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Rhodium-Catalyzed Oxygenative [2 + 2] Cycloaddition of Terminal Alkynes and Imines for the Synthesis of β-Lactams

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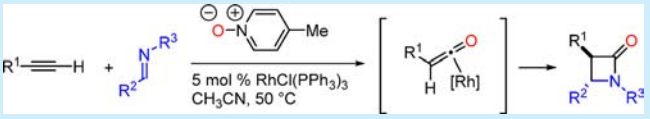
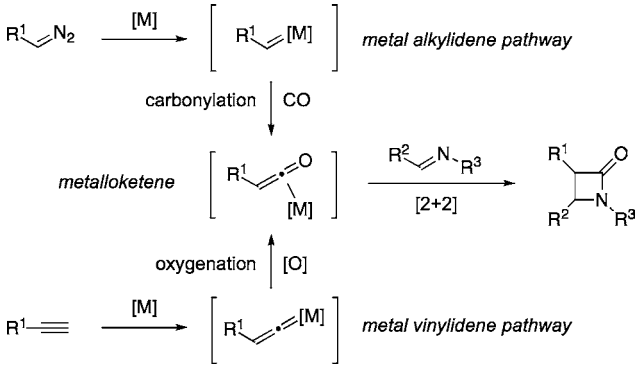
Supporting Information

ABSTRACT: A rhodium-catalyzed oxygenative [2 + 2] cycloaddition of terminal alkynes and imines has been developed, which gives β-lactams as products with high *trans* diastereoselectivity. In the presence of a Rh(I) catalyst and 4-picoline *N*-oxide, a terminal alkyne is converted to a rhodium ketene species via oxidation of a vinylidene complex and subsequently undergoes a [2 + 2] cycloaddition with an imine to give rise to the 2-azetidinone ring system. Mechanistic studies suggest that the reaction proceeds through a metalloketene rather than free ketene intermediate. The new method taking advantage of catalytic generation of a ketene species directly from a terminal alkyne provides a novel and efficient entry to the Staudinger synthesis of β-lactams under mild conditions.



The β-lactams are an important class of heterocycles that have been intensively investigated across diverse scientific disciplines as well as the pharmaceutical industry because of their potent antibacterial activity.[1] In addition to being the key pharmacophoric motif of β-lactam antibiotics, the 2-azetidinone ring system is also used in the development of various non-antibiotic therapeutic agents as exemplified by the cholesterol-lowering drug ezetimibe.[2] Furthermore, β-lactams have increasingly served as versatile intermediates for the synthesis of a wide variety of nitrogen-containing compounds,[3] rendering the development of methods for β-lactam synthesis an important objective.[4] Among the different synthetic approaches, the Staudinger reaction, a formal [2 + 2] cycloaddition of a ketene with an imine, is a powerful method that provides expeditious access to β-lactams.[5] While numerous applications employing this process have been reported, the practice of the protocol typically involves generation of the requisite ketene from activated carboxylic acid derivatives such as acyl chlorides, thus often limiting the scope. In this regard, noteworthy is the β-lactam synthesis using metalloketenes,[6] in which the ketene species is formed via carbene carbonylation, not derived from carbonyl compounds.[7] While this approach has focused mostly on the stoichiometric use of Fischer carbenes, catalytic examples based on the carbene carbonylation have been reported making use of diazo compounds (Scheme 1, metal alkylidene pathway).[8] An attractive alternative is formation of the metalloketene via oxygenation of a metal vinylidene (Scheme 1, metal vinylidene pathway). We recently described a rhodium-catalyzed oxygenative addition reaction that furnishes carboxylic acid derivatives from terminal alkynes and various nucleophiles.[9] In continuing efforts to further develop this process, we questioned if the metal-vinylidene-to-ketene transformation,[10] a crucial event in the catalytic cycle, could be tapped into for β-lactam synthesis. Notably, this reaction would enable readily available alkynes to be employed as substrates for β-lactam synthesis, mirroring the Kinugasa reaction but with a distinct mechanism.[11] Here, we report a rhodium-catalyzed oxygenative [2 + 2] cycloaddition of terminal alkynes and imines that affords β-lactam products with high *trans* selectivity.

Scheme 1. Synthesis of β-Lactams via Metalloketene-Mediated Catalysis



Our studies commenced with applying the conditions of the oxygenative alkyne addition[9] to the reaction of alkyne **1a** with imine **2a** (Table 1). Thus, the mixture of **1a** and **2a** was heated at 50 °C in the presence of 2.5 mol % $[Rh(COD)Cl]_2$, 10 mol % $P(4-F-C_6H_4)_3$, and 1.3 equiv 4-picoline *N*-oxide for 24 h. Gratifyingly, a smooth reaction took place to give rise to the desired β-lactam **3a** as a *trans* isomer exclusively in 90% yield (entry 1), indicating the metalloketene intermediate involved in the oxygenative addition to be also viable for cycloaddition with an imine. While ligand screening experiments revealed triphenylphosphine to be optimal (entries 1−4), the use of Wilkinson's catalyst proved equally efficient (entry 5). A brief survey of ruthenium catalysts established that the reaction could be more efficiently performed using a rhodium complex as the catalyst (entries 6−8). Similarly to the results of our previous studies,

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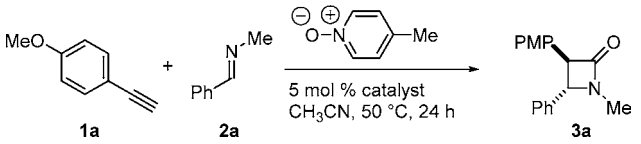
Table 1. Oxygenative [2 + 2] Cycloaddition of Alkyne 1a with Imine 2a under Various Conditions[a]



1a 2a 3a

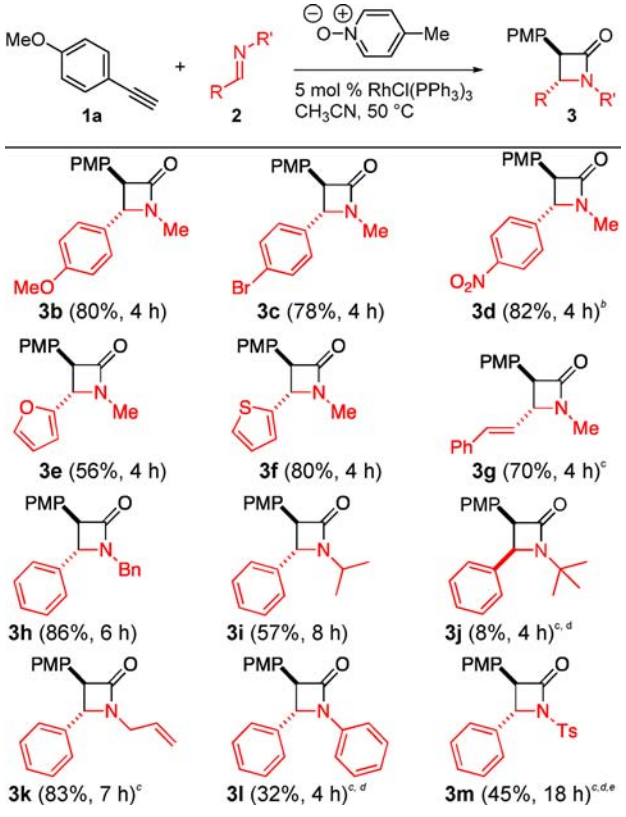
entry	catalyst	yield[b] (%)
1	$[Rh(COD)Cl]_2/P(4\text{-}F\text{-}C_6H_4)_3$	90
2	$[Rh(COD)Cl]_2/P(C_6H_5)_3$	93
3	$[Rh(COD)Cl]_2/P(4\text{-}MeO\text{-}C_6H_4)_3$	50
4[d]	$[Rh(COD)Cl]_2$/dppp	4
5[c]	$Rh(PPh_3)_3Cl$	93
6[d]	$TpRu(PPh_3)_2Cl$	0
7[d]	$CpRu(PPh_3)_2Cl$	8
8[d]	$Cp^*Ru(PPh_3)_2Cl$	38

[a]Alkyne (0.26 mmol), imine (0.2 mmol), and 4-picoline *N*-oxide (0.26 mmol) in CH_3CN (0.8 mL, 0.25 M), [Rh]/phosphine = 1:2 except for entry 5. [b]Determined by NMR. [c]Isolated yield, 4 h. [d]Alkyne and imine remained.

4-picoline *N*-oxide and acetonitrile were found to be the best oxidant and solvent, respectively.[12]

With encouraging results from the initial experiment, we explored the scope of the reaction with respect to the imine component (Table 2). Under the conditions using 5 mol % $Rh(PPh_3)_3Cl$, a variety of imines reacted with alkyne **1a** to provide the corresponding *β*-lactams with high 3,4-*trans* selectivity. Both aryl and heteroaryl imines with varying substituents as well as an alkenyl imine (**3g**) all participated well in the reaction.[13] In terms of *N*-substitution, methyl, benzyl, allyl, and isopropyl groups were well tolerated, whereas lower yields were obtained from the reactions of *N*-*tert*-butyl (**3j**), phenyl (**3l**), and tosyl (**3m**) substrates.

Table 2. Rh-Catalyzed Oxygenative [2 + 2] Cycloaddition of Alkyne 1a with Various Imines[a]

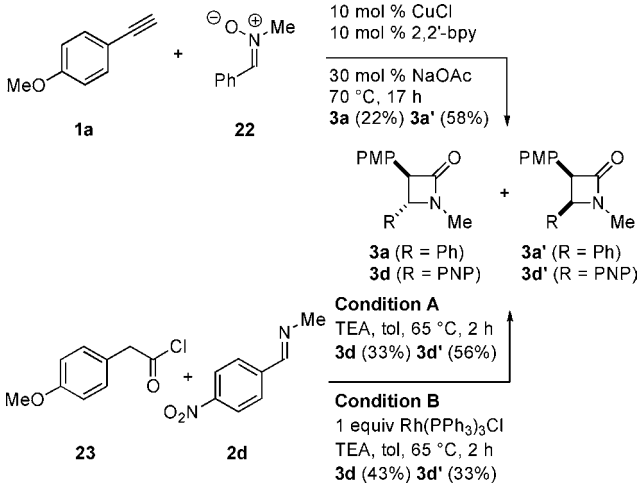


[a]Alkyne (0.65 mmol), imine (0.5 mmol), and 4-picoline *N*-oxide (0.65 mmol) in CH_3CN (2 mL, 0.25 M). [b]dr = 5.8:1. [c]Alkyne (0.5 mmol), imine (0.55 mmol), 4-picoline *N*-oxide (0.6 mmol), $Rh(PPh_3)_3Cl$ (7.5 mol %), and $ZnCl_2$ (15 mol %) in CH_3CN (2.5 mL, 0.20 M) at 65 °C. [d]Imine recovered. [e]dr = 7.7:1.

Having established a broad scope with regard to imine substrates, we next turned our attention to probing the alkyne structure amenable for the [2 + 2] cycloaddition with imine **2a**. As summarized in Table 3, the diversity of suitable alkynes proved extensive, and a variety of functional groups such as ether (OMe, OBn, OTBDPS), halide (Br, Cl), ester, and cyanide did not interfere with the reaction. A broad range of alkynes with aryl (**4**–**9**), heteroaryl (**10** and **11**), alkenyl (**12**), and linear alkyl (**13**–**19**) groups were found to be excellent participants of the reaction, affording the *β*-lactam products in good yield. In contrast, the reactions of the alkynes with branched alkyl (**20**) and potentially coordinating (**21**) substituents produced *β*-lactams in low yield, suggesting possible involvement of a metal-bound ketene, rather than free ketene, as an intermediate.[14] Interestingly, the reactions of alkyl-substituted alkynes, in general, were less efficient than those of aryl and alkenyl substrates under the standard conditions. In these cases, the addition of $ZnCl_2$ (15 mol %) to the reaction significantly accelerated the rate and increased the yield (**13**–**21**). In all cases, these rhodium-catalyzed reactions furnished *β*-lactams in *trans* configuration (dr > 25:1).

A set of control experiments were performed to gain insight into the mechanism (Scheme 2). First, whereas the reaction of

Scheme 2. Control Experiments



alkyne **1a** with nitrone **22** under Kinugasa conditions gave **3a′** (*cis β*-lactam) as the major product, no reaction occurred when $RhCl(PPh_3)_3$ was employed instead of CuCl.[15] Second, while **3d′** (*cis β*-lactam) was produced as the major product from the reaction of acid chloride **23** with imine **2d** using a Staudinger protocol (condition A),[16] running the same reaction in the presence of $RhCl(PPh_3)_3$ reoriented the diastereoselectivity to favor the formation of *trans* isomer **3d** as the major product (condition B), hinting at the possible intermediacy of a rhodium-bound ketene rather than free ketene.

The mechanism of the rhodium-catalyzed oxygenative [2 + 2] cycloaddition of alkynes and imines is proposed in Scheme 3.

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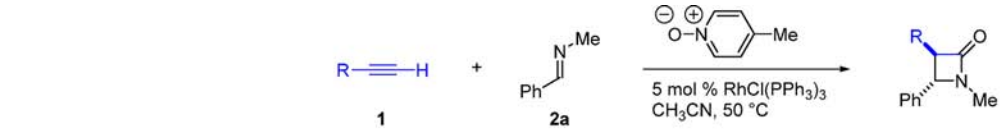
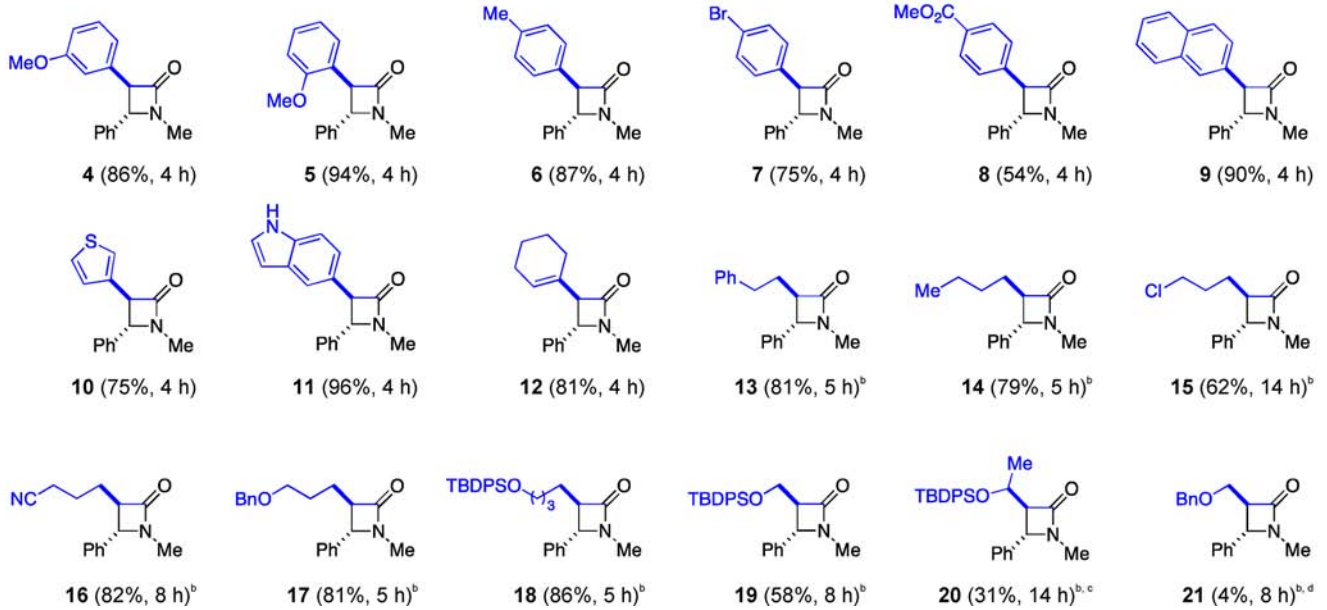
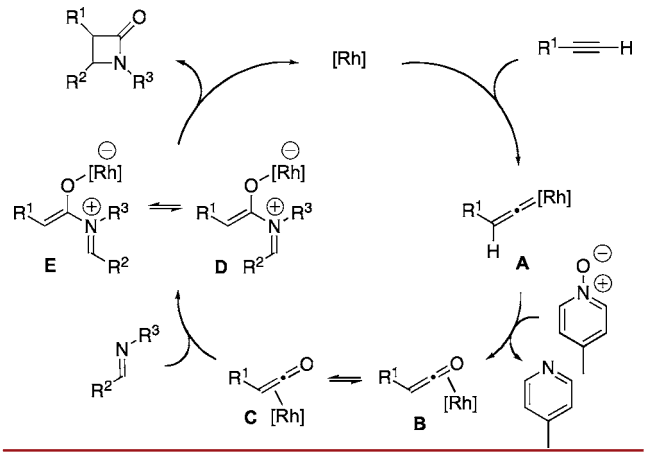
Table 3. Rhodium-Catalyzed [2 + 2] Cycloaddition of Various Alkynes with Imine 2a[a]





[a]Alkyne (0.65 mmol), imine (0.5 mmol), 4-picoline *N*-oxide(0.65 mmol), and $Rh(PPh_3)_3Cl$ (5 mol %) in CH_3CN (2.0 mL, 0.25 M) at 50 °C. [b]Alkyne (0.5 mmol), imine (0.55 mmol), 4-picoline *N*-oxide(0.6 mmol), $Rh(PPh_3)_3Cl$ (7.5 mol %), and $ZnCl_2$ (15 mol %) in CH_3CN (2.5 mL, 0.20 M) at 65 °C. [c]dr = 1:1. [d]3-(Benzyloxy)-*N*-methylpropanamide was obtained in 46% yield.

Scheme 3. Proposed Mechanism of the Rh-Catalyzed Oxygenative [2 + 2] Cycloaddition of Alkyne and Imine



Starting with the formation of a rhodium vinylidene from a terminal alkyne, the catalytic cycle consists of the generation of a metalloketene and its cycloaddition with an imine. In the first stage, the oxygen transfer from 4-picoline *N*-oxide to η^1-Rh vinylidene complex **A** produces η^2- Rh ketene **B**, which likely exists in equilibrium with **C**.[17] Subsequently, the nucleophilic addition of an imine to the metallo-ketene species generates a rhodium-complexed zwitterionic intermediate (**D**/**E**), which forms the *β*-lactam product. Given the high preference for *trans* product formation, the final step is believed to involve facile isomerization of iminium **D** to **E** prior to the ring closure that completes the catalytic cycle.[18]

The rhodium-catalyzed cycloaddition described here has several significant features. It demonstrates that an operationally simple Staudinger *β*-lactam synthesis can be practiced with readily available and easily handled terminal alkynes as substrates under mild rhodium catalysis without requiring activated carboxylic acid derivatives. Taking advantage of a mechanism based on catalytic oxidation of a metal vinylidene complex for metalloketene generation, our studies establish for the first time that a rhodium complexed ketene species can undergo efficient [2 + 2] cycloaddition with imines. Further explorations of this reaction, including the development of an asymmetric variant, are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) For details, see Table S2 and S3 in the Supporting Information.

(13) The reaction has been unsuccessful with alkyl imines. For example, the reaction of **1a** with *N*-methylcyclohexylimine gave a mixture of intractable products without forming a *β*-lactam product.

(14) Given the marked difference in reactivity between TBDPS (cf. **19**) and Bn (cf. **21**) protected substrates, the zwitterionic intermediate (e.g., **D** in Scheme 3) leading to **21** is likely to exist as a rhodium enolate chelated with the OBn group. The formation of a stable enolate may render the final electrocyclization step sluggish, while the hydrolysis of the intermediate to an amide byproduct (46%, footnote d of Table 3) becomes more competitive. Similarly, the reaction of *p*-nitro-substituted phenylacetylene with imine **2a** did not produce a *β*-lactam product but gave an *N*-methyl amide in 15% yield. See the Supporting Information for details.

(15) No oxygen transfer between imines and picoline was observed. For details of control experiments, see the Supporting Information.

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(18) For *cis*−*trans* imine isomerization, see: Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc.* **2006**, *128*, 6060. For *cis*−*trans* imine isomerization via a metallacycle formation, see ref 8b.