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Ruthenium Complex-catalysed Addition of *N*-Aryl substituted Amides to Alkynes: Novel Synthesis of Enamides

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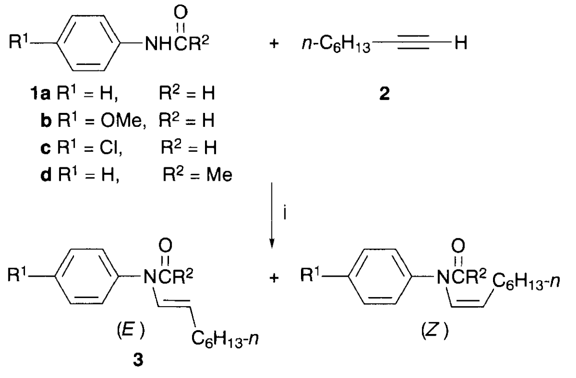
The addition of *N*-aryl substituted amides to non-activated terminal alkynes is efficiently promoted by the $Ru_3(CO)_{12}$–PCy_3 catalyst system, affording the corresponding linear (*E*)-enamides in good yields with high regio- and stereo-selectivity.

Since an intensive exploration of enamine chemistry got under way with Stork's appreciation and use of the tremendous potential of enamines for electrophilic substitution reactions in 1954,[1,2] interest in enamines has been stimulated.[3] In comparison with enamine chemistry, the chemistry of enamides has not been well developed, and synthetic methods to them are rather limited.[4,5] Recently, Stille *et al.* reported a transition metal complex-catalysed synthesis of enamides *via* the isomerization of *N*-allylamides.[6] But a more straightforward and intriguing synthesis of enamides by direct addition of carboxamide to alkynes has not yet been reported.

We have already found that ruthenium complexes show high catalytic activities in the activation of alkynes[7] and formyl compounds.[8] Here we report a low valent ruthenium complex-catalysed novel synthesis of linear (*E*)-enamides involving the direct addition of *N*-aryl substituted amides to terminal alkynes.



Scheme 1 *Reagents and conditions*: i, $Ru_3(CO)_{12}$, PCy_3, toluene, 180 °C under an argon atmosphere for 15 h

To the best of our knowledge, this is the first example of transition metal complex-catalysed addition of the N–H bond in carboxamide to non-activated alkynes.[3,9]

A typical procedure is as follows; a mixture of formanilide (5.0 mmol), oct-1-yne (10.0 mmol), $Ru_3(CO)_{12}$ (0.067 mmol), PCy_3 (tricyclohexylphosphine; 0.40 mmol) and dry toluene (3.0 ml) was placed in a 50 ml stainless steel autoclave equipped with a glass liner and a magnetic stirring bar under an argon atmosphere and stirred at 180 °C for 15 h. The products were isolated by vacuum distillation and/or TLC.

As shown in Table 1, in the presence of a catalytic amount of $Ru_3(CO)_{12}$, formanilide **1a** reacted smoothly with oct-1-yne **2** to give *N*-(oct-1-enyl)formanilide **3** (*E*/*Z* = 93:7) in 67% yield. Other *N*-(oct-1-enyl)formanilides bearing 4-MeO and 4-Cl substituents on the phenyl ring were also prepared by this method. Small amounts of *N*,*N*′-diarylureas were obtained as by-products.[10] *N*-Aryl substituted carboxamides as well as *N*-aryl substituted formamides can be employed in the present enamide synthesis. For example, acetanilide **1d** reacted smoothly with oct-1-yne **2** to give the corresponding linear (*E*)-enamide **3** selectively in 65% yield (run 4). The reaction using *N*-alkyl substituted formamides such as *N*-methylformamide and formamide itself, however, gave intractable mixtures, and the corresponding enamides were not obtained selectively. The aryl substituent on the nitrogen atom is essential for the present reaction.

Table 1 Ruthenium complex-catalysed synthesis of enamides from *N*-aryl substituted amides and oct-1-yne[a]

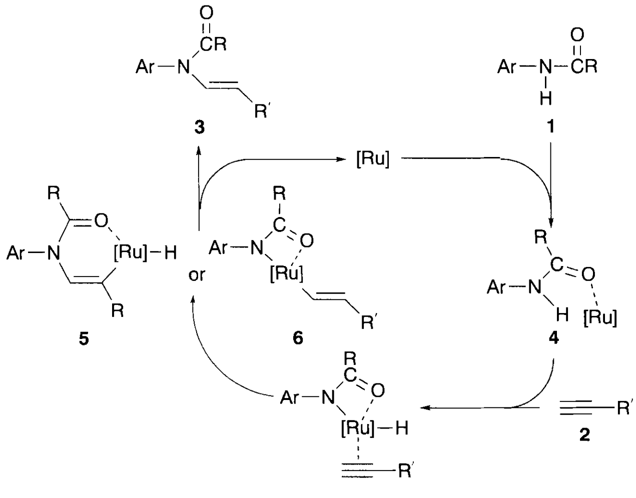
	Product 3				
Run	R^1	R^2	Conv. (%)[b]	Yield (%)[b]	*E*:*Z*[b]
1	4-H	H	95	67	93: 7
2	4-MeO	H	88	58	89:11
3	4-Cl	H	75	49	85:15
4	4-H	Me	91	65	100: 0

[a] A mixture of **1**, (5.0 mmol), **2** (10.0 mmol), $Ru_3(CO)_{12}$ (0.067 mmol), PCy_3 (0.40 mmol), and toluene (3.0 ml) was treated under an argon atmosphere at 180 °C for 15 h. [b] Determined by GLC based on the amount of **1** charged.

Table 2 Catalytic activity of several ruthenium complexes in the synthesis of *N*-(oct-1-enyl)formamide[a]

Run	Catalyst	Additive	Solvent	Conv. (%)[b]	Yield (%)[b]	(*E*):(*Z*)[b]
1[c]	$Ru_3(CO)_{12}$	PCy_3	toluene	95	67	93: 7
2[c]	$Ru_3(CO)_{12}$	PBu_3	toluene	93	66	83:17
3	Ru(cod)(cot)	PCy_3	toluene	77	53	90:10
4[c]	$Ru_3(CO)_{12}$	—	toluene	13	5	63:37
5	$RuH_2(PPh_3)_4$	—	toluene	43	18	68:32
6	$RuCl_2(PPh_3)_3$	—	toluene	31	10	71:29
7	$RuCl_3 \cdot nH_2O$	—	toluene	31	10	83:17
8	$C_5H_5RuCl(PPh_3)_2$	NH_4PF_6	toluene	0	0	—
9	$C_5Me_5RuCl(cod)$	—	toluene	0	0	—
10[c]	$Ru_3(CO)_{12}$	PCy_3	anisole	93	44	90:10
11[c]	$Ru_3(CO)_{12}$	PCy_3	1,4-dioxane	75	40	83:17
12[c]	$Ru_3(CO)_{12}$	PCy_3	THF	51	30	74:26
13[c]	$Ru_3(CO)_{12}$	PCy_3	DMA[d]	25	12	74:26

[a] Formanilide (5.0 mmol), oct-1-yne (10.0 mmol), catalyst (0.20 mmol), additive (0.40 mmol) and solvent (3.0 ml) under an argon atmosphere at 180 °C for 15 h. [b] Determined by GLC based on the amount of **1** charged. [c] $Ru_3(CO)_{12}$ (0.067 mmol) was used. [d] *N*,*N*-Dimethylacetamide.



Scheme 2

Among the ruthenium catalysts examined, $Ru_3(CO)_{12}$–PCy_3 showed the highest catalytic activity (Table 2, run 1). $Ru_3(CO)_{12}$–PBu_3 system and Ru(cod)(cot)–PCy_3 also showed good catalytic activity (runs 2, 3). The $C_5H_5RuCl(PPh_3)_2$ complex is highly effective for the activation of terminal alkynes affording a vinylidene complex in the presence of NH_4PF_6[11] but is totally ineffective in the present reaction (run 8). This result indicates that the present reaction did not involve a vinylidene intermediate. In addition, other di- and tri-valent ruthenium complexes showed low or almost no catalytic activity (runs 5–7, 9). As for the solvent, toluene is the best (runs 1, 10–13).

A tentative reaction mechanism is illustrated in Scheme 2. First, the *N*-aryl substituted amide coordinates to an active zero-valent ruthenium complex through its carbonyl oxygen atom, affording an intermediate **4** in which the N–H bond would be activated. Then the alkyne **2** coordination and the concomitant oxidative addition of the N–H bond followed by an alkyne insertion give an intermediate **5** or **6**. A subsequent reductive elimination gives the enamide, regenerating an active zero-valent ruthenium species.

In conclusion, we found that the addition of an *N*-aryl substituted amide to non-activated terminal alkynes is efficiently catalysed by a ruthenium complex to afford the (*E*)-enamides selectively in good yields. This reaction is the first example of transition metal complex-catalysed activation of the N–H bond of carboxamides and is characteristic of ruthenium complexes.

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