considerable experimental uncertainty, especially for rapid reactions at short time points).

[29] In light of Evans' work (refs. [23a,b]), one might have expected better results for the Rh^I catalyst here. In fact, whereas the unmodified Wilkinson catalyst proved to be much less efficient than the Ni^0 catalysts found for this reaction involving a lithiated carbamate as an internal nitrogen nucleophile, it proved to be a good catalyst for the reaction of a simple substrate (allyl ethyl carbonate) with a neutral, external nitrogen nucleophile (dibenzylamine; see the Supporting Information).

[30] With one exception, all cuvettes contain an organic layer: **1a** (110 μmol), LiHMDS (100 μmol), catalyst (10 mol %), with added PPh_3, where added, in 400 μL total organic solvent (THF:PhMe:hexane 2:1:1), over an aqueous layer containing: NAD^+ (7.4 mM), ADH (1.3 U) and AlDH (0.12 U; U = the amount of enzyme that leads to the oxidation of 1 μmol of ethanol under the standard assay conditions given in the Supporting Information) in sodium pyrophosphate buffer (15 mM, pH 8.8); final pH 7.7 in 900 μL total aqueous volume. The exception was the $[Mo(CO)_3(C_7H_8)]$/3PPh_3-catalyzed reaction (Figure 2), which was run at higher catalyst loading (50 mol % catalyst) on substrate **1b**, at half the usual concentration (i. e. 55 μmol in the same volume) for solubility reasons.

[31] RB-flask reactions contained the same concentrations of **1a** or **1b** and catalyst as the cuvette reactions, with one equivalent LiHMDS in THF:hexane (73:27). All reactions were stopped after 60 min and, where appropriate, the product (**2a** or **2b**) was isolated by SiO_2 chromatography.

[32] Of the several bases examined for carbamate deprotonation (*n*-BuLi, NaHMDS, KHMDS, LDA, NaOTMS), LiHMDS gave the best amination rates/yields. Interestingly, Evans and co-workers also settled upon this base for his Rh^I-mediated aminations (refs. [23a,b]).

[33] While Mo^0-mediated allylic alkylation is well-developed chemistry (For leading references, see; a) O. Belda, N. F. Kaiser, U. Bremberg, M. Larhed, A. Hallberg, C. Moberg, *J. Org. Chem.* **2000**, *65*, 5868–5870; b) B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, *121*, 10416–10417; c) F. Glorius, A. Pfaltz, *Org. Lett.* **1999**, *1*, 141–144), we have been unable to find a report of Mo^0-mediated allylic amination. Kocovsky et al. have developed a mechanistically distinct Mo^{IV}-mediated allylic-amination reaction upon allylic alcohols (ref. [23i]).

[34] The PG screens were run at half the usual substrate concentration (138 mM), but at the usual concentrations of $Ni(cod)_2$ (27.5 mM) and PPh_3 (110 mM). On the other hand, the ligand screens (entries 7–16) were run at the usual concentrations of substrate (275 mM) and metal (27.5 mM), but at half of the typical ligand concentration (55 mM for monodentate ligands or 27.5 mM for bidentate ligands). These changes are apparently approximately compensatory. For example, for the PPh_3 ligand/PMP PG case, the PG-screening conditions gave a rate of 35 mAbs/min, whereas the ligand-screening conditions gave slopes of 36 and 41 mAbs/min, in two independent runs.

[35] A complete description of these experiments is included in the Supporting Information.

[36] a) C. Cho, R. Ishii, S. Hyeon, A. Suzuki, *Agric. Biol. Chem.* **1987**, *51*, 2597–2598; b) N. W. Cornell, P. F. Zuurendonk, M. J. Kerich, C. B. Straight, *Biochem. J.* **1984**, *220*, 707–716; c) T. S. Soper, J. M. Manning, P. A. Marcotte, C. T. Walsh, *J. Biol. Chem.* **1977**, *252*, 1571–1575; d) R. R. Rando, N. Relyea, L. Cheng, *J. Biol. Chem.* **1976**, *251*, 3306–3312; e) R. R. Rando, *Biochemistry* **1974**, *13*, 3859–3863.

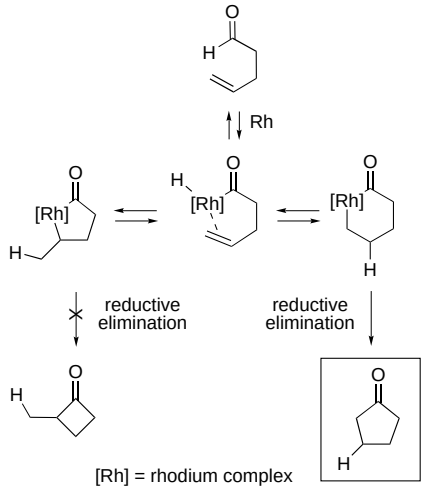
[37] For other syntheses of APPA, see: a) M. Fukuari, I. Ichimoto, K. Mitsunori, *Biosci. Biotech. Biochem.* **1996**, *60*, 680–682; b) H. Allgeier, C. Angst, G. Bold, R. Duthaler, R. Heckendorn, A. Togni, Eur. Pat. Appl. EP 302826 A2 19890208, **1989**.

[38] a) T. Clausen, M. C. Wahl, A. Messerschmidt, R. Huber, J. C. Fuhrmann, B. Laber, W. Streber, C. Steegborn, *Biol. Chem.* **1999**, *380*, 1237–1242; b) B. Laber, K. P. Gerbling, C. Harde, K. H. Neff, E. Nordhoff, H. D. Pohlenz, *Biochemistry* **1994**, *33*, 3413–3423.

A Novel Rhodium-Catalyzed Reduction–Oxidation Process: Reaction of 4-Alkynals with Phenol to Provide *cis*-4-Alkenoates**

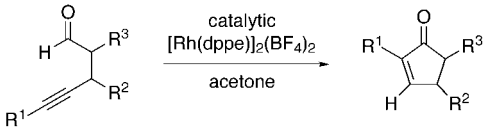
Ken Tanaka and Gregory C. Fu*

For the rhodium-catalyzed intramolecular hydroacylation of a 4-alkenal, five- and six-membered metallacycles have both been shown to be generated during the course of the reaction, although it is the six-membered metallacycle that selectively reductively eliminates to furnish the cyclopentanone product (Scheme 1).[1–3] We have recently reported that



Scheme 1. Rhodium-catalyzed intramolecular hydroacylation of 4-alkenals to form cyclopentanones.

rhodium complexes also catalyze the corresponding cyclization of a 4-alkynal to afford a cyclopentenone [Eq. (1); dppe = 1,1′-bis(diphenylphosphanyl)ethane], presumably through an analogous six-membered metallacycle (see pathway to **A** in Scheme 2).[4]



(1)

This new catalytic process is mechanistically interesting from several standpoints, including the question of whether a five-membered metallacycle (**M**; Scheme 2) is formed tran-

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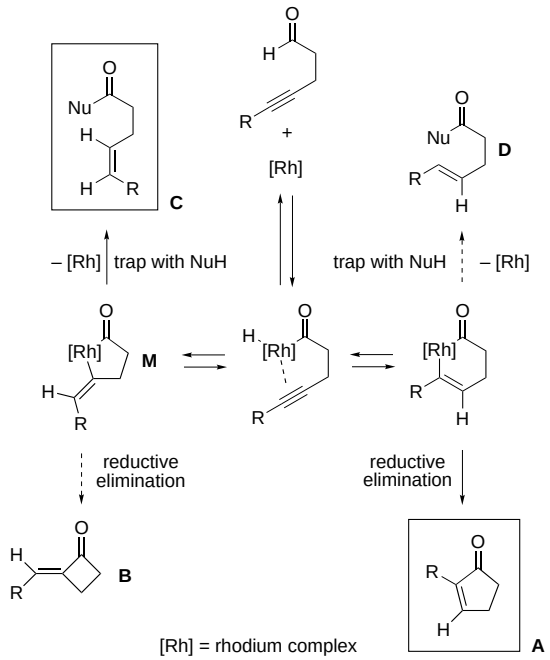
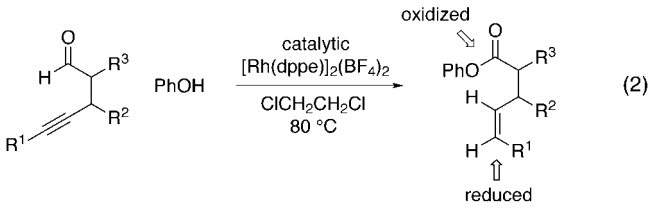
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



Scheme 2. Rhodium-catalyzed intramolecular hydroacylation of 4-alkynals to form cyclopentenones.

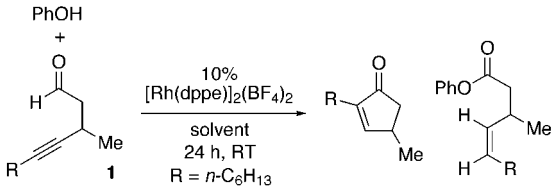
siently under the reaction conditions, as for the cyclization of a 4-alkenal (Scheme 1). We do not observe the generation of strained cyclobutanone **B** (Scheme 2) under the hydroacylation conditions outlined in Equation (1); we anticipated, however, that if we treated the 4-alkynal with $[Rh(dppe)]_2(BF_4)_2$ in the presence of a nucleophile (e.g., an alcohol), we might by trapping obtain evidence for the intermediacy of metallacycle **M**.[5, 6]

The overall transformation achieved by this sequence of events would be an intriguing new rhodium-catalyzed tandem reduction–oxidation: reaction of a 4-alkynal with an alcohol to provide a *cis*-4-alkenoate [see pathway to **C** in Scheme 2; Equation (2)]. Here we report that this novel transformation, which simultaneously effects oxidation of an aldehyde to an ester and reduction of an alkyne to an alkene, can in fact be accomplished in good yield for a range of substrates.



(2)

In an initial investigation, we determined that, in contrast to the reaction in the absence of phenol [Eq. (1)], when 4-alkynal **1** is treated with $[Rh(dppe)]_2(BF_4)_2$ in acetone in the presence of five equivalents of phenol, the major product is the *cis*-4-alkenoate, rather than the cyclopentenone [Eq. (3)]. Simply by employing dichloromethane, instead of acetone, as the solvent, we can completely eliminate formation of the cyclopentenone [Eq. (3)].[7] We do not detect the generation of the *trans*-4-alkenoate or the cyclobutanone



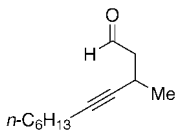
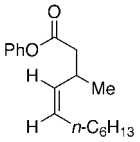
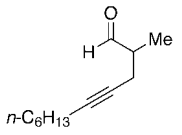
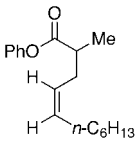
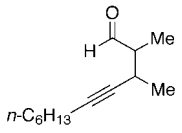
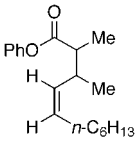
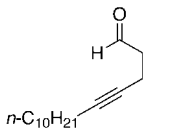
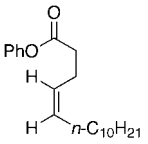
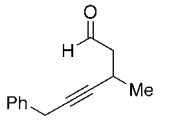
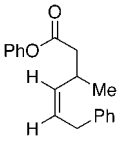
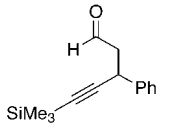
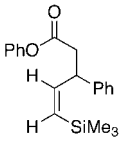
(3)

Equiv of Phenol	Solvent	% Yield by GC	
0	acetone	36	0
5	acetone	34	58
5	CH_2Cl_2	0	87

under any of these conditions (**D** and **B**, respectively, in Scheme 2).

When we conducted the reaction at higher temperature (80 °C; $ClCH_2CH_2Cl$), the catalyst loading could be lowered to 2.5 % $[Rh(dppe)]_2(BF_4)_2$. This interesting catalytic tandem reduction–oxidation process can be applied to the reaction of phenol with a wide variety of 4-alkynals to furnish phenyl *cis*-4-alkenoates in good yields (Table 1).[8, 9] The method tolerates substituents in the β (entry 1) and the α position (entry 2). Furthermore, 1,2-disubstituted (entry 3) as well as 1,2-unsubstituted (entry 4) substrates are suitable reactants.

Table 1. Rhodium-catalyzed reactions of 4-alkynals with phenol to form *cis*-4-alkenoates.[a]

Entry	Substrate	Product	Yield [%][b]
1			87
2			69
3[c]			76
4[c]			65
5			85
6			95

[a] Conditions: 2.5 % $[Rh(dppe)]_2(BF_4)_2$, PhOH (5 equiv), $ClCH_2CH_2Cl$, 80 °C, 16–65 h. [b] Yields of isolated products, average of two runs. [c] 5 % catalyst was used.

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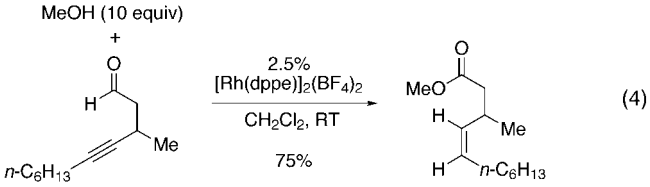
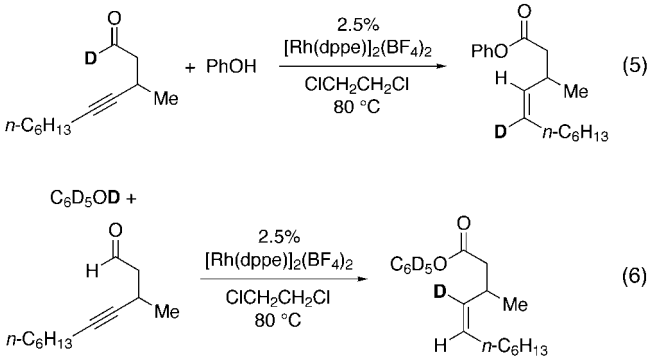
Not only alkyl, but also benzyl (entry 5) and trimethylsilyl (entry 6) groups can occupy the 5-position; in the case of the benzyl-substituted alkyne, no isomerization to the styrene derivative is observed.[10]

Use of methanol, rather than phenol, as the nucleophile, also leads to tandem reduction – oxidation of the 4-alkynal in good yield [Eq. (4)].[11]



Our preliminary mechanistic data are consistent with the pathway for formation of *cis*-4-alkenoate **C** that is outlined in Scheme 2. For example, we have established that the aldehyde hydrogen (deuterium) atom of the starting material migrates stereospecifically and exclusively to the 5-position of the product [Eq. (5)].[12] Furthermore, the oxygen-bound hydrogen (deuterium) atom of phenol is transferred cleanly to the 4-position [Eq. (6)].



In conclusion we have developed an unprecedented rhodium-catalyzed transformation in which an alcohol reacts with a 4-alkynal to furnish a *cis*-4-alkenoate in good yield. This novel tandem process couples the reduction of an alkyne to an alkene with the oxidation of an aldehyde to an ester. Our mechanistic data are consistent with a five-membered rhodium metallacycle as a key intermediate in the catalytic cycle. Future work will focus on additional studies of the reaction pathway, as well as on the exploitation of metallacycles in other interesting transformations.

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[1] For examples of rhodium-catalyzed cyclizations of 4-alkenals to cyclopentanones, see: a) K. Sakai, J. Ide, N. Nakamura, *Tetrahedron Lett.* **1972**, 1287 – 1290 (stoichiometric $[Rh(PPh_3)_3Cl]$); K. Sakai, Y. Ishiguro, K. Funakoshi, K. Ueno, H. Suemune, *Tetrahedron Lett.* **1984**, *25*, 961 – 964; b) C. F. Lochow; R. G. Miller, *J. Am. Chem. Soc.* **1976**, *98*, 1281 – 1283; c) R. C. Larock, K. Oertle, G. F. Potter, *J. Am. Chem. Soc.* **1980**, *102*, 190 – 197; d) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 936 – 945.

[2] For mechanistic studies of rhodium-catalyzed cyclizations of 4-alkenals to cyclopentanones, see: a) R. E. Campbell, Jr., R. G. Miller, *J. Organomet. Chem.* **1980**, *186*, C27 – C31; R. E. Campbell, Jr., C. F. Lochow, K. P. Vora, R. G. Miller, *J. Am. Chem. Soc.* **1980**, *102*, 5824 – 5830; b) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 946 – 954; B. Bosnich, *Acc. Chem. Res.* **1998**, *31*, 667 – 674, and references therein.

[3] For the isolation of a *cis*-hydridopent-4-enoylrhodium(III) complex, see: D. Milstein, *J. Chem. Soc. Chem. Commun.* **1982**, 1357 – 1358.

[4] K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 11492 – 11493.

[5] For rhodium-catalyzed cyclizations of 4-alkenals, the issue of reversible formation of a five-membered metallacycle was addressed through deuterium labeling/scrambling studies (ref. [2]). Unfortunately, this approach cannot be applied to the corresponding reactions of 4-alkynals.

[6] The reaction of acylrhodium species with nucleophiles is, of course, precedented. For example, see: a) Monsanto acetic acid process (I^- as the nucleophile). Leading references: J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**, Chapt. 12.6; b) phenol as the nucleophile: M. Murakami, T. Tsuruta, Y. Ito, *Angew. Chem.* **2000**, *112*, 2600 – 2602; *Angew. Chem. Int. Ed.* **2000**, *39*, 2484 – 2485.

[7] At room temperature in THF, benzene, and CH_3CN, we observe no reaction when 4-alkynal **1** is treated with $[Rh(dppe)]_2(BF_4)_2$.

[8] Notes: a) Among the ligands that we have surveyed (e.g., dcpe, dppf, and BINAP), dppe provides the cleanest and the fastest reactions; b) with less than five equivalents of phenol, we obtain a somewhat lower yield of product. With more than five equivalents of phenol, we observe a slower reaction.

[9] Sample experimental (Table 1, entry 1): In the air, $[Rh(dppe)]_2(BF_4)_2$ (16 mg, 0.013 mmol) was placed into a Schlenk tube, which was then filled with argon. Under a positive pressure of argon, a solution of PhOH (260 mg, 2.76 mmol) and 3-methylundec-4-ynal (100 mg, 0.555 mmol) in $ClCH_2CH_2Cl$ (5 mL) was added. The vessel was closed, and the mixture was stirred at 80 °C for 40 hours. The resulting solution was concentrated and purified by column chromatography (pentane:Et_2O = 20:1), which furnished phenyl (*Z*)-3-methylundec-4-enoate (131 mg, 0.477 mmol, 86 %) as a colorless oil.

[10] For the reaction of 3-methyl-5-(1-cyclohexenyl)pentyn-4-al, we obtain a modest yield of the *cis*-4-alkenoate (38 %), because of the formation of a significant quantity of the cyclopentenone.

[11] With water as the nucleophile in acetone, we obtain a 53 % yield of the target carboxylic acid. Use of a hindered alcohol results in the formation of an acetal as well as the desired ester.

[12] In a preliminary kinetic study, we observed $k_H(CHO)/k_D(CDO) \approx 1.0$ at 80 °C.

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