

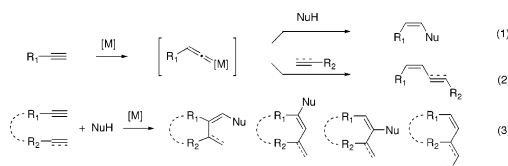
Ruthenium-Catalyzed Carboxylative Cyclization of 1,6-Diynes

Hahn Kim, Stephen D. Goble, and Chulbom Lee*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received October 12, 2006; E-mail: cblee@princeton.edu

Over the last two decades, metal vinylidene-mediated catalysis has emerged as a useful means of alkyne functionalization.¹ At the core of these developments resides the multifaceted reactivity of metal vinylidenes, from which a wide variety of transformations may be derived. For example, metal vinylidenes ($M=C_{\alpha}=C_{\beta}$) can react with a nucleophile through the electrophilic α -carbon² or engage in bond formation through their two π -systems.³ However, rarely have these reactivities been probed in mechanistically interwoven contexts, whereas simultaneous exploitation of distinctive processes has been a successful approach in other metal-mediated catalyzes of alkynes.⁴ In ongoing efforts aimed at the development of metal vinylidene-catalyzed C–C bond-forming reactions,⁵ we recently questioned whether the addition reactions involving a nucleophile (eq 1) and a π -unsaturation (eq 2), the two most well-studied subjects in metal vinylidene catalysis, could be formulated into a tandem process. Conceivably, this reaction would allow for coupling of two or more components through construction of C–O and C–C bonds with potential control of selectivity (eq 3). In this paper, we report the discovery of a ruthenium-catalyzed addition-cyclization of 1,6-terminal alkynes with carboxylic acids.⁶



To commence the studies, a 1:1 mixture of diyne **1** and benzoic acid was exposed to a series of ruthenium catalysts known to form a metal vinylidene species (Table 1). However, this initial set of experiments was not fruitful, as the majority of Ru(II) complexes induced no reaction or a simple addition of benzoic acid to **1** to give enol benzoates **2b** and **2c** as (*E*)- and (*Z*)-mixtures in low yields. A more encouraging result came from the reaction with [Ru(*p*-cymene)Cl₂]₂/P(4-Cl-C₆H₄)₃/DMAP, a catalyst system used to promote a *Z*-selective anti-Markovnikov addition of carboxylic acids to alkynes,⁷ which produced cyclohexenylidene enol ester **2a**, and uncyclized mono- and bisbenzoates **2b** and **2c** in 42%, 6%, and 20% yields, respectively (entry 1).⁸ Further screening efforts led to the following findings: (1) The best results were obtained using 1,4-dioxane as the solvent. Nonpolar media gave good conversion but decreased the selectivity while coordinating solvents resulted in poor conversion (entries 1–6). (2) Moderately electron-withdrawing phosphine ligands proved most efficient, among which P(4-F-C₆H₄)₃ gave the best outcome (entry 10). (3) Replacement of DMAP with other amine additives was found to be detrimental to the reaction, significantly diminishing both the yield and selectivity.⁹

With the optimized reaction conditions in hand, we then tested an assortment of 1,6-diynes and carboxylic acids to evaluate the scope of the addition-cyclization process (Table 2). The survey revealed a range of aliphatic and aromatic carboxylic acids to be good participants of the reaction, giving rise to the corresponding

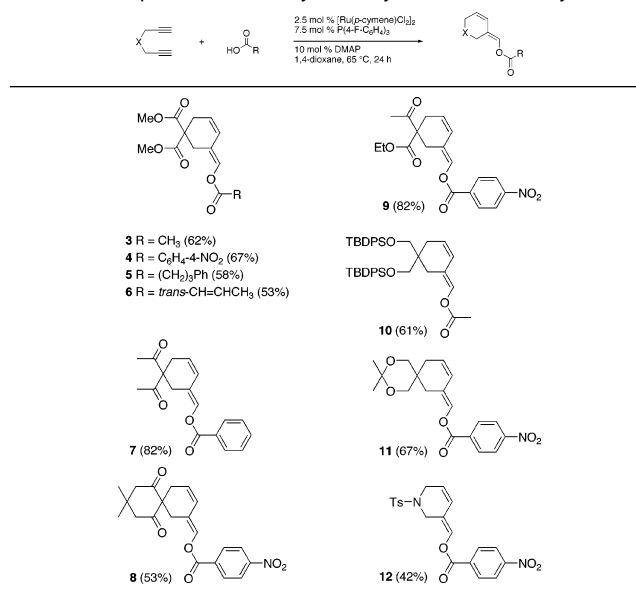
Table 1. Ru-Catalyzed Addition-Cyclization of **1** with Benzoic Acid^a

entry	ligand	solvent	yield ^b	ratio ^c 2a/2b/2c
1	P(4-Cl-C ₆ H ₄) ₃	toluene	42%	64:9:27
2	P(4-Cl-C ₆ H ₄) ₃	DCE	30%	50:17:33
3	P(4-Cl-C ₆ H ₄) ₃	acetone	35%	70:12:18
4	P(4-Cl-C ₆ H ₄) ₃	CH ₃ CN	10%	
5	P(4-Cl-C ₆ H ₄) ₃	THF	45%	75:8:17
6	P(4-Cl-C ₆ H ₄) ₃	dioxane	68%	100:0:0
7	P(OPh) ₃	dioxane	<5%	
8	PCy ₃	dioxane	10%	29:57:14
9	P(3-Cl-C ₆ H ₄) ₃	dioxane	62%	100:0:0
10	P(4-F-C ₆ H ₄) ₃	dioxane	74%	100:0:0

^a All reactions were run with a 1:1 mixture of benzoic acid and diyne **1**.

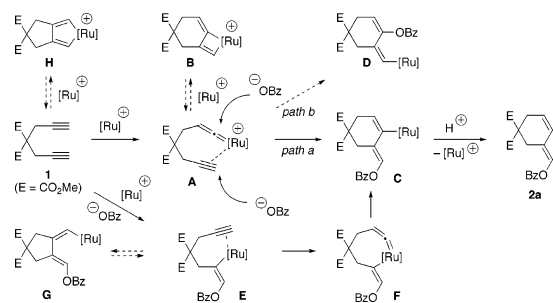
^b Isolated yields of **2a**. ^c Determined by ¹H NMR.

Table 2. Scope of the Carboxylative Cyclization of 1,6-Diynes^a

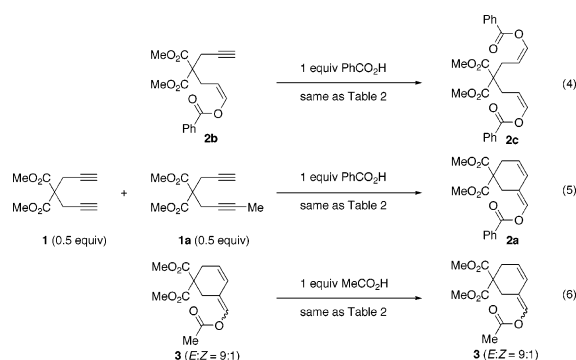


^a All reactions were carried out using 2.5 mol % [Ru(*p*-cymene)Cl₂]₂, 7.5 mol % P(4-F-C₆H₄)₃ and 10 mol % DMAP in 1,4-dioxane (0.25 M) for 24 h at 65 °C. All yields are isolated yields.

enol esters as single geometric isomers. In all cases, formation of the simple addition products such as **2b** and **2c** was not observed or amounted only to less than 5%. As expected from the isolation of both acid- and base-sensitive enol carboxylates as the products, the reaction tolerated various functional groups such as ester, ketone, silyl ether, ketal, and tosyl amine. While the nature of the carboxylic acids had only a small influence on the reaction (cf. **3**–**6**), variations in the tether led to a wide fluctuation in the yield.¹⁰

Scheme 1. Proposed Mechanism for Carboxylative Diyne Cyclization

Several observations made in a set of further experiments are noteworthy (eq 4–6). When monobenzoate **2b** was resubjected to the standard conditions, only bisbenzoate **2c** was generated over a prolonged reaction time (ca. 10%, 48 h) (eq 4). This result renders the possibility of **2b** as an intermediate of the reaction highly unlikely, thereby excluding the mechanism involving an enyne cycloisomerization of **2b** to **2a**.¹¹ The present addition-cyclization proved infeasible with the methyl-substituted diyne **1a**. Interestingly, the reaction of a 1:1:2 mixture of **1**, **1a**, and benzoic acid gave only a 20% yield of **2a** with nearly quantitative recovery of unreacted **1a**, indicating possible deactivation of the catalyst by **1a** (eq 5). Finally, the formation of (*E*)-isomers as the products appears to be kinetic in origin, since no isomerization occurs under the reaction conditions (eq 6).



While further studies are currently in progress, a mechanistic proposal may be advanced on the basis of the observations made thus far (Scheme 1). Upon formation of ruthenium vinylidene **A**, the pendent alkyne is coordinated to the metal center. While it may not or may only reversibly undergo a [2+2] cycloaddition to **B**, addition of the benzoate anion induces cyclization of **A** to **C** or **D**. Given the exclusive generation of **2a** in (*E*)-configuration, the outer-(path a) rather than inner-(path b) nucleophilic attack appears to be favored, a type of process reminiscent of the nucleophile-promoted electrophilic cyclization of alkynes.¹² The final protio-demetalation then furnishes the product and turns the catalyst over. Alternatively, **C** may be formed via α -migration of **F** which could arise from vinyl ruthenium **E**.¹³

In summary, we have developed a ruthenium-catalyzed tandem addition-cyclization of 1,6-terminal diynes and carboxylic acids. In contrast to typical metal-mediated processes of diynes that give five-membered-ring products, the reaction provides six-membered-carbo- and heterocyclic systems decorated with useful functional groups.¹⁴ Also proposed here is an unprecedented anti attack of a nucleophile on a π -alkyne ruthenium vinylidene complex. This new reactivity is anticipated to open up new opportunities for further development of catalytic alkyne functionalization.

Acknowledgment. We thank the NSF (Grant CHE 518559) and Amgen for financial support of this research, Princeton University for a Harold W. Dodds Fellowship (H.K.), and Merck for graduate support (S.D.G.). We also thank Jimin Kim and Dr. Doug Ho for the X-ray analysis of **2a**.

Supporting Information Available: Experimental details (pdf and cif). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For reviews, see: (a) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (b) Varela, J. A.; Saá, C. *Chem.—Eur. J.* **2006**, *12*, 6450. (c) Wakatsuki, Y. *J. Organomet. Chem.* **2004**, *689*, 4092. (d) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (e) McDonald, F. E. *Chem.—Eur. J.* **1999**, *5*, 3103.
- (2) For examples of the addition of various nucleophiles, carboxylic acids: (a) Doucet, H.; Höfer, J.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1993**, 850. (b) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *69*, 7247. Carbamate, see: (c) Sasaki, Y.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1986**, 790. Intermolecular addition of alcohols: (d) Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809. (e) Gemel, C.; Trimmel, G.; Slugovc, C.; Kremel, S.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 3998. Intramolecular addition of alcohols: (f) Trost, B. M.; Flygare, J. A. *J. Org. Chem.* **1994**, *59*, 1078. (g) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952. Hydration: (h) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867. (i) Alvarez, P.; Bassetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* **2001**, *42*, 8467. (j) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232. Amine: (k) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687. Hydrazine: (l) Fukumoto, Y.; Dohi, T.; Masaoka, H.; Chatani, N.; Murai, S. *Organometallics* **2002**, *21*, 3845. Stabilized carbanions: (m) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691. Silyl enol ethers: (n) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. Phosphine: (o) Jérôme, F.; Monnier, F.; Lawicka, H.; Dérien, S.; Dixneuf, P. H. *Chem. Commun.* **2003**, 696.
- (3) Alkyne dimerization: (a) Bianchini, C.; Peruzzini, M.; Zanolini, F.; Frediani, P.; Albinati, A. *J. Am. Chem. Soc.* **1991**, *113*, 5453. (b) Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. Y. *J. Am. Chem. Soc.* **1991**, *113*, 9604. (c) Fryzuk, M. D.; Huang, L.; McManus, N. T.; Paglia, P.; Rettig, S. J.; White, G. S. *Organometallics* **1992**, *11*, 2979. (d) Braun, T.; Meuer, P.; Werner, H. *Organometallics* **1996**, *15*, 4075. (e) Slugovc, C.; Mereiter, K.; Zobetz, E.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 5275. Alkyne-alkene coupling: (f) Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361. (g) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720. (h) Bigault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753.
- (4) For a review, see: (a) Ojima, I.; Tzamaridou, M.; Li, Z.; Donovan, R. *J. Chem. Rev.* **1996**, *96*, 635. For examples of addition/cyclization of 1,6-diynes, see, hydrostannanes: (b) Lautens, M.; Smith, N. D.; Ostrovsky, D. *J. Org. Chem.* **1997**, *62*, 8970. Stannyllanes: (c) Greau, S.; Radetich, B. N.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **2000**, *122*, 8579. Boryllanes: (d) Onozawa, S.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229. Boryllanes: (e) Onozawa, S.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389. Hydrogen: (f) Jang, H. Y.; Kische, M. *J. Am. Chem. Soc.* **2004**, *126*, 7875. Hydrogen equivalent: (g) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. Hydrosilylation: (h) Ojima, I.; Zhu, J.; Viadal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690. (i) Madine, J. W.; Wang, X.; Widenhoefer, R. A. *Org. Lett.* **2001**, *3*, 385. Hydration: (j) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516.
- (5) (a) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180. (b) Chen, Y.; Ho, D.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 12184. (c) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 6336.
- (6) Goble, S. D. Ph.D. Dissertation, Princeton University, NJ, Sept. 2006.
- (7) Goossen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706.
- (8) The structure of **2a** has been determined by an X-ray crystallographic analysis. See Supporting Information for details.
- (9) For comprehensive screening results, see Supporting Information.
- (10) The reaction of substrates with an ether tether gave a complex mixture of intractable products presumably due to the formation of allenylidene and/or allenyl alkylidene complexes. For examples, see ref 1a and (b) Castarlenas, R.; Eckert, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 2576. The reactions of 1,5- and 1,7-diynes did not give the cyclized product, but led to alkyne dimerization after 48 h (see ref 3).
- (11) See ref 5a and: Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 4967.
- (12) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612.
- (13) This pathway involving the transient formation of **F** was suggested by a reviewer. The possible intermediacy of **G** and **H** cannot be excluded at the present time. The deuterium labeling experiments were inconclusive because of significant scrambling. For details, see Supporting Information.
- (14) For examples showing the product utility, see Supporting Information.

JA067336E