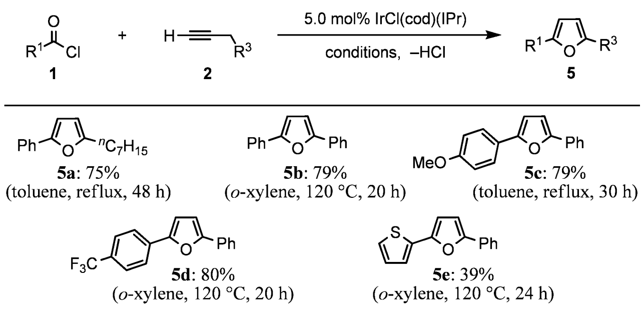
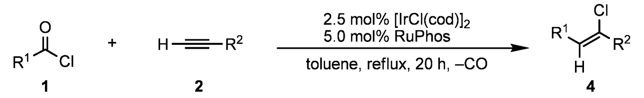
Table 2. Iridium-Catalyzed Synthesis of Furans **5**[a]



[a] Conditions: acid chloride (0.50 mmol), alkyne (0.75 mmol), IrCl(cod)(IPr) (0.025 mmol, 5.0 mol %), solvent (1.0 mL). Isolated yields of **5** are shown.

Table 3. Decarbonylative Addition of **1** to **2**[a]



entry	**1**: R^1	**2**: R^2	**4**	% yield[b]
1	**1a**: Ph	**2a**: Ph	**4a**	70
2	**1b**: 4-MeC_6H_4	**2a**: Ph	**4b**	84
3	**1d**: 4-ClC_6H_4	**2a**: Ph	**4c**	69 (75[c])
4	**1i**: (*E*)-$C_6H_5CH{=}CH$	**2a**: Ph	**4d**	88
5	**1a**: Ph	**2g**: $^nC_6H_{13}$	**4e**	81

[a] Conditions: acid chloride (0.50 mmol), alkyne (0.75 mmol), $[IrCl(cod)]_2$ (0.0125 mmol, 2.5 mol %), RuPhos (0.025 mmol, 5.0 mol %), toluene (1.0 mL), reflux, 20 h. [b] Isolated yield. [c] *o*-Xylene, reflux, 20 h.

isolated **3m** as a substrate afforded **5a** in 86% yield under similar conditions (5.0 mol % IrCl(cod)(IPr), *o*-xylene, 120 °C, 20 h). This observation unambiguously indicated that **5a** was produced via **3m**. As shown in Table 2, terminal alkynes bearing a methylene unit adjacent to the triple bond afforded the corresponding 2,5-disubstituted furans (**5b**−**e**) in moderate to high yields at elevated temperatures. To the best of our knowledge, the present reaction is the first example of a catalytic furan synthesis from acid chlorides and alkynes.[11,12]

In contrast, when the NHC ligand (IPr) in eq 1 was changed to a phosphine ligand (RuPhos),[13] the addition occurred with decarbonylation[14] to afford the corresponding (*Z*)-vinyl chlorides **4a**−**e** in high isolated yields as the pure forms (eq 2, Table 3). Thus, the ligands in the catalytic reaction play a critical role in distinguishing the products **3** and **4**.

To gain further insight into the mechanisms, reactions of an acid chloride with the two catalyst precursors in eqs 1 and 2, IrCl(cod)(IPr) and $[IrCl(cod)]_2$/RuPhos, respectively, were carried out. Surprisingly, in a stoichiometric reaction of IrCl(cod)(IPr) with **1a**, most of the **1a** (>91% by GC) remained intact, even at 90 °C for 4 h. However, when **2a** was further added into the reaction system, most of **1a** was converted and **3a** was obtained in 52% yield (eq 3):[8]

$$\text{IrCl(cod)(IPr)} + \mathbf{1a} \xrightarrow[\text{toluene, 90 °C, 4 h}]{\text{conv. of } \mathbf{1a} < 9\%} \xrightarrow[\text{toluene, 90 °C, 18 h}]{\text{1.5 equiv. } \mathbf{2a}} \underset{\text{52\% yield}}{\mathbf{3a}} \qquad (3)$$

Thus, in eq 1 (Table 1), **2** may first coordinate to the iridium center, after which oxidative addition of **1** followed by a fast insertion of **2** would afford **3** without decarbonylation.[15] On the other hand, a stoichiometric reaction of $[IrCl(cod)]_2$/RuPhos (1:1 Ir/P) with **1a** resulted in complete conversion of **1a** and provided the complex $IrCl_2(CO)(Ph)(RuPhos)$ (**6**), as confirmed by an X-ray diffraction study,[8] in 46% yield via decarbonylation (eq 4):

$$\underset{\text{(Ir/P = 1)}}{[\text{IrCl(cod)}]_2\text{/RuPhos}} + \mathbf{1a} \xrightarrow[\text{toluene, 90 °C, 4 h}]{\text{conv. of } \mathbf{1a} > 99\%} \underset{\mathbf{6}\ \text{46\% yield}}{\text{IrCl}_2\text{(CO)(Ph)(RuPhos)}} \qquad (4)$$

Treatment of **6** with **2a** in refluxing toluene for 2 h afforded **4a** in 55% yield. Hence, in eq 2 (Table 3), oxidative addition of **1** followed by a fast decarbonylation and a successive insertion of **2** might afford **4** as the product. These quite different reactivities of the two catalyst precursors toward acid chlorides must be crucial in the catalysis.

In conclusion, (*Z*)-*β*-chloro-α,*β*-unsaturated ketones (**3**) or (*Z*)-vinyl chlorides (**4**) were selectively obtained by the iridium-catalyzed addition of acid chlorides (**1**) to terminal alkynes (**2**) upon the proper choice of the IPr or RuPhos ligand. The synthesis of **3** was applied to the preparation of 2,5-disubstituted furans (**5**). Further studies on the reaction mechanism and application of the catalysis are now in progress.

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Supporting Information Available: Experimental procedures, product characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) IrCl(cod)(IPr) generated in situ from $[IrCl(cod)]_2$ and IPr·HCl/KO^{t}Bu was also active, affording **3a** in 80% yield with $Z/E = 98{:}2$.[8]
(11) For a synthesis of furans from acid chlorides and alkynes with a stoichiometric amount of $ZnBr_2$, see: Lee, K. Y.; Lee, M. J.; Kim, J. N. *Tetrahedron* **2005**, *61*, 8705.
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(15) A plausible reaction mechanism is shown in the Supporting Information.

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