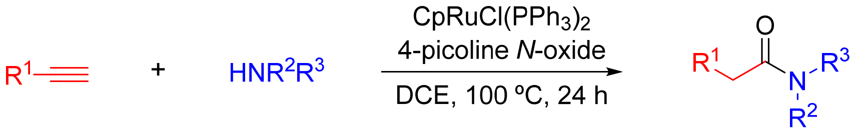
Ruthenium-Catalyzed Oxidative Amidation of Alkynes to Amides

Andrea Álvarez-Pérez,[†] Miguel A. Esteruelas,[§,*] Susana Izquierdo,[§] Jesús A. Varela,[†] and Carlos Saá[†,*]

[†]Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

[§]Departamento de Química Inorgánica-Instituto de Síntesis Química y Catálisis Homogénea (ISQCH)–Centro de Innovación en Química Avanzada (ORFEO–CINQA), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain.

Supporting Information Placeholder

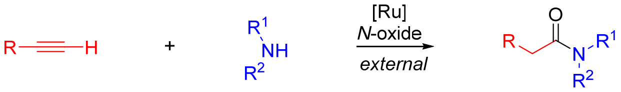


ABSTRACT: Complex $CpRuCl(PPh_3)_2$ catalyzes reactions of terminal alkynes with 4-picoline *N*-oxide and primary and secondary amines to afford the corresponding amides. The reactions occur in chlorinated solvent and aqua medium showing applications in peptide chemistry. Stoichiometric studies reveal that the true catalysts of the processes are the vinylidene cations $[CpRu(=C=CHR)(PPh_3)_2]^+$ which are oxidized to the Ru(η^2-CO)-ketenes by the *N*-oxide. Finally, nucleophilic additions of primary and secondary amines to the free ketenes yield the corresponding amides.

Amide bonds play a crucial role in living organisms and are present in a great number of pharmacologically active compounds. Furthermore, they are widely used as synthetic materials, including nylon, hydrogels, supported catalysts, etc.[1] The conventional approach to amide formation is the condensation of an amine with a carboxylic acid via an active ester. In the last years, new catalytic methods, which offer alternatives for selective amide bond formation, have emerged to overcome some of the limitations of these standard protocols.[2] In this context, the use of surrogates of the reaction partners is currently being intensively assayed.[1] Although terminal alkynes are promising surrogates of acyls in reactions with amines, through catalytic oxidative amidations, their use remains largely underused.[3]

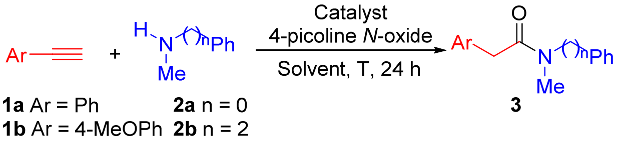
Formation of ketenes[4] from alkynes is essential for successful amidations. These electrophilic species can be readily formed via rearrangement of oxirene intermediates[5] or by oxidation of metal vinylidenes,[6] which are also electrophilic at the carbene center.[7] Lee recently reported Rh-catalyzed oxidations of terminal alkynes to ketenes, with internal and external oxidants, along with subsequent [2+2] cycloaddition reactions,[8] or intermolecular trapping with heteronucleophiles, to give lactams, or linear amides. Ruthenium promoted oxidative transformations of terminal alkynes into ketenes, with substrates bearing internal oxidants,[9] have been also performed, to finally afford efficient intramolecular electrocyclic reactions and intermolecular [2+2] cycloadditions. Following with our interest on the chemistry of M-vinylidenes,[10] we herein report a new and efficient Ru-catalyzed oxidative amidation of alkynes to primary and secondary amides, using 4-picoline *N*-oxide as external oxidant (Scheme 1). Mechanistic studies indicate that the catalysis involves the oxidation of metal-vinylidene intermediates to free ketenes, which are trapped by the nucleophile.

Scheme 1. Ruthenium catalyzed oxidative amidations of terminal alkynes, using an *N*-oxide as external oxidant.



We initially tested the oxidative amidation of phenylacetylenes **1a** and **1b** with secondary amines **2a** and **2b** using Rh catalysts (Lee's conditions, Table 1). To our initial surprise, while **1a** and **1b** reacted smoothly with aniline **2a** to give the secondary amides **3aa** and **3ba** in fairly good yields (entry 1), **1a** and **1b** were recovered when reacted with *N*-Me-phenethylamine **2b** either in CH_3CN or DCE or in the presence of catalyst $RhCl(PPh_3)_3$ (entry 2).[8,2a] It was mandatory to use the ammonium salt of **2b** in order to get the corresponding amides **3ab** and **3bb** in fairly good yields (entry 3).[3b] After this singular behavior of secondary amines under Rh catalysts (aniline **2a** *vs* alkylamine **2b**), we decided to compare these results against ruthenium catalysts. To our delight, we found that the use of electron-rich CpRu catalysts[11] in non-coordinating DCE[9e,12] as solvent[13] gives good to excellent yields of amides **3aa, 3ab, 3ba** and **3bb** in two sets of conditions using always the free amines (entries 1-2). Both *N*-oxide (entry 4) or Ru catalyst (entry 5) are required for the reaction to take place (see SI for other conditions tried).

Table 1. Comparative results of Rh- and Ru-catalyzed oxidative amidations of arylacetylenes 1a,b with secondary amines 2a,b.

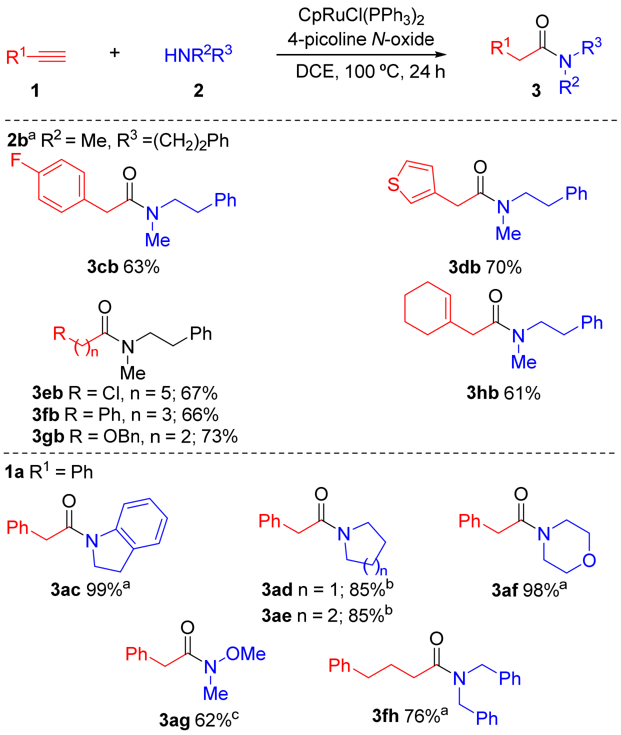


entry	alkyne	amine	amide	[Rh][a] cat	[Ru] cat[b] *Method A* (amine 2 equiv)	*Method B* (amine 1 equiv/KPF_6 1 equiv)
1	**1a**	**2a**	**3aa**	79%	99%	95%
2	**1b**	**2a**	**3ba**	85%	92%	90%
3	**1a**	**2b**	**3ab**	—[c,d]	96%	91%
4	**1b**	**2b**	**3bb**	traces[a,d]	88%	89%
5	**1a**	**2b**·HCl	**3ab**	92%[e]		96%[f]

[a] *Reaction conditions* Rh: alkyne **1** (0.4 mmol), amine **2** (1.2 equiv), $[Rh(cod)Cl]_2$ (3 mol %), $P(4\text{-}FC_6H_4)_3$ (12 mol %), 4-picoline *N*-oxide (1.2 equiv), CH_3CN (0.8 mL), 60 ºC. [b] *Ru conditions*: alkyne **1** (0.4 mmol), $CpRuCl(PPh_3)_2$ (5 mol %), 4-picoline *N*-oxide (2 equiv), DCE (3 mL), 100 ºC, amine **2** (2equiv) (*Method A*) or amine **2** (1 equiv) + KPF_6 (1 equiv) (*method B*) [c] Starting material recovered either with CH_3CN or DCE as solvents. [d] $CpRhCl(PPh_3)_3$ (6 mol %) was used as catalyst. [e] K_2CO_3 (0.3 equiv) and KPF_6 (1 equiv) were added. [f] K_2CO_3 (0.3 equiv) was added.

The substrate scope varying the nature of the alkyne was then examined under optimized conditions A (Scheme 2). Either electron-poor or electron-rich heteroaryl alkynes also participate as active substrates giving rather good yields of tertiary amides **3cb** and **3db**. In addition, aliphatic and functionalized aliphatic alkynes (Cl, OBn) as well as enynes were also tolerated to give tertiary amides **3eb**, **3fb**, **3gb** and **3hb**, respectively, in fairly good yields. Secondly, other secondary amines were also tested. Thus, five- and six-membered cyclic amines reacted smoothly to give good to excellent yields of cyclic tertiary amides **3ac**, **3ad**, **3ae**, and **3af**, respectively. In addition, the linear *N,O*-dimethylhydroxylamine and dibenzylamine gave the interesting Weinreb amide[14] **3ag** and dibenzyl protected amide **3ah** in rather good yields.

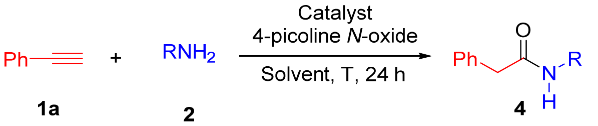
Scheme 2. Ru-catalyzed oxidative amidations of alkynes 1c-h with secondary amines 2c-h



[a] Reaction conditions A_{Ru}. [b] Reaction conditions B_{Ru}. [c] Reaction conditions B_{Ru} with **2g**·HCl (1 equiv) + K_2CO_3 (0.3 equiv).

We also evaluated whether this oxidative amidation is suitable for the preparation of the interesting secondary amides (peptide bonds). As we already did with the secondary amines, we tested and compared the oxidative amidations of phenylacetylene **1a** with three different primary amines **2i-k** under Rh and Ru catalytic conditions (Table 2). While the employment of Rh catalyst (Lee's conditions)[5,15,2a] probed relatively efficient for the preparation of anilide **4ai** from aniline **2i** (entry 1, 72%), it gave lower to negligible yields in the case of phenethyl and benzyl amides **4aj** and **4ak** from the free amines **2j** and **2k** (entries 2 and 3). Once again, it was mandatory to use the ammonium salts of **2j,k** in order to get the corresponding amides **4aj** and **4ak** in excellent yields (entries 2 and 3). By contrast, amides **4ai-4ak** were always obtained in excellent yields from the free amines **2i-k** using Ru catalysts (entries 1-3). Scaling was also possible since amide **4ak** could be obtained in 94% isolated yield using 1 mmol of alkyne **1a**.

Table 2. Comparative results of Rh- and Ru-catalyzed oxidative amidations of phenylacetylene 1a with primary amines 2i,j,k.

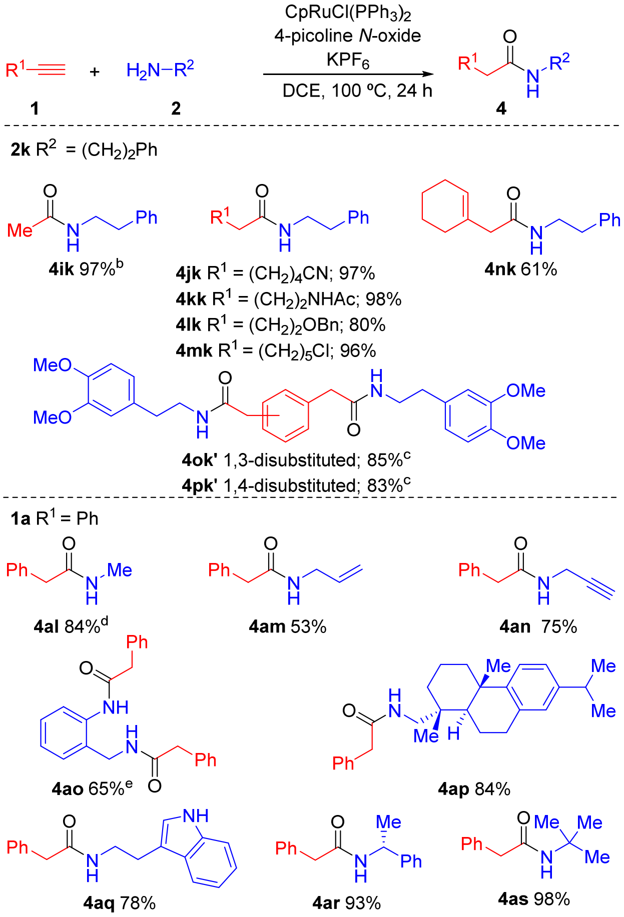


entry	R	amine	amide	[Rh]	[Ru][a]
1	Ph	**2i**	**4ai**	72%	98%[b]
2	Bn	**2j**	**4aj**	23%	96%
		2j·HCl		99%[c]	
3	$(CH_2)_2Ph$	**2k**	**4ak**	traces	98% (94%)[d]
		2k·HCl		98%[c]	

[a] *Method B*. [b] A mixture of H_2O/DCE 95:5 was used as solvent. [c] K_2CO_3 (0.3 equiv) and KPF_6 (1 equiv) were added. [d] Isolated yield using 1 mmol of **1a.**

The substrate scope varying the nature of the alkyne was first examined (Scheme 3). The (trimethylsilyl)acetylene **1i** was found to be a good substrate for this amidation reaction to deliver the desilylated *N*-acetyl amide **4ik** in excellent yield. Gratifyingly, functionalized aliphatic alkynes bearing CN, NHAc, OBn and Cl groups as well as enynes and aromatic diynes were all well tolerated to afford moderate to excellent yields of the corresponding amides **4jk-4pk'**. Then, variation of the amine partner was analyzed. Either simple methylamine **2l** or functionalized allyl- and propargylamines **2m** and **2n** gave moderate to good yields of the corresponding amides **4al-4an**. Pleasingly, 2-(aminomethyl)aniline **2o**, a difunctional aniline and benzyl amine, could be conveniently diacylated to give the diamide **4ao** in fairly good yield. Natural alkaloids bearing primary amines like (-)leelamine **2p** and tryptamine **2q** were also acylated to the corresponding amides **4ap** and **4aq** with very good yields. Interestingly, oxidative amidations with the more challenging chiral secondary (*R*)-1-phenylethylamine **2r** and tertiary *tert*-butylamine **2s** smoothly occurred to give the chiral secondary amide **4ar** and *N*-(*tert*-butyl)phenylacetamide **4as** with excellent yields.

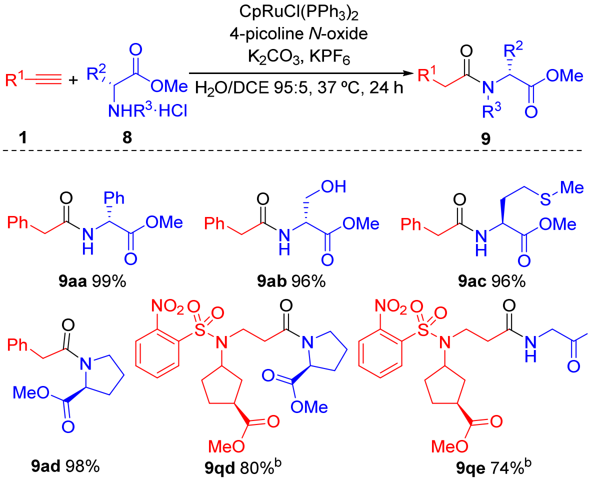
Scheme 3. Ru-catalyzed oxidative amidations of alkynes 1i-1p with primary amines 2l-2s.[a]



[a] Reaction conditions B_{Ru}. [b] (Trimethylsilyl)acetylene **1i** was used. [c] **1o** 1,3-diethynylbenzene, **1p** 1,4-diethynylbenzene. [d] Reaction conditions B_{Ru} with **2l**·HCl + K_2CO_3 (0.3 equiv) [e] **1a** (2 equiv) were used.

The oxidative amidation not only occurred in boiling chlorinated solvents but also in aqueous media at 37ºC which foresees interesting applications in peptide chemistry (Scheme 4). Thus, excellent yields of the secondary amide **4ai** (98%) were obtained when the reaction was run either in pure DCE or in a mixture DCE/H_2O 5:95 (Table 2). Oxidative amidations of phenylacetylene **1a** with methylester derivatives of (*L*)-aminoacids bearing primary amines such as phenylglycine **8a**, serine **8b** and MeS-cysteine **8c** and secondary amines such as proline **8d** smoothly occurred to give the corresponding *N*-acyl derivatives **9aa-9ad** in excellent yields. Interestingly, the oxidative amidation end up completely chemoselective since reaction only by the more nucleophilic amino group of serine **8b** was observed. On the other hand, oxidative amidations of *N*-nosyl-*N*-propargyl γ-aminoester **1q**[16] occurred uneventfully to give the amidoester derivatives **9qd** and **9qe** in quite good yields.[17]

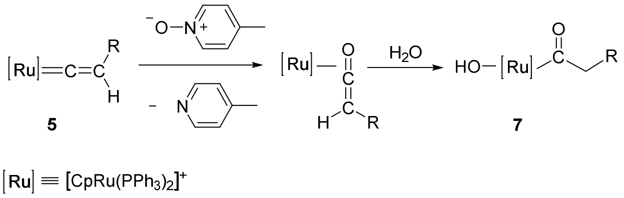
Scheme 4. Ru-catalyzed oxidative amidations of alkynes 1 with aminoesters 8 in aqueous media at 37 ºC.[a]



[a] Reaction conditions: alkyne **1** (0.4 mmol), aminoester·HCl **8** (1 equiv), $CpRuCl(PPh_3)_2$ (5 mol%), 4-picoline *N*-oxide (1.1 equiv), KPF_6 (1 equiv), K_2CO_3 (0.3 equiv), H_2O/DCE (3 mL), 37 ºC, 24 h. [b] 4-picoline *N*-oxide (2 equiv), 100 ºC, 24 h.

To gather information about the mechanism of the amination, we reproduced the elemental steps of the catalysis through stoichiometric reactions performed at room temperature. In DCE, the ruthenium complex $CpRuCl(PPh_3)_2$ reacts with phenylacetylene (**1a**) in the presence of KPF_6 to give the previously reported vinylidene salt $[CpRu(=C=CHPh)(PPh_3)_2]PF_6$[18] (**5**), as a result of the extraction of the chloride anion and the alkyne-vinylidene tautomerization of the hydrocarbon. Phosphine dissociation is not observed. The addition of the stoichiometric amount of 4-picoline N-oxide to a NMR tube containing a dichloromethane-d_2 solution of **5** smoothly affords a mixture of **5** (10%), the picoline derivative $[CpRu(4\text{-}Me\text{-}py)(PPh_3)_2]PF_6$[19] (**6**; 59%) and a Ru-C(=O)CH_2Ph acyl species (31%). Noticeable spectroscopic features of the latter are a singlet at 3.34 ppm due to the CH_2 group in the ^1H NMR spectrum, two singlets at 194.5 and 48.1 ppm corresponding to the CO and CH_2 acyl-carbon atoms in the $^{13}C\{^1H\}$ NMR spectrum, and a singlet at 39.0 ppm in the $^{31}P\{^1H\}$ NMR spectrum. Its formation is a strong indirect evidence of the oxidation of the Ru=C bond of **5** to give a Ru(η^2-CO)-ketene intermediate,[20] which is trapped by traces of water present in the medium (Scheme 5). The dissociation of the ketene and the subsequent coordination of the generated 4-picoline leads to **6**. In addition, it should be pointed out that traces of phosphine oxide does not observe. The formation of the acyl species does not appear to take place under catalytic conditions; i.e., in the presence of an excess of amine. When 4-picoline N-oxide and benzylamine (**2j**) were added to the dichloromethane-d_2 solution of **5,** N-benzyl-2-phenylacetamide (**4aj**) and **6** were formed. Complex **6** reacts with phenylacetylene to regenerate the vinylidene **5** and release 4-picoline. [21]

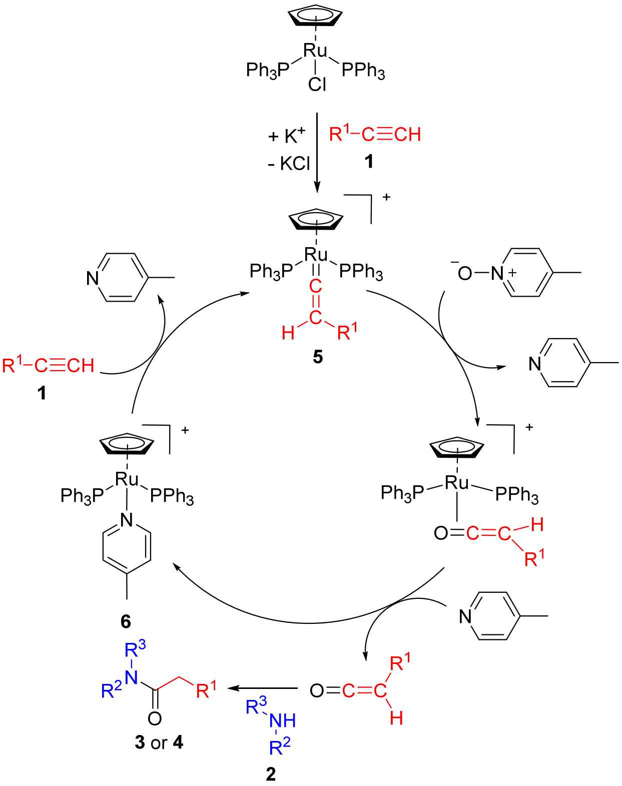
Scheme 5. Formation of the acyl species.



$[Ru] \equiv [CpRu(PPh_3)_2]^+$

The previously mentioned stoichiometric results reveal that: i) complex $CpRuCl(PPh_3)_2$ is the catalytic precursor, whereas the vinylidene derivative **5** is the true catalyst of the amidation; ii) the catalysis takes place via Ru(η^2-CO)-ketene intermediates, which are formed by oxygen transfer from 4-picoline N-oxide; iii) 4-picoline, which is generated from the oxidation of the vinylidene, displaces the ketene from the ruthenium coordination sphere; and iv) the formation of the amide is an outer-sphere process involving the capture of the released ketene by the amine. The cycle shown in Scheme 6 summarizes these features.

Scheme 6. Mechanism proposed for the Ru-catalyzed oxidative amidation of terminal alkynes with amines.



In conclusion, efficient ruthenium-catalyzed oxidative amidations of alkynes to primary and secondary amides have been developed using 4-picoline *N*-oxide as external oxidant. Remarkably, the catalysis not only takes place in chlorinated solvents but also in aqueous media, which opens challenging applications in peptide chemistry. The process occurs by conversion of terminal alkynes to Ru-ketenes via oxidation of the initially formed Ru-vinylidene intermediates. Ketenes are released and trapped by the nucleophilic primary and secondary amines to yield the corresponding amides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

* carlos.saa@usc.es, maester@unizar.es

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(17) Amides **3bj-k**, **3bn** and **3br** could be also obtained by reaction of alkyne **1b** with the corresponding amine **2·HCl** in aqueous media at 37 ºC. For amide **3bi**, free amine **2i** was used. Alkyne **1b** was partially recovered unchanged. See Supp Info for details.

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