Synthetic Methods

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Rhodium-Catalyzed Oxygenative Addition to Terminal Alkynes for the Synthesis of Esters, Amides, and Carboxylic Acids**

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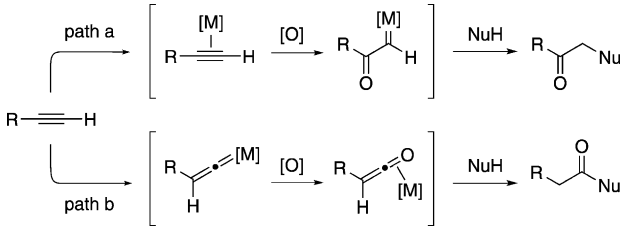
Transition-metal-catalyzed transfer oxygenation of alkynes is a useful means for the synthesis of carbonyl compounds. While an oxirene generated by the direct alkyne oxidation under metal-oxo-mediated catalysis has traditionally been used as an intermediate,[1] recent approaches exploiting alkynes as metallocarbene precursors have led to an array of reactions which can be performed under mild reaction conditions. Mechanistically, these reactions involve oxygen transfer to an η^2-alkyne metal complex to produce a metal carbene, which undergoes a variety of reactions as exemplified by the α-oxo gold carbene catalysis (Scheme 1, path a).[2]

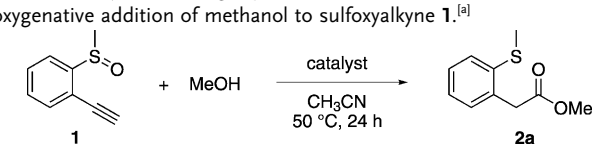


Scheme 1. Transition-metal-catalyzed oxygenative addition to terminal alkynes.

Additionally, it has also been shown that a metallocarbene resulting from a metal-mediated process involving an alkyne can be oxidatively demetalated to install a carbonyl group.[3] These examples collectively illustrate the viability of effecting catalysis by making use of alkyne-derived metal alkylidenes for catalyst turnover. A distinct opportunity exists for catalytic oxygenative alkyne functionalization, wherein the unsaturated carbene (vinylidene) metal intermediate, an η^1-isomer of the π-alkyne metal complex, is oxidized (path b). In this scenario, a ketene arising from oxygenation of a vinylidene complex may be exploited in the subsequent addition process. Conceivably, this mechanistic modality offers a versatile platform for alkyne functionalization since the metal vinylidene species resulting from alkynes by mild catalysis can be readily channeled to the synthetic utility of ketenes. The strategy based on oxygenation of a metal vinylidene complex has indeed been practiced, but only in intramolecular settings for the cycloisomerization of aromatic substrates.[4] Despite the potential utility for catalytic alkyne functionalization, the general approach taking advantage of the oxidative pathway from metal vinylidenes to ketenes has remained largely unexplored. Herein, we describe the rhodium-catalyzed oxygenative addition to terminal alkynes, a reaction which can be carried out with a broad range of alcohol and amine nucleophiles, and water to furnish carboxylic acid derivatives.

Our study began with evaluating the feasibility of the reaction inducing methanol addition to sulfoxyalkyne **1** with concomitant intramolecular oxygen transfer (Table 1). Thus,

Table 1: Catalyst screening experiments for intramolecular transfer oxygenative addition of methanol to sulfoxyalkyne **1**.[a]



1 **2a**

Entry	Catalyst	Yield [%][b]
1	$[CpRu(PPh_3)_2Cl]$	5
2	$[\{Ru(p\text{-cymene})_3Cl\}_2]/PPh_3$	4
3	$[CpRu(CH_3CN)_3]PF_6/PPh_3$	3
4	$[TpRu(PPh_3)_2Cl]$	4
5	$[Rh(PPh_3)_3Cl]$	51
6	$[Rh(C_2H_4)_2Cl]_2/PPh_3$	56
7	$[\{Rh(cod)OH\}_2]/PPh_3$	54
8	$[\{Rh(cod)Cl\}_2]/PPh_3$	59
9	$[\{Rh(cod)Cl\}_2]/P(4\text{-}MeOC_6H_4)_3$	40
10[c]	$[\{Rh(cod)Cl\}_2]/P(4\text{-}FC_6H_4)_3$	76

[a] Reaction conditions: alkyne **1** (0.1 mmol), methanol (0.3 mmol), catalyst (5 mol% entries 1–5; 3 mol%, entries 6–10), CH_3CN (0.25 mL), [Ru] or [Rh]/phosphine = 1:2 except for entry 5. [b] Determined by GC. [c] The reaction was completed in 12 h. Yield of isolated product. cod = cyclo-1,5-octadiene, Cp = cyclopentadienyl.

a series of screening experiments were conducted by employing a set of metal complexes known to mediate catalysis by vinylidene formation. The reactions using various ruthenium catalysts did produce the desired methyl ester **2a** but in very low yield (≤5%), while mostly returning unreacted **1** (Table 1, entries 1–4). In contrast, when the mixture of **1** and methanol in acetonitrile was heated at 50°C in the presence of Wilkinson's catalyst, complete conversion took place to give **2a** in 51% yield (entry 5). A brief survey of the phosphine ligand revealed that the rhodium-catalyzed reaction could be most efficiently carried out by using tri(4-fluorophenyl)phosphine, which afforded **2a** in 76% yield within 12 hours (entry 10).

With an effective catalyst identified, we examined extension of the addition process to include other nucleophiles

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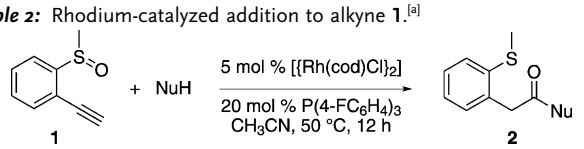
(Table 2). Under the reaction conditions using [{Rh(cod)Cl}$_2$] and P(4-FC$_6$H$_4$)$_3$ as the catalyst, a variety of alcohols and amines reacted with **1** to provide the corresponding esters and amides as products. The scope of the nucleophile was considerable in that the reaction was tolerant of primary as well as secondary substitutions and fared well with both aliphatic and aromatic substrates.

Table 2: Rhodium-catalyzed addition to alkyne **1**.[a]



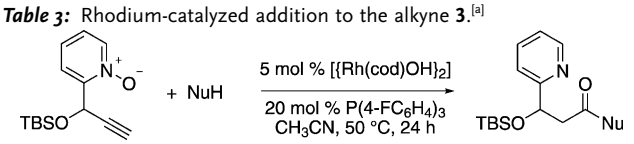
1 2

Entry	NuH	Yield [%][b]
1	ethanol	**2b** (74)
2	isopropyl alcohol	**2c** (50)
3	phenol	**2d** (45)
4	aniline	**2e** (94)
5	butylamine	**2f** (61)
6	morpholine	**2g** (69)

[a] Reaction conditions: alkyne **1** (0.5 mmol), alcohol (2.5 mmol) or amine (0.6 mmol) in CH$_3$CN (1.25 mL). [b] Yield of isolated product.

Encouraged by these initial results obtained with the sulfoxide **1**, we investigated the applicability of the protocol to an *N*-oxide substrate (Table 3). When the alkyne-tethered pyridine *N*-oxide **3** was subjected to the rhodium-catalyzed conditions with a collection of alcohols and amines, the oxygenative addition reaction took place smoothly to yield the ester and amide products **4**. Interestingly, however, the use of [{Rh(cod)OH}$_2$] instead of [{Rh(cod)Cl}$_2$] gave higher yields in these reactions.[5] As in the case of **1**, the reaction of *N*-oxide **3** was also compatible with a wide range of nucleophiles possessing varying steric and electronic properties.

Table 3: Rhodium-catalyzed addition to the alkyne **3**.[a]



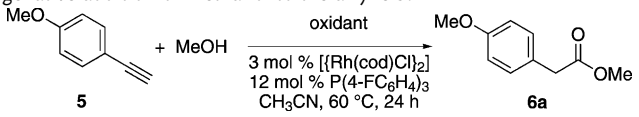
3 4

Entry	NuH	Yield [%][b]
1	methanol	**4a** (51)
2	ethanol	**4b** (70)
3	isopropyl alcohol	**4c** (37)
4	phenol	**4d** (41)
5	aniline	**4e** (46)
6	butylamine	**4f** (77)
7	morpholine	**4g** (88)

[a] Reaction conditions: alkyne **3** (0.2 mmol), alcohol (1.0 mmol) or amine (0.24 mmol) in CH$_3$CN (0.5 mL). [b] Yield of isolated product. TBS = *tert*-butyldimethylsilyl.

Having established the feasibility of oxygenative alkyne addition through an intramolecular S-to-C or N-to-C oxygen transfer, we next turned our attention to the development of an intermolecular process. Thus, an assortment of sulfoxides and N-oxides were screened for their ability to serve as oxygen donors in the oxygenative coupling of alkyne **5** with methanol (Table 4). Initial results from the use of sulfoxides were not too promising, as no reaction took place in these cases (entries 1–3). Similarly, *N*-methylmorpholine *N*-oxide (NMO) was ineffective (entry 4). In sharp contrast, when pyridine *N*-oxide was employed as an oxidant, methyl ester **6a** was produced in 87% yield (entry 5). Further examination showed that the intermolecular transfer oxygenative addition could be accomplished with a variety of pyridine *N*-oxide derivatives (entries 5–12), among which 4-picoline *N*-oxide proved most effective (entry 10). It was intriguing to note that 8-methylquinoline *N*-oxide, an oxidant most commonly employed in gold catalysis,[2h] displayed only modest performance in this rhodium catalysis to give a 54% yield of **6a** (entry 12).

Table 4: Screening of various oxidants for intermolecular transfer oxygenative addition of methanol to the alkyne **5**.[a]



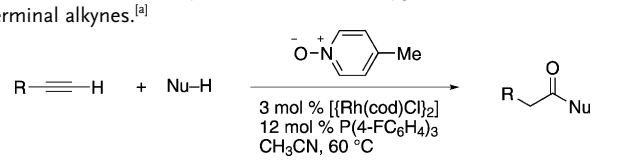
5 6a

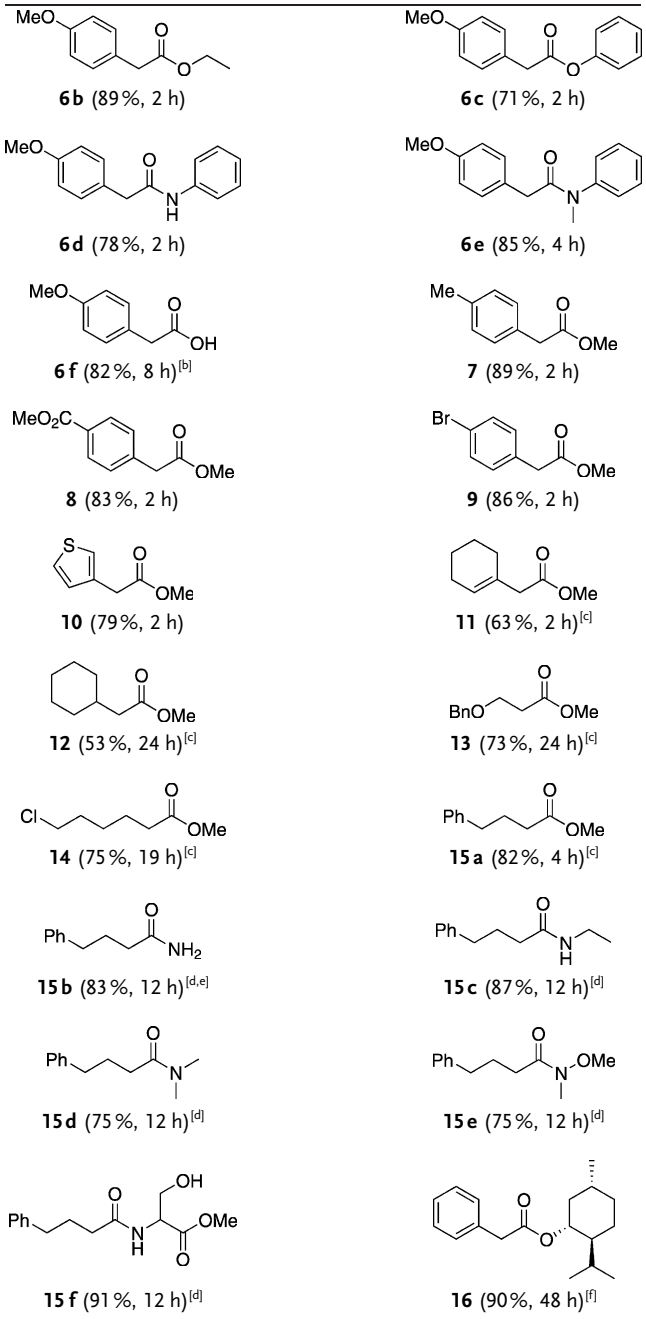
Entry	Oxidant	Yield [%][b]
1	dimethylsulfoxide	0
2	diphenylsulfoxide	0
3	methylphenylsulfoxide	0
4	*N*-methylmorpholine *N*-oxide	0
5	pyridine *N*-oxide	87
6	3,5-dichloropyridine *N*-oxide	54
7	3,5-dibromopyridine *N*-oxide	44
8	2-picoline *N*-oxide	81
9	3-picoline *N*-oxide	92
10[c]	4-picoline *N*-oxide	95
11	2,6-lutidine *N*-oxide	13
12	8-methylquinoline *N*-oxide	54

[a] Reaction conditions: alkyne **5** (0.2 mmol), oxidant (0.4 mmol), methanol (0.8 mmol) in CH$_3$CN (0.4 mL). [b] Yields determined by GC. [c] Yield of isolated product.

With the optimized reaction conditions in hand, we tested various alkynes and nucleophiles to probe the scope and limitations of the intermolecular oxygenative coupling reaction. As summarized in Table 5, the diversity of alkynes and nucleophiles suitable for this reaction proved quite extensive. Furthermore, a variety of functional groups did not interfere, thus highlighting the highly chemoselective feature of the process. In the reactions of the alkyne **5**, both aliphatic and aromatic alcohols and anilines were found to be competent nucleophiles to give esters and amides (**6b–6e**). Notably, the reaction proceeded well in wet acetonitrile to furnish the carboxylic acid **6f** as the product. From the perspective of the alkyne structure, the reaction tolerated aryl (**6–9** and **16**), heteroaryl (**10**), alkenyl (**11**), branched alkyl (**12**), and linear alkyl (**13–15**) substituents. Various amines also participated well in the reaction to give rise to primary (**15b**), secondary (**15c**), and tertiary (**15d**) amides, including a Weinreb's amide (**15e**).[6] When serine methyl ester was employed as the

Table 5: Rhodium-catalyzed intermolecular oxygenative addition to terminal alkynes.[a]

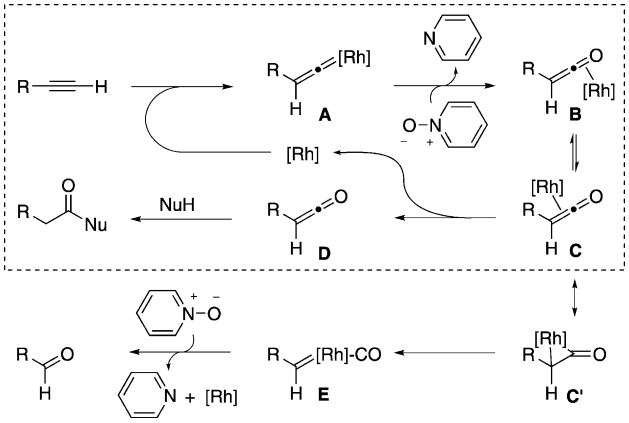




[a] Reaction conditions: alkyne (1.0 mmol), alcohol (3.0 mmol) or amine (1.2 mmol), 4-picoline *N*-oxide (1.2 mmol) in CH_3CN (2 mL). The yield is of the isolated product. [b] H_2O (10 mmol). [c] MeOH (5.0 mmol). [d] Alkyne (0.5 mmol), amine·HCl (0.6 mmol), $NaPF_6$ (0.6 mmol), K_2CO_3 (0.1 mmol). [e] NH_4NO_3 (0.6 mmol). [f] Phenylacetylene (2.45 g, 24 mmol), L-menthol (3.13 g, 20 mmol), 4-picoline *N*-oxide (2.62 g, 24 mmol), [{Rh(cod)Cl}$_2$] (1 mol%), P(4-F-C_6H_4)$_3$ (4 mol%).

nucleophile, the reaction occurred exclusively at the amino group in preference to the alcohol, thus providing the N-acyl product **15 f**. These amide-forming reactions benefited from the use of ammonium salts rather than free amines as nucleophiles, as higher yields were consistently obtained from the reactions of amine salts compared to those of the free amines.[7] It should also be noted that only 1.2 equivalents of the nucleophile were required in these reactions. Similarly, although the reactions forming methyl esters were carried out employing 3 equivalents of methanol and 3.0 mol% of the rhodium catalyst, the amounts of the alcohol and the rhodium catalyst could be reduced without a decrease in the yield. For example, the reaction of a 1:1.2 mixture of L-menthol and phenyl acetylene could be performed on a multigram scale with only 1.0 mol% of the catalyst to produce menthyl phenylacetate (**16**) in 90% yield.

The mechanism of the rhodium-catalyzed oxygenative alkyne addition is proposed in Scheme 2. In this catalytic cycle, the oxygen transfer from an *N*-oxide to the η^1-Rh vinylidene complex **A** delivers η^2-Rh ketene species **B**, which



Scheme 2. Proposed mechanism of the rhodium-catalyzed oxygenative addition to terminal alkynes.

may exist in equilibrium with **C**.[8] Subsequent to demetalation, the free ketene **D** undergoes a nucleophilic addition to provide the carbonyl product.[9,10] Alternatively, the nucleophile may add to a rhodium-coordinated ketene (**B** or **C**), in which case the catalyst turnover would involve protonation of a rhodium enolate. The intermediacy of a ketene species is supported by the result of a control experiment, where subjection of the alkyne **5** to the reaction without a nucleophile generates *p*-anisaldehyde (42%) presumably by the oxidation of the alkylidene **E** derived from CO deinsertion of rhodium ketene complex **C**/**C′**.[11]

The findings from this study are significant in several respects. They demonstrate that terminal alkynes can be directly transformed into carboxylic acid derivatives under mild rhodium catalysis by a distinct mechanism. The oxygenative coupling process occurring in an anti-Markovnikov fashion represents a novel method for alkyne 1,1-difunctionalization,[12] thus providing a selectivity complementary to that of the process mediated by α-oxo metallocarbene catalysis. The facile transfer oxygenation of metal vinylidene species established in both intra- and intermolecular settings by this study also offers a new mechanistic manifold through

which the rich chemistry of ketenes might be harnessed in the context of catalytic alkyne functionalization.[13] Further investigations in this direction are currently underway in our laboratory, and the results will be reported in due course.

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[9] The intermediacy of rhodium vinylidene **A** was supported by a deuterium-labeling experiment, where a reaction of deuterio-**5** (98% alkynyl D) with methanol led to the formation of **6a** in 78% yield (92% deuterium incorporation). See the Supporting Information.

[10] The involvement of a rhodium Fischer carbene intermediate resulting from the nucleophilic addition to the vinylidene complex prior to the oxygenation step (see Ref. [3a]) is less likely, as indicated by the facile formation of a carboxylic acid (e.g. **6f**) from the addition of water.

[11] The reaction of deuterio-**5** under the same methanol-free conditions gave deuterio-*p*-anisaldehyde (43% yield, 64% aldehydic D). See the Supporting Information. For decarbonylation of ketene complexes, see: a) T. Mitsudo, M. Kadokura, Y. Watanabe, *Tetrahedron Lett.* **1985**, *26*, 3697 – 3698; b) D. B. Grotjahn, G. A. Bikzhanova, L. S. B. Collins, T. Concolino, K. C. Lam, A. L. Rheingold, *J. Am. Chem. Soc.* **2000**, *122*, 5222 – 5223; c) H. Urtel, G. A. Bikzhanova, D. B. Grotjahn, P. Hofmann, *Organometallics* **2001**, *20*, 3938 – 3949; d) J. M. Goll, E. Fillion, *Organometallics* **2008**, *27*, 3622 – 3625; e) T. Kondo, Y. Tokoro, Y. Ura, K. Wada, T. Mitsudo, *ChemCatChem* **2009**, *1*, 82 – 84.

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