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ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · DECEMBER 2006

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J Am Chem Soc. 2006 November 22; 128(46): 14818–14819.

Tandem Cyclization of Alkynes via Rhodium Alkynyl and Alkenylidene Catalysis

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Transition metal alkynyl α-complexes are among the mainstay organometallics that are of broad utility in organic synthesis.[1] The sp-hybridized carbon–metal bond of such complexes reacts with electrophiles typically through the R-carbon to effect alkynylation under metal catalysis.[2,3] An alternative pathway of metal alkynyls involves a reaction of the β-carbon that leads to the formation of a metal alkenylidene (vinylidene) species (Scheme 1). Unlike the alkynylation process, however, this type of reactivity has been established only in stoichiometric settings, requiring a preformed metal alkynyl and a separate step for demetalation of the resulting alkenylidene complex.[4,5] Despite its conceivable synthetic value, a catalytic protocol accomplishing bond formation based on this modality remains to be developed.[6] Noting the feasibility of the generation and turnover of metal alkynyls and alkenylidenes via catalytic mechanisms,[7] we envisioned a tandem process that could couple these events with a β-alkylation as mediated by a single catalyst. This process would enable multiple C–C bond formations to occur at both the α- and β-positions of alkynes in one synthetic operation. In this communication, we report a tandem cyclization of terminal alkynes that provides expedient access to fused ring systems via combined rhodium alkynyl/alkenylidene-mediated catalysis.

In light of our previous experience in the Rh(I)-catalyzed enyne cycloisomerization,[8] the present study was initiated by examining the possibility of these catalyst systems to promote a β-alkylation in the context of 3-haloalkyl-1,6-enyne system **1** (Table 1). While subjecting **1a** to our previously developed conditions gave none of **2** (entries 1 and 2),[9] the otherwise same reaction in the presence of DBU resulted in a yield of 25% (entry 3). Further screening revealed TEA to be an optimal base increasing the yield to 85% (entry 6). The electronic character of the arylphosphines exerted only marginal effects on the present reaction with P(4-F-C_6H_4)$_3$ being most effective (entries 6–10). The double cyclization could also be carried out with substrates bearing bromide (**1b**) and tosylate (**1c**) leaving groups, albeit with diminished yields (entries 11 and 12).

Scheme 1.
Strategy for Catalytic Terminal Alkyne Functionalization

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

Scheme 2.
Proposed Mechanism for the Rh-Catalyzed Alkylation–Cycloaddition of 3-Haloalkyl-1,6-enynes

Reaction scope was probed with a range of substrates (Table 2). Similar to the model study, hydrindene ring systems possessing substituents of differential positions and stereochemistry (entries 1–3) as well as a spirotricyclic derivative (entry 4) were accessed from the corresponding enynes. In addition to these carbocycles, the Rh(I)-catalyzed tandem cyclization proved feasible for the preparation of various aza- (entry 5) and oxacycles (entries 6–9), including the tricyclic hydrofurodecaline **18**. For the reaction of **19**, the use of [Rh$(C_2H_4)_2Cl]_2$ was found to be effective inducing the cyclization at 25 °C (entry 9). Interestingly, the simple enyne cycloisomerization without alkylation of the iodide took place when the reaction was performed in THF instead of DMF (entry 10). This dichotomy of reaction pathways suggests the presence of a subtle kinetic balance in the catalytic cycle (vide infra).

The mechanism of the present tandem cyclization is proposed to involve a reversible formation of rhodium alkynyl complex **B**(Scheme 2). Subsequent to an irreversible alkylation with the pendent alkyl halide, the resultant β,β-substituted alkenylidene **C** undergoes a [2 + 2] cycloaddition to accomplish an additional ring closure via **D** and **E**.[10] When the alkylation step is slow or infeasible, intermediate **A**, existing in equilibrium with **B**,[11] may directly enter on the cycloisomerization course to give rise to a monocyclization product such as **21**.

On the basis of the intermediacy of an alkenylidene complex of type **C**, we hypothesized that the alkylative approach might be extended to construct other ring structures by replacing the alkene with other reactive components such as hydroxyl (**22**) and phenyl (**26**) groups. Under the same reaction conditions employed for the alkylation-cycloaddition, alcohol **22** was converted to enol ether **24** in 52% yield, presumably through β-alkylation followed by addition of the hydroxyl group to the rhodium alkenylidene **23**, and the simple cycloisomerization product **25** in 15% yield (eq 1).[7c,12] A tandem cyclization took place in the reaction of **26**, which afforded the tetracyclic naphthalene **28** in 83% yield (eq 2). In this case, the incipient alkenylidene **27** is believed to follow a 6π-electrocyclization process,[13] leading to aromatization.[14]

In summary, we have developed a rhodium-catalyzed tandem cyclization of alkynes. The reaction allows for the rapid assembly of various fused ring systems from terminal alkyne derivatives in a single step under mild conditions through a novel mechanism that merges transition metal alkynyl and alkenylidene chemistry. The findings described in this paper suggest that the uniquely unified catalytic cycle may be permuted in many ways for further development of new methods of alkyne functionalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank the NSF (CHE 0518559) and the NIH-NIGMS (GM 073065) for support of this research, Princeton University for a Hugh Stott Taylor fellowship (J.M.J.), and FMC Corporation for a graduate fellowship (Y.Y.).

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9. While the base-free conditions (ref 8a) returned unreacted **1a** (64%) along with 19% of its formate (X) OCHO) derived from a DMF adduct of **1a** after 6 h, the reaction in the presence of DABCO (ref 8b) led to rapid decomposition of **1a**, presumably via *N*-alkylation.

10. The formation of **4b** from **3b** (entry 1, Table 2) together with the results of the labeling studies reported in ref [8a] supports this mechanism.

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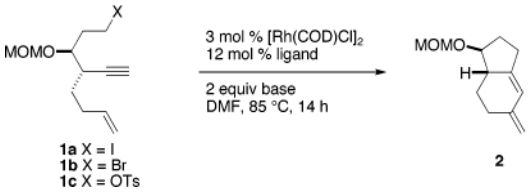
Table 1

Rhodium-Catalyzed Alkylative Cyclization of Enyne **1**[a]



entry	X	ligand	base	yield (%)[b]
1	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	—	—
2	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	DABCO	—
3	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	DBU	25
4	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	NMM[c]	62
5	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	DIPEA	80
6	I (**1a**)	$P(4\text{-F-}C_6H_4)_3$	TEA	85
7	I (**1a**)	PPh_3	TEA	80
8	I (**1a**)	$P(4\text{-MeO-}C_6H_4)_3$	TEA	73
9	I (**1a**)	$P(3\text{-Cl-}C_6H_4)_3$	TEA	69
10	I (**1a**)	$P(3,5\text{-}CF_3\text{-}C_6H_3)_3$	TEA	50
11	Br (**1b**)	$P(4\text{-F-}C_6H_4)_3$	TEA	62
12	OTs (**1c**)	$P(4\text{-F-}C_6H_4)_3$	TEA	46

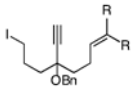
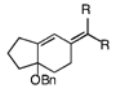
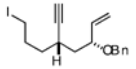
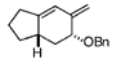
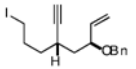
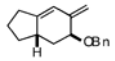
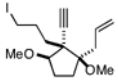
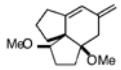
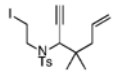
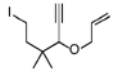
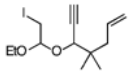
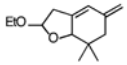
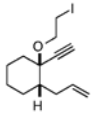
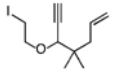
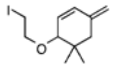
[a] All reactions were performed with 0.20 mmol of **1** and 0.40 mmol of base at 85 °C in DMF (0.1 M) for 14 h.

[b] Isolated yield of **2**.

[c] NMM = *N*-methylmorpholine.

Table 2

Rhodium-Catalyzed Alkylative Cyclization of Iodoenynes[a]

entry	reactant		product		yield (%)[b]
1		**3a** (R=H) **3b** (R=D)[c]		**4a** (R=H) **4b** (R=D)[d]	73% 75%
2		**5**		**6**	54%
3		**7**		**8**	55%
4		**9**		**10**	69%
5		**11**		**12**	78%
6		**13**		**14**	45%
7[e]		**15**		**16**	66%
8		**17**		**18**	96%
9[f]		**19**		**20**	81%
10,[fg]	**19**			**21**	65%

[a] All reactions were performed with 0.20 mmol of substrate, 0.40 mmol of TEA, 3 mol % of $[Rh(COD)Cl]_2$, and 12 mol % of $P(4\text{-}F\text{-}C_6H_4)_3$ at 85 °C in DMF (0.1 M), unless otherwise noted.

[b] Isolated yield. For entries 2, 3, 4, 7, and 8, the yields were averaged over two runs.

[c] DI (Deuterium incorporation) = 86%.

[d] DI = 83%.

[e] Diastereomeric mixtures were employed and obtained (dr = 1.2:1).

[f] $[Rh(C_2H_4)_2Cl]_2$ was used as the catalyst at 25 °C.

[g]The reaction was performed in THF for 48 h.