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Rhodium-Catalyzed Addition of Alkynes to Activated Ketones and Aldehydes

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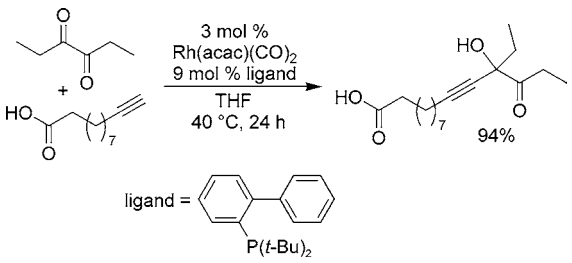
ABSTRACT



The rhodium-catalyzed addition of alkynes to 1,2-diketones, 1,2-ketoesters, and aldehydes provides a method for the synthesis of tertiary alkynyl alcohols under mild conditions. The reaction tolerates many functional groups (such as carboxylic acids) that are incompatible with other methods. The alkyne addition reaction proceeds best using bulky phosphine ligands such as 2-(di-*tert*-butylphosphino)biphenyl. This method fills a void in the more common zinc-catalyzed processes, which give poor yields with enolizable 1,2-dicarbonyl substrates.

Great strides have been made in the development of catalytic methods for the addition of alkynes to aldehydes, ketones, and imines.[1,2] Such transformations have attracted considerable interest due to the versatility of the alkyne addition products which are useful intermediates in the synthesis of complex molecules.[3] Although the development of catalytic methods for the addition of alkynes to aldehydes and ketones has received significant attention, the catalytic addition of alkynes to 1,2-dicarbonyl compounds has been explored in only a cursory fashion. Although catalytic zinc conditions are compatible with 1,2-dicarbonyls, they are limited to non-enolizable systems, with enolizable 1,2-dicarbonyls providing only low yields.[4]

Rhodium acetylides provide a useful solution to this limitation of catalytic zinc chemistry. Use of catalytic amounts of $Rh(acac)(CO)_2$ in the presence of phosphine ligands has been shown to form acetylides with nucleophilic properties.[5] These rhodium acetylides act as selective nucleophiles under mild conditions. Indeed, alkyne addition reactions catalyzed by rhodium complexes tolerate functional groups (such as unprotected alcohols and carboxylic acids) that are not tolerated by many other metal-catalyzed alkyne addition reactions.

(1) For recent reviews, see: (a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (b) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (d) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.

(2) For some selected examples, see: (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843. (d) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (e) Gao, G.; Xie, R.-G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417. (f) Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* **2005**, *70*, 1084. (g) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057. (h) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. (i) Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 1463. (j) Cozzi, P. G.; Alesi, S. *Chem. Commun.* **2004**, 2448. (k) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (l) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.−Eur. J.* **2003**, *9*, 2797. (m) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363 and references therein.

(3) (a) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274. (b) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813. (c) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun.* **2004**, 406. (d) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790.

(4) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

(5) Lerum, R. V.; Chisholm, J. D. *Tetrahedron Lett.* **2004**, *45*, 6591.

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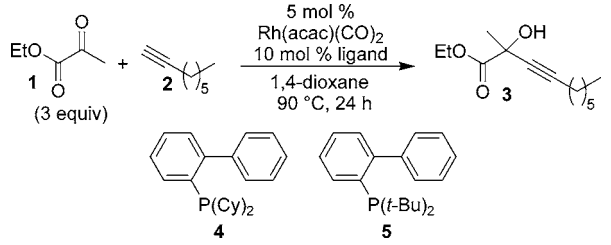
Initial attempts focused on the addition of 1-octyne to ethyl pyruvate (Table 1). Only when the phosphine was changed

Table 1. Phosphine Ligand Screen



entry	ligand	yield (%)
1	triphenylphosphine (**6**)	13
2	tris(*o*-methoxyphenyl)phosphine (**7**)	9
3	tri-*o*-tolylphosphine (**8**)	24
4	dppf[a] (**9**)	26
5	2-(dicyclohexylphosphino)biphenyl (**4**)	71
6	2-(di-*tert*-butylphosphino)biphenyl (**5**)	83
7	tri-*tert*-butylphosphine (**10**)	95

[a] Only 5 mol % of dppf was used.

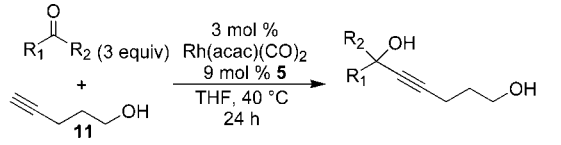
to the bulky, electron-rich 2-(di-*tert*-butylphosphino)biphenyl[6] (**5**) and tri-*tert*-butylphosphine (**10**) did the yields become excellent (Table 1, entries 6 and 7). Triaryl phosphines were much less effective ligands for this transformation (Table 1, entries 1−4). Control experiments showed that both the rhodium complex and the phosphine ligand were required for activity, precluding a phosphine-catalyzed process and implicating a rhodium−phosphine complex as the active catalyst. In support of this hypothesis, numerous literature reports describe activation of the C−H bond of monosubstituted alkynes using rhodium−phosphine complexes.[7]

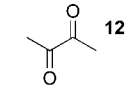
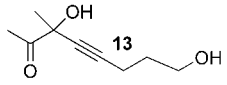
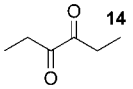
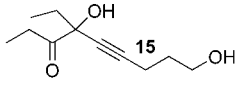
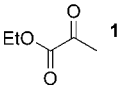
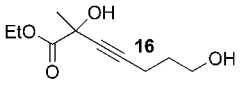
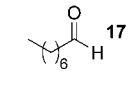
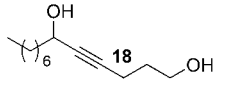
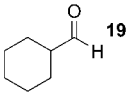
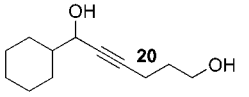
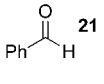
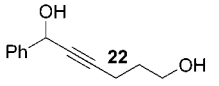
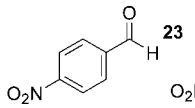
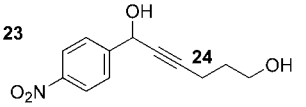
With the realization that the reaction required a bulky, electron-rich phosphine, 2-(di-*tert*-butylphosphino)biphenyl **5** was chosen as the ligand of choice. This decision was based on the ease of handling of this stable, white solid in contrast to tri-*tert*-butylphosphine (**10**), which oxidizes quickly when exposed to air.

Other parameters were then modified to determine the optimal reaction conditions. Temperatures as low as 40 °C were found to give excellent yields of the alkyne addition product. Further optimization showed that use of 3 mol % of $Rh(acac)(CO)_2$ and 9 mol % of phosphine **5** gave an optimal yield with a minimum of catalyst. Use of THF instead of 1,4-dioxane provided a small increase in yield. The ratio of alkyne to dicarbonyl was also assessed. Lowering the amount of ethyl pyruvate to two equivalents provided a 50% yield of product, whereas one equivalent gave a modest 26% yield. Increasing the amount of octyne (**2**) in relation to ethyl pyruvate (**1**) to more than one equivalent did not produce any increase in yield due to alkyne dimerization.[8]

Once reaction conditions were optimized, a survey of electrophiles was performed (Table 2).

Table 2. Variation of the Electrophile



entry	electrophile	product	yield
1			91%
2			95%
3			94%
4			68%
5			80%
6			34%
7			94%

Reaction of 2,3-butanedione (**12**), 3,4-hexanedione (**14**), and ethyl pyruvate (**1**) gave excellent yields of alkyne addition products with 4-pentyn-1-ol (**11**). Alkyl aldehydes also gave good yields of addition product, whereas aromatic aldehydes gave lower yields unless they were highly activated, as in the case of 4-nitrobenzaldehyde **23**.

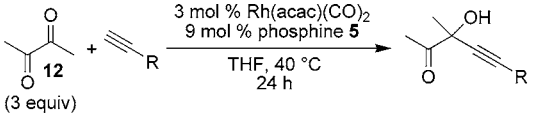
Different alkynes were also evaluated as coupling partners (Table 3). As in the case of 4-pentyn-1-ol (**11**), unprotected alcohols are well tolerated in the rhodium-catalyzed alkyne addition reaction. Aromatic alkynes such as phenylacetylene (**26**) also provide excellent yields of product. To further demonstrate the functional-group tolerance of the reaction, an alkyne containing a carboxylic acid was also used as a nucleophile providing an excellent yield of addition product (Table 3, entry 8).

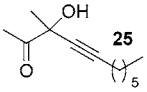
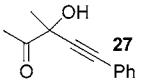
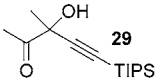
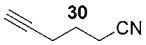
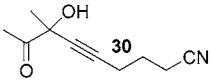
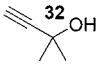
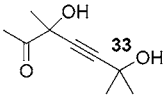
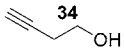
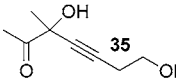
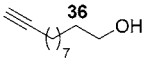
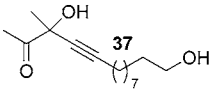
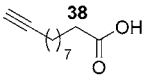
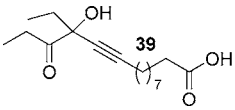
(6) (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(7) (a) Esteruelas, M. A.; Lahoz, F. J.; Onate, E.; Oro, L. A.; Rodriguez, L.; Steinert, P.; Werner, H. *Organometallics* **1996**, *15*, 3436. (b) Zargfarian, D.; Chow, P.; Taylor, N. J.; Marder, T. B. *J. Chem. Soc., Chem. Commun.* **1989**, *9*, 540. (c) Garcia Alonso, F. J.; Höhn, A.; Wolf, J.; Otto, H.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 406.

(8) (a) Singer, H.; Wilkinson, G. *J. Chem. Soc. A* **1968**, *4*, 849. (b) Yoshikawa, S.; Kiji, J.; Furukawa, J. *Makromol. Chem.* **1977**, *178*, 1077. (c) Lee, C.-C.; Lin, Y.-C.; Liu, Y.-H.; Wang, Y. *Organometallics* **2005**, *24*, 136.

Table 3. Variation of the Alkyne Nucleophile

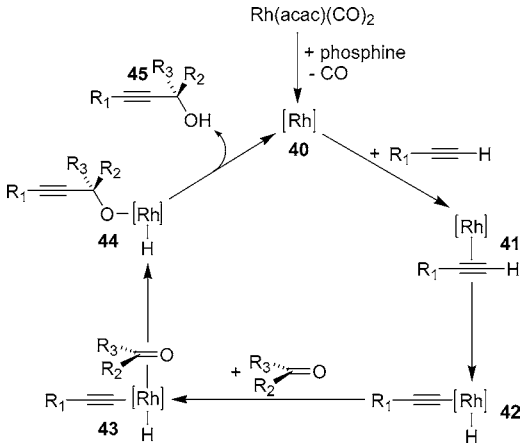


entry	alkyne	product	yield
1			83%
2			82%
3			99%
4			98%
5			63%
6			94%
7			96%
8[a,b]			94%

[a] 3,4-Hexanedione (**14**) was used instead of 2,3-butanedione (**12**). [b] One equivalent of triethylamine was added.

A proposed reaction mechanism is shown in Scheme 1. Displacement of one carbon monoxide ligand by a phosphine is well precedented[9] for $Rh(acac)(CO)_2$, and this is assumed to be the first step. Coordination of the alkyne to the newly formed Rh complex followed by insertion of the metal into the alkyne C−H bond provides rhodium acetylide **42**. Rhodium complexes similar to intermediate **42** have been isolated by Esteruelas and Werner.[7a] Coordination of the carbonyl to the alkynylrhodium **42** is followed by carbon−carbon bond formation, leading to rhodium alkoxide **44**.

Scheme 1. Proposed mechanism for the Rh-catalyzed alkyne addition



Reductive elimination then provides the propargylic alcohol product, regenerating the active catalyst.

In summary, a rhodium-catalyzed method for the addition of alkynes to aldehydes, 1,2-diketones, and 1,2-ketoesters under mild conditions has been described. The reaction tolerates the presence of a variety of functional groups including unprotected alcohols and carboxylic acids. Studies to elucidate the reaction mechanism, the development of an enantioselective variant, and the application of this reaction to the synthesis of bioactive substances are currently underway.

Acknowledgment. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund, for support of this research.

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

OL0525260

(9) (a) Serron, S.; Huang, J.; Nolan, S. P. *Organometallics* **1998**, *17*, 534. (b) Pruchnik, F. P.; Smolenski, P.; Wajda-Hermanowicz, K. *J. Organomet. Chem.* **1998**, *570*, 63.