JOC*Article*

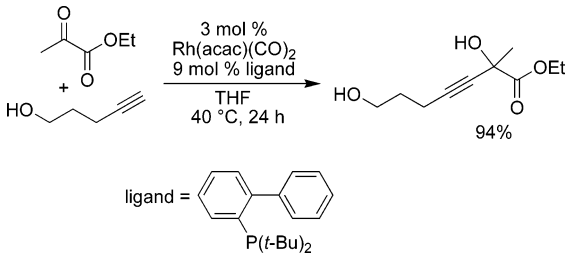
Addition of Alkynes to Aldehydes and Activated Ketones Catalyzed by Rhodium−Phosphine Complexes

Pawan K. Dhondi, Patrick Carberry, Lydia B. Choi, and John D. Chisholm*

Department of Chemistry, 1-014 Center for Science and Technology, Syracuse University, Syracuse, New York 13244

jdchisho@syr.edu

Received July 26, 2007



A mixture of 2-(di-*tert*-butylphosphino)biphenyl and dicarbonylacetonato rhodium(I) provides an effective catalyst system for the addition of alkynes to aldehydes and activated ketones. In contrast to the more common zinc-catalyzed processes, enolizable 1,2-dicarbonyls are excellent substrates for these rhodium-catalyzed additions. This reaction allows for the formation of propargylic alcohols under mild conditions, tolerating many functional groups (such as carboxylic acids) that are incompatible with other methods. Little selectivity was observed in cases of unsymmetrical 1,2-diketones. Addition of alkynes to aldehydes with an adjacent chirality center usually provides the Felkin addition product with excellent selectivity in some cases. Studies on the catalyst structure show that both the β-diketonate and a carbon monoxide ligand appear to be bound to the active catalyst. The use of chiral phosphines to induce asymmetry in the propargyl alcohol products provided low enantioselectivity, which may be due to the phosphine having a distal relationship to the reacting centers. Modification of other ligands, such as the β-diketonate, appears to be a more promising avenue for the development of an enantioselective variant.

Introduction

The area of catalytic nucleophilic addition reactions of alkynes has seen significant development in the past decade, with these results being summarized in several excellent reviews.[1−4] Transition metal catalyzed additions of alkynes to aldehydes,[5−21] ketones,[14,22−27] imines,[28−39] and α,β-unsaturated ketones[40−45] have been the subject of numerous studies from many investigators. Several investigators have also published case studies in which several of these different methods were compared and evaluated.[46,47] These developments have focused primarily on

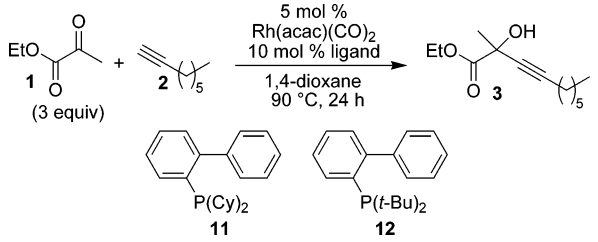
(1) Pu, L. *Tetrahedron* **2003**, *59*, 9873.
(2) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373.
(3) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095.
(4) Garcia, C.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849.
(5) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806.
(6) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(7) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143.
(8) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555.
(9) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122.
(10) Rajaram, A. R.; Pu, L. *Org. Lett.* **2006**, *8*, 2019.
(11) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.
(12) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.
(13) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948.
(14) Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P.-O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733.
(15) Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W.-J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747.
(16) Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron: Assymmetry* **2004**, *15*, 3155.
(17) Kang, Y.-F.; Wang, R.; Liu, L.; Da, C.-S.; Yan, W.-J.; Xu, Z.-Q. *Tetrahedron Lett.* **2005**, *46*, 863.
(18) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323.
(19) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524.
(20) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8.

10.1021/jo701643h CCC: $37.00
Published on Web 11/14/2007

alkynes because they require no prior modification for use in these nucleophilic additions, as the acidic alkyne C−H bond readily undergoes activation in the presence of catalytic amounts of transition metals. Since no activating group is required, these processes are inherently environmentally friendly and show excellent atom economy.[48] Addition reactions of alkynes both create a new carbon−carbon bond and establish a new stereocenter in a single operation. In many cases both high yields and enantioselectivity can be realized from these transformations under catalytic conditions. 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 such as pharmaceuticals and natural products.[49−53]

While 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 a more cursory fashion. Catalytic zinc conditions are compatible with 1,2-dicarbonyls, but they are limited to nonenolizable systems,[54] with enolizable 1,2-dicarbonyls providing very low yields. The high Lewis acidity of the zinc reagents promotes enolization of the reactive ketones, resulting in intermolecular Aldol reactions that limit the effectiveness of zinc catalysts in these cases.

TABLE 1. Phosphine Ligand Screen



entry	ligand	yield (%)
1	none	0
2	triphenylphosphine (**4**)	13
3	tris(pentafluorophenyl)phosphine (**5**)	trace
4	tris(2-methoxyphenyl)phosphine (**6**)	9
5	tris(2-methylphenyl)phosphine (**7**)	24
6	dppf[a] (**8**)	26
7	dppb[a] (**9**)	11
8	tri-*n*-butylphosphine (**10**)	12
9	2-(dicyclohexylphosphino)biphenyl (**11**)	71
10	2-(di-*tert*-butylphosphino)biphenyl (**12**)	83
11	tri-*tert*-butylphosphine (**13**)	95

[a] Only 5 mol % of the phosphine was used.

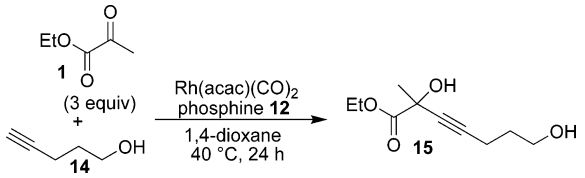
One solution to this limitation of catalytic zinc chemistry was the use of other transition metals to activate the alkyne under more neutral conditions. Recently our group has reported that the use of catalytic amounts of $Rh(acac)(CO)_2$ in the presence of phosphine ligands leads to acetylides with nucleophilic properties.[43,55] These rhodium acetylides act as selective nucleophiles under mild, neutral conditions. Alkyne addition reactions catalyzed by rhodium complexes tolerate functional groups (such as unprotected alcohols and carboxylic acids) that are not compatible with many other metal catalyzed alkyne addition reactions. Additional studies reported herein on these rhodium-catalyzed reactions include the results of alkyne additions to unsymmetrical 1,2-diketones, diastereoselective additions to chiral aldehydes, the exploration of chiral phosphines as ligands as well as a more complete account of optimization studies and studies on functional group tolerance.

Results and Discussion

Initial attempts at alkyne addition with rhodium catalysis focused on the addition of 1-octyne to ethyl pyruvate as a test reaction (Table 1). Use of $Rh(acac)(CO)_2$ as a precatalyst and triphenylphosphine **4** as a ligand produced trace amounts of 1,2-addition products (Table 1, entry 2). Only when the phosphine was changed to the bulky, electron-rich 2-(di-*tert*-butylphosphino)biphenyl (**12**)[56,57] and tri-*tert*-butylphosphine (**13**) did the yields become noteworthy (Table 1, entries 10 and 11). More highly functionalized triaryl phosphines were much less effective ligands for this transformation (Table 1, entries 2−5). Bidentate phosphines were also poor ligands for the addition reaction (Table 1, entries 6 and 7). Control experiments showed that both the phosphine ligand (Table 1, entry 1) and the rhodium complex were required for the reaction to proceed. These experiments implicate a rhodium−phosphine complex as the active catalyst. The formation of rhodium acetylides with

(21) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525.
(22) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895.
(23) Cozzi, P. G.; Alesi, S. *Chem. Commun.* **2004**, 2448.
(24) Liu, L.; Kang, Y.-F.; Wang, R.; Zhou, Y.-F.; Chen, C.; Ni, M.; Gong, M.-Z. *Tetrahedron*: *Assymmetry* **2004**, *15*, 3757.
(25) 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.
(26) Wang, Q.; Zhang, B.; Hu, G.; Chen, C.; Zhao, Q.; Wang, R. *Org. Biomol. Chem.* **2007**, *5*, 1161.
(27) Liu, L.; Wang, R.; Kang, Y.-F.; Cai, H.-Q.; Chen, C. *Synlett* **2006**, 1245.
(28) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497.
(29) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054.
(30) Fischer, C.; Carreira, E. M. *Synthesis* **2004**, 1497.
(31) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473.
(32) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.
(33) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731.
(34) Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 1558.
(35) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.
(36) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535.
(37) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797.
(38) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.
(39) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767.
(40) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682.
(41) Knöpfel, T. F.; Boyall, D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2281.
(42) Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089.
(43) Lerum, R. V.; Chisholm, J. D. *Tetrahedron Lett.* **2004**, *45*, 6591.
(44) Chen, L.; Li, C.-J. *Chem. Commun.* **2004**, 2362.
(45) Nishimura, T.; Washitake, Y.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2004**, 1312.
(46) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197.
(47) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219.
(48) Trost, B. M. *Science* **1991**, *254*, 1471.
(49) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. *Org. Lett.* **2007**, *9*, 1895.
(50) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274.
(51) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.
(52) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun.* **2004**, 406.
(53) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790.
(54) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.
(55) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67.
(56) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.
(57) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

TABLE 2. Variation of Phosphine−Transition Metal Ratio



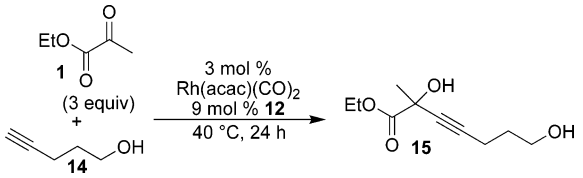
entry	mol % of $Rh(acac)(CO)_2$	mol % of phosphine **12**	yield (%)
1	5	10	80
2	3	6	84
3	3	3	59
4	3	9	90
5	3	12	86
6	3	15	90
7	1	3	22
8	1	5	52

rhodium−phosphine complexes has been observed several times in the organometallic literature,[58−60] supporting the hypothesis of a rhodium−phosphine complex as the active catalyst.

Further optimization of the reaction conditions was performed with 2-(di-*tert*-butylphosphino)biphenyl **12** instead of tri-*tert*-butylphosphine **13**. Due to its propensity to undergo oxidation, tri-*tert*-butylphosphine can be difficult to handle and store over long periods, whereas phosphine **12** is much more stable and less prone to oxidation, being a white solid instead of a liquid. A number of rhodium sources were also examined for their ability to function as precatalysts in the reaction. While $Rh(acac)(CO)_2$ provided an active catalyst, use of other rhodium(I) complexes (including $Rh(acac)(C_2H_4)_2$, $[RhCl(COD)]_2$, and $[RhCl(CO)_2]_2$) did not provide any alkyne addition products. Evidently both the carbon monoxide and the β-diketonate ligand are required for catalytic activity. The ratio of alkyne to electrophile was also evaluated. Using only 2 equiv of ethyl pyruvate resulted in a 50% yield, while use of only 1 equiv gave a 26% yield of propargyl alcohol **3**. The alkyne addition appears to require a high concentration of electrophile for high yields. Decomposition of the alkyne was minimal, as significant amounts of unreacted alkyne were recovered from these reactions.

A number of other reaction parameters were varied during the optimization of the reaction by using 4-pentyn-1-ol and ethyl pyruvate as the test substrates. The reaction was found to proceed to completion in 24 h at temperatures as low as 40 °C with no reduction in yield. The reaction proceeded at room temperature but after 24 h the yield was only 29%. Allowing the reaction to proceed for 48 h increased the yield to 57%, indicating that the catalyst was viable for extended periods at room temperature but the addition reaction was sluggish. Variation of the ratio of phosphine to transition metal indicated that 3 equiv of phosphine ligand to rhodium precatalyst provided the best yield of alkyne addition product (Table 2, entry 4). Catalyst loadings of 3 mol % were easily tolerated, but the use of 1 mol % led to a significant decrease in the yield of the reaction. Increasing the amount of phosphine ligand at 3 mol % rhodium catalyst loading did not further increase the yield of the reaction. Adding more phosphine at a 1 mol % catalyst loading did lead to a significant increase in yield (Table 2, entry 8), indicating that adventitious oxidation of the phosphine may limit the lifetime of the catalyst at very low catalyst loadings.

TABLE 3. Variation of Solvent



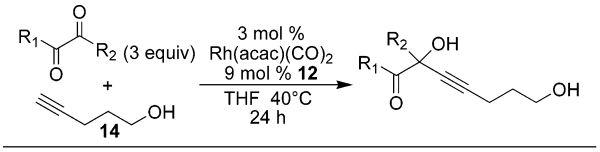
entry	solvent	yield (%)
1	1,4-dioxane	90
2	THF	94
3	1,2-DME	62
4	benzene	75
5	toluene	76
6	1,2-DCE	36
7	DMF	60
8	DMSO	0
9	MeOH	trace
10	EtOH	27
11	10% H_2O/1,4-dioxane	49
12	*i*-PrOH	74

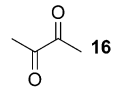
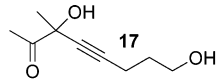
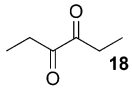
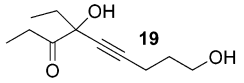
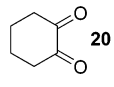
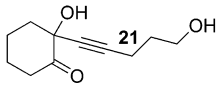
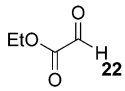
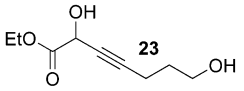
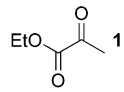
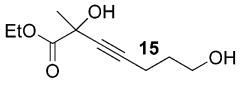
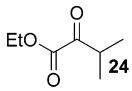
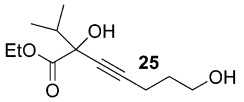
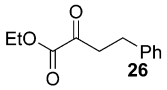
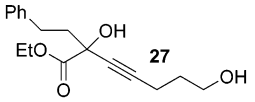
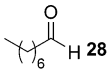
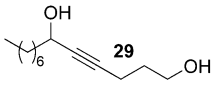
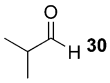
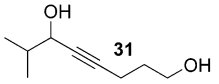
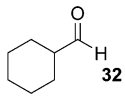
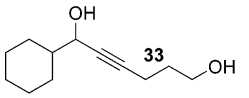
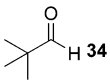
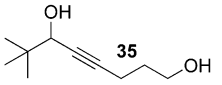
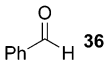
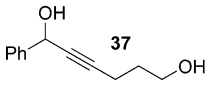
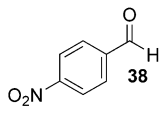
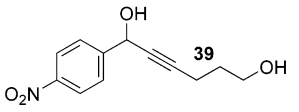
The reaction was also evaluated with respect to concentration and solvent. Concentrations between 0.6 and 1.0 M were found to be optimal. A variety of solvents were evaluated in the alkyne addition reaction (Table 3). Ethereal solvents consistently gave excellent yields with THF providing the highest yield of 94% (Table 3, entry 2). Benzene and toluene also gave reasonable yields. Halogenated solvents, such as 1,2-dichloroethane, gave much lower yields. While DMSO was completely incompatible with the reaction (this may be due to its ability to compete as a ligand for the transition metal, or due to oxidation as DMSO has been shown to oxidize some transition metal complexes[61]) other polar aprotic solvents like DMF performed adequately. Polar protic solvents, like methanol and ethanol, proved detrimental to the reaction, as did the addition of significant amounts of water (Table 3, entries 9−11). As the stability of rhodium acetylides in polar protic solvents like water has been well documented,[62] this may indicate a lack of solubility of the rhodium−phosphine complex in polar protic media, as the phosphine ligand is quite hydrophobic. Isopropanol proved to be an adequate solvent as well, supporting the hypothesis that the lower yields are due to poor catalyst solubility (Table 3, entry 12).

With the experimental conditions optimized, the scope of the reaction with regard to electrophile was explored (Table 4). Acyclic 1,2-diketones like 2,3-butanedione (**16**) and 3,4-hexanedione (**18**) proved to be excellent substrates for the addition reaction. Cyclic 1,2-diketones like 1,2-cyclohexanedione (**20**) were not good substrates for the addition reaction (Table 4, entry 3). Inspection of the ^1H NMR of 1,2-cyclohexanedione showed that one of the ketones was completely enolic, unlike acyclic 1,2-diketones. This imparts significantly lower reactivity in comparison to acyclic 1,2-diketones. 1,2-Ketoesters like ethyl pyruvate (**1**) are also reactive

(58) Esteruelas, M. A.; Lahoz, F. J.; Onate, E.; Oro, L. A.; Rodriguez, L.; Steinert, P.; Werner, H. *Organometallics* **1996**, *15*, 3436.
(59) Zargfarian, D.; Chow, P.; Taylor, N. J.; Marder, T. B. *J. Chem. Soc., Chem. Commun.* **1989**, *9*, 540.
(60) Garcia Alonso, F. J.; Höhn, A.; Wolf, J.; Otto, H.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *97*, 406.
(61) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411.
(62) Marder, T. B.; Zargarian, D.; Calabrese, J. C.; Herskovitz, T. H.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1484.

TABLE 4. Addition of 4-Pentyn-1-ol to Aldehydes, 1,2-Diketones, and 1,2-Ketoesters

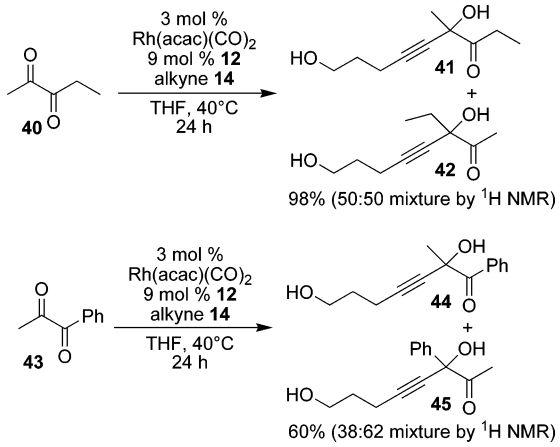


entry	electrophile	product	yield
1			91%
2			95%
3			0%
4			55%[a]
5			94%
6			43%[a]
7			61%
8			68%
9			67%
10			80%
11			6%
12			34%
13			94%

[a] The reaction was performed at 60 °C.

in the rhodium-catalyzed 1,2-addition. Increasing the size of the alkane next to the ketone did result in lower yields, however (Table 4, entries 6 and 7). Aldehydes were also investigated as substrates for the addition reaction. Aromatic aldehydes like benzaldehyde (**36**) provided only poor yields of addition product (Table 4, entry 12) unless the aromatic group was quite electron poor, as in the case of 4-nitrobenzaldehyde **38**, which gave a

SCHEME 1



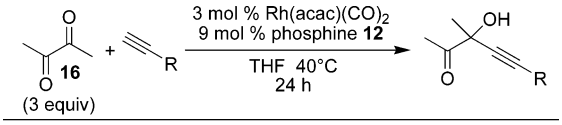
94% yield (Table 4, entry 13). More reactive alkyl aldehydes provided good yields of the propargylic alcohol product except for pivaldehyde **34**, which was too sterically hindered and gave only a 6% yield of addition product (Table 4, entry 11).

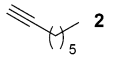
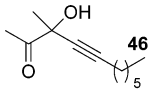
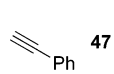
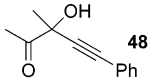
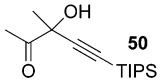
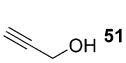
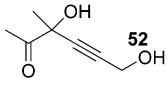
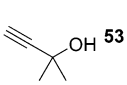
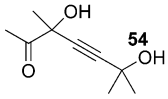
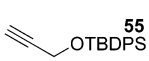
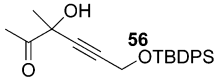
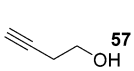
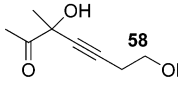
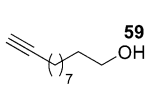
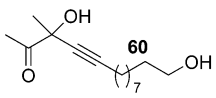
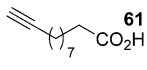
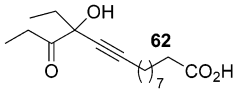
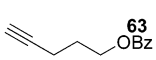
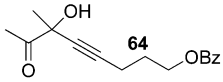
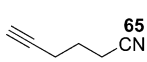
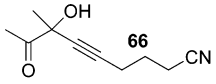
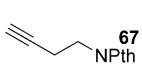
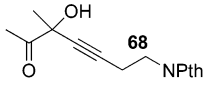
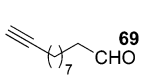
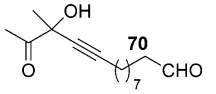
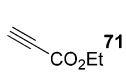
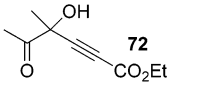
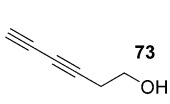
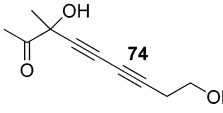
Additions were also performed on differentially substituted 1,2-diketones to evaluate the selectivity of the process. Addition to 2,3-pentanedione **40** gave a 50:50 mixture of ketone regioisomers (Scheme 1). Addition to 1-phenyl-1,2-propanedione **43** gave a 62:38 mixture of ketone regioisomers favoring addition of the alkyne to the ketone next to the phenyl ring. This result is, in hindsight, not surprising, as the internal ketone cannot enolize and is flanked by two electron-withdrawing groups, which increases its electrophilicity.

Different alkynes were also evaluated as nucleophiles in the addition reaction (Table 5). Simple alkyl alkynes like 1-octyne (**2**) performed well, as did aryl alkynes and silyl protected alkynes (Table 5, entries 1−3). The presence of a propargylic alcohol was somewhat problematic with propargyl alcohol itself providing only an 8% yield of product (Table 5, entry 4). Protection of the alcohol as a silyl ether greatly improved the yield, as did the use of a more hindered propargyl alcohol like 2,2-dimethylpropargyl alcohol **53** (Table 5, entries 5 and 6). Moving the hydroxyl group further from the propargylic position provided much higher yields of product (Table 5, entries 7 and 8). The reaction otherwise showed a remarkable tolerance to functional groups present on the alkyne. Esters, nitriles, carboxylic acids, and imides were all well tolerated and provided excellent yields of alkyne addition product. In the case of 10-undecynoic acid **61**, the addition product with 2,3-butanedione was difficult to separate from the starting material, leading to lower yields due to repeated chromatography. However, the use of 3,4-hexanedione (**18**) provided **62** in 94% yield. One equivalent of triethylamine (with respect to the carboxylic acid) was also added to the reaction when an unprotected carboxylic acid was used to keep the conditions neutral. Use of an alkyne bearing an aldehyde was also explored, and this provided a 59% yield of product (Table 5, entry 13). Addition of diyne **73** and ethyl propiolate **71** to 2,3-butanedione was also evaluated. Diynes[47,51] and ethyl propiolate[10,20,21,63,64] can be problematic substrates in zinc-catalyzed systems, requiring specific reaction conditions to mediate the addition reactions. The rhodium-catalyzed conditions did not prove to be useful for these systems

(63) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122.
(64) Meta, C. T.; Koide, K. *Org. Lett.* **2004**, *6*, 1785.

TABLE 5. Addition of Alkynes to 2,3-Butanedione



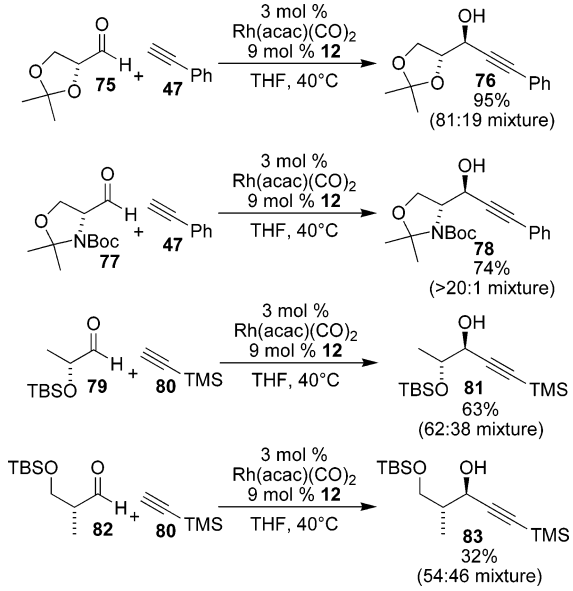
entry	alkyne	product	yield
1	 **2**	 **46**	83%
2	 **47**	 **48**	82%
3	 **49**	 **50**	99%
4	 **51**	 **52**	8%
5	 **53**	 **54**	63%
6	 **55**	 **56**	51%
7	 **57**	 **58**	94%
8	 **59**	 **60**	96%
9	 **61**	 **62**	94%[a,b]
10	 **63**	 **64**	86%
11	 **65**	 **66**	98%
12	 **67**	 **68**	60%
13	 **69**	 **70**	59%
14	 **71**	 **72**	0%
15	 **73**	 **74**	8%

[a] 3,4-Hexanedione was used instead of 2,3-butanedione. [b] One equivalent of Et_3N was added.

(Table 5, entries 14 and 15), as conversions were poor and the reaction mixtures were complicated by numerous side products.

A number of chiral aldehyde substrates was also evaluated to determine the degree of diastereoselectivity in cases where

SCHEME 2

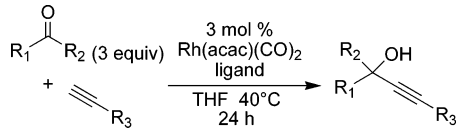


the aldehydes have a chirality center next to the carbonyl (Scheme 2). Addition of phenylacetylene to glyceraldehyde acetonide **75** gave a 81:19 mixture of diastereomers favoring the shown diastereomer **76** (Scheme 2, in all cases the major isomer is shown). The stereochemistry of the major product was confirmed by Mosher's acid analysis[65] after separation of the diastereomers by HPLC (see the Supporting Information for details). This ratio is significantly higher than when the same addition was performed with the lithium acetylide at −78 °C,[66] perhaps due to the larger size of the rhodium complex. Addition of phenylacetylene to Garner's aldehyde **77** was even more selective, providing a single addition product **78**. The selectivity of these additions proved to be highly dependent on the chiral aldehyde used as a coupling partner, as use of the protected lactate **79** gave only a 62:38 mixture of diastereomers and aldehyde **82** provided only a 54:46 mixture. Additionally, without a nearby electronegative atom to activate the aldehyde, the yield of the addition reaction decreased to only 32%, as in the case of aldehyde **82**. The selectivity of these additions can be rationalized by using the Felkin−Anh model[67,68] for asymmetric induction except for aldehyde **82**, where the selectivity is quite poor.

Attempts were made to render the rhodium-catalyzed alkyne addition process enantioselective through the use of an enantiomerically pure chiral phosphine ligand. With few bulky electron-rich derivatives of chiral phosphines readily available, a number of chiral triaryl phosphines were screened for enantioselectivity, with the synthesis of a dialkyl analogue to be pursued in the event good enantioselectivity was obtained (Table 6, see the Supporting Information for a complete list). Only some of these reactions gave enough product for analysis and none gave high asymmetric induction (Table 6, entries 1−3). After an evaluation of 2,3-butanedione **16** as an electrophile, there was concern that the poor enantioselectivity was related to an inability to differentiate the methyl and methyl ketone

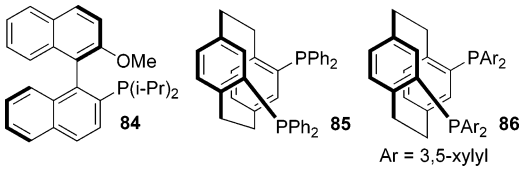
(65) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(66) Kang, S. H.; Kim, W. J. *Tetrahedron Lett.* **1989**, *30*, 5915.
(67) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(68) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 4199.

TABLE 6. Use of Chiral Phosphines



entry	electrophile	alkyne	ligand[a]	yield (%)	ee (%)
1	**16**	**63**	**84** (6 mol %)	69	1
2	**16**	**63**	**85** (4.5 mol %)	13	12
3	**16**	**63**	**86** (4.5 mol %)	5	20
4	**38**	**14**	**85** (4.5 mol %)	17	27
5	**38**	**14**	**86** (4.5 mol %)	10	25

[a] Ligand structures.



groups on either side of the reactive ketone. Additional experiments were therefore performed with 4-nitrobenzaldehyde **38**, where differentiation of the enantiotopic faces should be less problematic. While the enantioselectivity improved with use of this substrate, they were still far from useful.

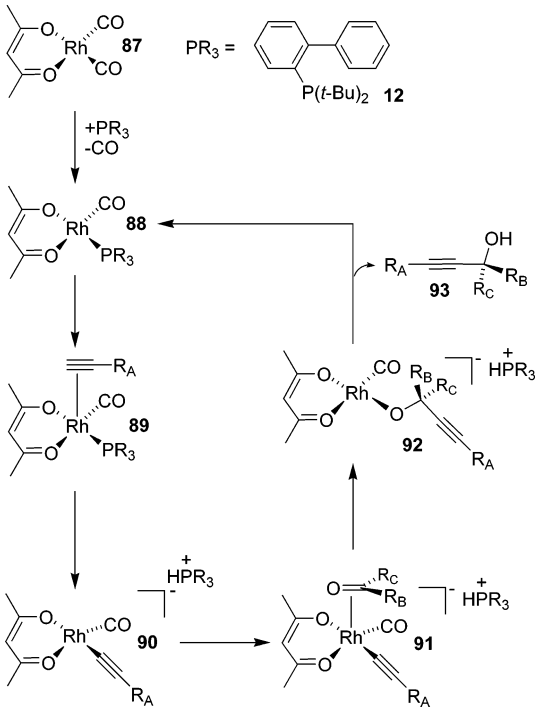


FIGURE 1. Mechanistic hypothesis for the alkyne addition reaction.

The poor enantioselectivity resulting from the use of chiral phosphines prompted further investigation into the mechanism of the reaction (Figure 1). Displacement of one carbon monoxide ligand from Rh(acac)$(CO)_2$ by a phosphine is the first step in the reaction mechanism, forming the rhodium−phosphine complex **88**. This step is a well-precedented reaction of this rhodium complex in the presence of phosphine ligands.[69,70]

Formation of complex **88** was verified by mixing Rh(acac)$(CO)_2$ and phosphine **12** together in benzene-d_6 and observing the reaction with ^{31}P NMR and IR. The ^{31}P NMR spectra of the reaction showed two signals: one for unbound phosphine (a singlet at 19.4 ppm) and one for complex **88** (a doublet at 79.9 ppm). Multiplicity was observed because ^{103}Rh (the single naturally occurring isotope of rhodium) is NMR active with a spin of $^1/_2$, the coupling constant (J_{Rh-P} = 182 Hz) being consistent with other rhodium−phosphine complexes.[70] The IR spectra of the reaction showed the disappearance of the carbonyl peaks for complex **87** (two absorbances at 2082 cm^{-1} and 2011 cm^{-1}) and the appearance of a new signal at 1957 cm^{-1}, also consistent with **88**.[70] Infrared absorbances at 1590 cm^{-1} and 1523 cm^{-1} showed the β-diketonate ligand was still bound to the rhodium.

After formation of the rhodium−phosphine complex, the alkyne coordinates leading to complex **89**. Evidence for this coordination was obtained from the ^{1}H NMR of phenylacetylene taken in the presence of Rh(acac)$(CO)_2$ and phosphine **12**. The ^{1}H NMR of phenylacetylene typically shows a peak at 2.72 ppm for the alkyne C−H proton in benzene-d_6. This proton shifts downfield to 2.96 ppm in the presence of rhodium complex **88**. The chemical shift change is indicative of a reversible binding of the alkyne to the transition metal complex.[2,71] Alkyne complex **89** was the last complex that can be observed spectroscopically, as addition of an electrophilic carbonyl leads directly to product formation without any intermediates being observed by NMR. The lifetime of these intermediates may be too short or the amount generated under the catalytic conditions may be too small to be observed with NMR.

Coordination of the alkyne to the rhodium complex results in the alkyne C−H becoming much more acidic.[72] The excess phosphine in the reaction can then act as a base, removing the proton from the alkyne to form a rhodium(I) acetylide such as **90**. Deprotonation likely occurs from an equivalent of free phosphine, followed by dissociation of the phosphine bound to the rhodium (3 equiv of phosphine with respect to the rhodium are present). Coordination of the electrophile to the rhodium complex can then lead to a complex such as **91**, in which the carbonyl is activated by coordination to the rhodium center. The distal relationship between the phosphine and the electrophile provides an explanation as to why such low enantioselectivities are observed with chiral phosphines. The low enantioselectivities can be rationalized by interactions with the chiral counterion, which can enforce some stereocontrol.[73] Bond formation between the acetylide and the carbonyl leads to rhodium alkoxide **92**, which is then protonated by the phosphonium salt to provide propargylic alcohol product **93** and regenerate the resting state of the catalyst, complex **88**. Given the difficulties associated with engineering a phosphine that can control the enantioselectivity of the alkyne addition, we have changed our focus to modifying the β-diketonate ligand, which may be more fruitful.

(69) Serron, S.; Huang, J.; Nolan, S. P. *Organometallics* **1998**, *17*, 534.

(70) Pruchnik, F. P.; Smolenski, P.; Wajda-Hermanowicz, K. *J. Organomet. Chem.* **1998**, *570*, 63.

(71) De Koning, A. J.; Van Rijn, P. E.; Boersma, J.; Van der Kerk, G. J. M. *J. Organomet. Chem.* **1979**, *174*, 129.

(72) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. In *Advanced Inorganic Chemistry*; Wiley: New York, 1999; p 681.

(73) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

Conclusions

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. Additions to α-chiral aldehydes usually provide the Felkin product in moderate to high selectivity depending on the substrate. Further studies to elucidate the reaction mechanism, the development of an enantioselective variant, and application of this reaction to the synthesis of bioactive substances are currently underway.

Experimental Section

2-Hydroxy-2-methyl-dec-3-ynoic Acid Ethyl Ester (3). A solution of octyne (**2**) (45 mg, 0.4 mmol) and ethyl pyruvate **1** (142 mg, 1.2 mmol) in 0.5 mL of 1,4-dioxane was added to a mixture of $Rh(acac)(CO)_2$ (5.2 mg, 0.02 mmol, 5 mol %) and 2-(di-*tert*-butylphosphino)biphenyl **12** (12 mg, 0.04 mmol, 10 mol %) under argon. The reaction was then heated to 90 °C. After 24 h at 90 °C the reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, preadsorbed on silica gel, and purified by silica gel chromatography (80%CH_2Cl_2/hexane-0.7%acetone/CH_2Cl_2) providing 75 mg of **3** (83% yield) as a thick oil. TLC R_f 0.23 (0.7% acetone/CH_2Cl_2). IR (neat) 3502, 2934, 2860, 2250, 1739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, $J = 7.1$ Hz, 2H), 3.42 (s 1H), 2.18 (t, $J = 7.0$ Hz, 2H), 1.64 (s, 3H), 1.53−1.42 (m, 2H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.40−1.19 (m, 2H), 0.87 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 85.2, 80.0, 68.1, 62.9, 31.5, 28.6, 28.5, 27.5, 22.7, 18.8, 14.2. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.67; H, 9.74.

2,7-Dihydroxy-2-methyl-hept-3-ynoic Acid Ethyl Ester (15). A solution of 4-pentyn-1-ol (**14**) (34 mg, 0.4 mmol) and ethyl pyruvate (**1**) (142 mg, 1.2 mmol) in 0.5 mL of THF was added to a mixture of $Rh(acac)(CO)_2$ (3.1 mg, 0.012 mmol, 3 mol %) and 2-(di-*tert*-butylphosphino)biphenyl **12** (11 mg, 0.036 mmol, 9 mol %) under argon. The reaction mixture was then warmed to 40 °C. After 24 h at 40 °C the mixture was allowed to cool to room temperature, diluted with CH_2Cl_2, preadsorbed on silica gel, and purified by silica gel chromatography (30−50% ethyl acetate/CH_2Cl_2) providing 75 mg of propargyl alcohol **15** (94% yield). TLC R_f 0.39 (50% ethyl acetate/CH_2Cl_2). IR (neat) 3449, 2985, 2940, 2248, 1741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, $J = 7.1$ Hz, 2H), 3.59 (t, $J = 6.2$ Hz, 2H), 2.21 (t, $J = 7.0$ Hz, 2H), 1.63 (p, $J = 6.6$ Hz, 2H), 1.53 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H) (the protons for both alcohols had exchanged with deuterium in the spectra for this compound, and are therefore not reported). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 84.2, 80.3, 67.9, 62.5, 60.9, 30.8, 37.4, 15.1, 13.9. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.22; H, 8.11.

3,8-Dihydroxy-3-methyl-oct-4-yn-2-one (17). A solution of 2,3-butanedione (**16**) (104.4 mg, 1.2 mmol) and 4-pentyn-1-ol (**14**) (34.7 mg, 0.4 mmol) in 0.5 mL of THF was added to a mixture of $Rh(acac)(CO)_2$ (0.012 mmol, 3.1 mg, 3 mol %) and 2-(di-*tert*-butylphosphino)biphenyl **12** (0.036 mmol, 10.9 mg, 9 mol %) under an argon atmosphere. The reaction tube was then placed in a preheated oil bath at 40 °C and stirred for 24 h. The reaction mixture was then preadsorbed on silica gel and purified by silica gel chromatography (30−50% ethyl acetate/CH_2Cl_2). This sequence provided propargyl alcohol **13** (62 mg) in 91% yield. TLC R_f 0.31 (50% ethyl acetate/CH_2Cl_2). IR (neat) 3415, 2936, 2243, 1723 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.16 (s, 1H), 3.69 (t, $J = 6.1$ Hz, 2H), 2.36 (s, 3H), 2.33 (t, $J = 7.0$ Hz, 2H), 2.08 (s, 1H), 1.73 (p, $J = 6.6$ Hz, 2H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 85.5, 79.6, 72.2, 60.3, 30.5, 26.4, 23.0, 14.7. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.51; H, 8.22.

1-(4-Nitrophenyl)hex-2-yne-1,6-diol (39). A solution of 4-pentyn-1-ol (**14**) (34.7 mg, 0.4 mmol) in 0.5 mL of THF was added to a mixture of 4-nitrobenzaldehyde **38** (222 mg, 1.2 mmol), $Rh(acac)(CO)_2$ (0.012 mmol, 3.1 mg, 3 mol %), and 2-(di-*tert*-butylphosphino)biphenyl **12** (0.036 mmol, 10.9 mg, 9 mol %) under an argon atmosphere. The reaction tube was then placed in a preheated oil bath at 40 °C and stirred for 24 h. The reaction mixture was then preadsorbed on silica gel and purified by silica gel chromatography (6−18% acetone/CH_2Cl_2). This sequence provided propargyl alcohol **39** (88 mg) in 94% yield. Mp 53.5−54.5 °C ($CHCl_3$); TLC R_f 0.32 (50% ethyl acetate/CH_2Cl_2). IR (neat) 3347, 2949, 2227, 1606, 1519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, $J = 8.7$ Hz, 2H), 7.70 (d, $J = 8.9$ Hz, 2H), 5.53 (s, 1H), 3.75 (t, $J = 6.1$ Hz, 2H), 2.95 (s, 1H), 2.40 (dt, $J = 7.0$, 2.1 Hz, 2H), 1.78 (p, $J = 6.5$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.7, 127.5, 123.8, 87.7, 79.9, 63.6, 61.5, 30.9, 15.5. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.22; H, 5.72; N, 6.11.

12-Ethyl-12-hydroxy-13-oxo-pentadec-10-ynoic Acid (62). A solution of triethylamine (81 mg, 0.8 mmol) in 0.5 mL of THF, followed by a solution of 3,4-hexanedione (**18**) (288.4 mg, 2.4 mmol, in 0.5 mL of THF) was added to a mixture of 10-undecynoic acid (**61**) (153.5 mg, 0.8 mmol), $Rh(acac)(CO)_2$ (6.3 mg, 0.024 mmol, 3 mol %), and 2-(di-*tert*-butylphosphino)biphenyl **12** (21.7 mg, 0.072 mmol, 9 mol %) under an argon atmosphere. The reaction was then warmed to 40 °C. The reaction was quenched after 24 h by the addition of 0.5 mL of glacial acetic acid. The reaction mixture was then preadsorbed on silica gel and purified by silica gel chromatography (5% acetone/CH_2Cl_2) providing alcohol **51** (224 mg) in 94% yield. TLC R_f 0.20 (4% acetone/CH_2Cl_2). IR (neat) 3438, 2936, 2857, 2234, 1716, 1646 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (dq, $J = 18.0$, 7.3 Hz, 1H), 2.48 (dq, $J = 18.0$, 7.3 Hz, 1H), 2.25 (t, $J = 7.4$ Hz, 2H), 2.13 (t, $J = 7.0$ Hz, 2H), 1.87 (sextet, $J = 7.3$ Hz, 1H), 1.67 (sextet, $J = 7.0$ Hz, 1H), 1.56−1.49 (m, 2H), 1.46−1.37 (m, 2H), 1.22 (m, 8H), 1.05 (t, $J = 7.3$ Hz, 3H), 0.85 (t, $J = 7.4$ Hz, 3H) (the protons for the alcohol and the carboxylic acid had exchanged with deuterium in the spectra for this compound, and are therefore not reported). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 179.7, 86.8, 79.0, 76.0, 34.0, 33.2, 29.1, 29.0, 28.9, 28.8, 28.7, 28.3, 24.6, 18.6, 8.1, 7.8. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.77; H 9.46.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Syracuse University for partial support of this research. L.B.C. thanks Pfizer for funding during the summer of 2005.

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.

JO701643H