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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8743–8746

Ligand effects in the rhodium-catalyzed addition of alkynes to aldehydes and diketones. Modification of the β-diketonate ligand

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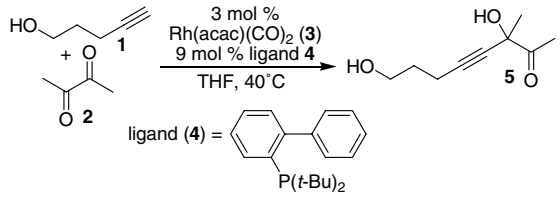
Received 7 August 2007; revised 1 October 2007; accepted 2 October 2007
Available online 6 October 2007

Abstract—A catalytic amount of dicarbonylacetonato rhodium(I) and a phosphine ligand bearing bulky electron-donating alkyl groups has been shown to generate an effective catalyst for the addition of alkynes to aldehydes and activated ketones under mild, neutral conditions. While previous studies have shown that modification of the phosphine has significant effects on the activity of the catalyst, the role of the β-diketonate ligand has not been probed. Six different β-diketonate rhodium complexes were synthesized and their ability to catalyze the alkyne addition reaction was evaluated. Changing the structure of the β-diketonate ligand can have a noticeable effect on the reaction rate. Acetylacetonate derivatives with strong electron withdrawing groups have a detrimental effect on the catalytic activity, while bulky and electron rich β-diketonate derivatives provide more efficient catalysts.

The transition-metal catalyzed addition of alkynes to aldehydes and ketones has become an intensely investigated area.[1–4] These reactions have been applied to the synthesis of natural products and other compounds of medicinal interest.[5–9] Recently our group disclosed a rhodium-catalyzed alkyne addition method using $Rh(acac)(CO)_2$ (**3**) as the metal precatalyst in the presence of bulky, electron-rich phosphine ligands such as 2-(di-*t*-butylphosphino)biphenyl (**4**) (Scheme 1).[10] The advantages of this method include mild conditions, improved functional group tolerance, and good reactivity with enolizable 1,2-diketones and 1,2-ketoesters, which are problematic substrates for the more common zinc-catalyzed transformations.[11]



Scheme 1.

One significant advantage that zinc-catalyzed reactions hold over the rhodium-catalyzed reaction is the control of the absolute stereochemistry of the propargyl alcohol products.[1–4] Zinc mediated reactions take advantage of chiral alcohol and phenol based ligands to control asymmetry, which provide enantioenriched products with high selectivity.[12,13] Given that the rhodium-catalyzed reaction uses a phosphine ligand, use of a chiral phosphine ligand is an obvious choice to induce asymmetry in the propargyl alcohol products. In our previous work we examined the effect changing the structure of the phosphine ligand had on the alkyne addition reaction and found that only phosphines with at least two bulky alkane substituents provided acceptable yields in the rhodium-catalyzed addition reaction.[10] As these phosphines are relatively new,[14,15] there are few readily available chiral phosphine ligands that possess the requisite bulky alkyl groups required to facilitate the rhodium-catalyzed alkyne addition reaction. Attempts to examine available chiral phosphine ligands for a platform to modify into a dialkyl chiral phosphine have met with difficulties, as conversions tend to be quite low. This casts doubt on the results of the ligand screen.[16]

Faced with difficulties in using chiral phosphines, a second approach was considered. The precatalyst has a β-diketonate ligand, and therefore the use of a chiral β-diketonate may induce asymmetry in the reaction products. Unlike the phosphine, the structure of the

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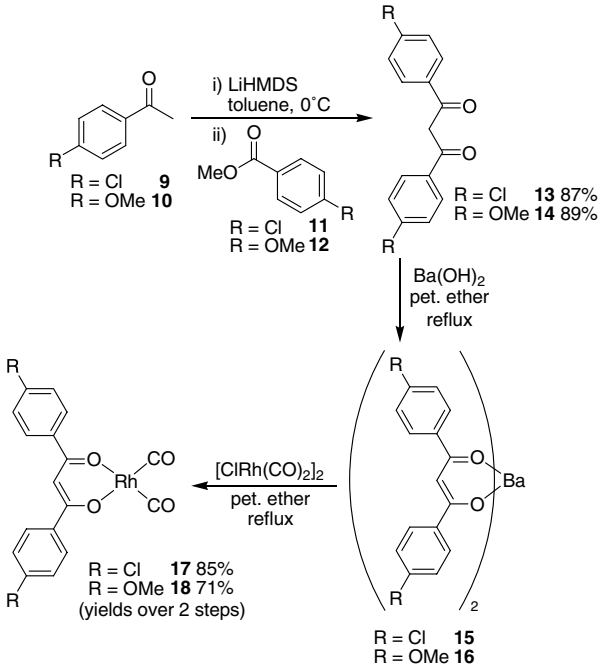
doi:10.1016/j.tetlet.2007.10.010

β-diketonate ligand was not varied in our initial catalyst screens, as these complexes must be synthesized and isolated. Use of a chiral β-diketonate ligand also attracted our attention as an underutilized approach for controlling the enantioselectivity in an organic transformation. While numerous variants of chiral β-diketonates have been described,[17–22] only a few have been used effectively in asymmetric transformations.[17,22]

Modification of the β-diketonate ligand will only have a chance to impart enantioselectivity on the products if the ligand stays bound to the rhodium catalyst during the catalytic cycle. To probe this point ^{1}H NMR, ^{31}P NMR, and IR were used to monitor any intermediates in the reaction. A typical alkyne addition was prepared in an NMR tube using phenylacetylene, 2,3-butanedione, the rhodium precatalyst, and phosphine **4** in benzene-d_6. Use of ^{1}H NMR to monitor ligand changes on the catalyst proved difficult, as the methyl groups of the β-diketonate ligand were obscured by signals from 2,3-butanedione. No change in chemical shift was observed on the signal for the C–H present on C3 of the β-diketonate, which appeared as a singlet at 5.14 ppm throughout the catalytic reaction. Three peaks were observed in the ^{31}P NMR spectra during the experiment, a doublet at 79.9 ppm, a singlet at 57.2 ppm, and a singlet at 19.4 ppm. The singlet at 19.4 ppm was attributed to phosphine **4**, while the signal at 57.2 ppm represented small amounts of phosphine oxide formed from adventitious oxidation of the phosphine.[23] Consistent with this analysis, the signal at 57.2 ppm was slowly growing larger during the course of the reaction, while the peak at 19.4 ppm was slowly decreasing in size. The doublet observed at 79.9 ppm had a coupling constant of 182 Hz, which was consistent with rhodium phosphine coupling constants in complexes with the general formula Rh(acac)(CO)(PR_3).[24,25]

The same signal at 79.9 ppm was observed in the ^{31}P NMR of the product of the reaction between Rh(acac)-$(CO)_2$ and phosphine **4** in benzene-d_6 with no added alkyne or 1,2-diketone. Further confirmation on the structure of the persistent intermediate Rh(acac)-(CO)(PR_3) came from IR studies on the reaction of rhodium complex **3** and ligand **4**. The loss of a CO ligand and the continued presence of the β-diketonate was detected in the IR spectra, which showed the disappearance of the carbonyl peaks for complex **3** (two absorbencies at 2082 cm^{-1} and 2011 cm^{-1}) and the appearance of a new signal at 1957 cm^{-1}, consistent with Rh(acac)-(CO)(PR_3).[24,25] Infrared absorbencies at 1590 cm^{-1} and 1523 cm^{-1} showed the β-diketonate ligand was still bound to the rhodium. Given the persistent nature of the signal at 79.9 ppm in the ^{31}P NMR during the alkyne addition reaction, the β-diketonate ligands presence on the active catalyst seemed secure.

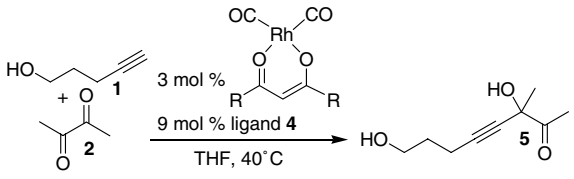
Before synthesizing any chiral β-diketonate rhodium complexes, it would be prudent to determine the effect modifying the β-diketonate has on the catalytic reaction. To facilitate this study, the synthesis of several rhodium complexes was undertaken. Derivatives of Rh(acac)-$(CO)_2$ in which the methyl groups of the β-diketonate have been replaced with trifluoromethyl (**6**), *t*-butyl (**7**), and phenyl (**8**) groups were prepared.[26] In addition, β-diketonate ligands with modified phenyl rings were prepared by Claisen condensation of the corresponding esters and ketones (Scheme 2). Deprotonation of the 1,3-diketones with barium hydroxide followed by salt metathesis with rhodium using $[ClRh(CO)_2]_2$ provided the desired rhodium complexes.[27]



Scheme 2.

With the modified precatalysts in hand, their effect on the alkyne addition reaction of 4-pentyn-1-ol (**1**) with 2,3-butanedione (**2**) was examined (Table 1). The yields of the reactions using complexes **7** and **18** were better than with the parent precatalyst **3**. Conversely, the yield decreased when electron-withdrawing groups were incorporated on the β-diketonate ligand. Furthermore, the stronger the electron-withdrawing character of the ligand, the worse the yield became (Table 1, entries 2 and 5).

Table 1. Effect of catalyst structure on the yield of the addition reaction



Entry	Rh Catalyst	Yield (%)
1	R = Me (**3**)	86
2	R = CF_3 (**6**)	6
3	R = *t*-Bu (**7**)	99
4	R = Ph (**8**)	91
5	R = 4-Cl–Ph (**17**)	72
6	R = 4-OMe–Ph (**18**)	98

While comparing the yield of the reactions is one way of determining the reactivity differences of the β-diketonate ligands, another measure is the rate of the reactions. Toward this end, the rates of the reactions were compared by monitoring the reactions using ^{1}H NMR (Fig. 1). The reaction between phenylacetylene and 2,3-butanedione was used as it occurs rapidly even at room temperature and can be easily monitored by the disappearance of the alkyne C–H in the ^{1}H NMR. Deuterated benzene was used as a solvent for these reactions, as the reaction performs nearly as well in benzene as in THF. In all cases the reactions were very clean with only signals for the starting material, addition product, and excess 2,3-butanedione appearing in the spectra (as well as trace amounts of the phosphine ligand). As the hexafluoro derivative **6** was shown to provide poor conversion in the addition reaction, it was omitted from the rate study.

In all cases, the reactions showed excellent agreement with a first-order relationship in regard to the starting alkyne. With the data from the rate studies in hand, the relative rates of the reactions were calculated (Table 2). While the rate of the addition reaction was changed by the modification of the group on the β-diketonate ligand, these changes were quite subtle. Substitution of the methyl group with a bulky *t*-butyl group appeared to slightly increase the reaction rate. This could be due to steric effects increasing the facility of ligand substitution or electronic effects increasing the electron density on the rhodium center. Comparison of the three catalysts bearing aromatic rings allowed for a more relevant comparison of electronic factors on the reaction, since the catalysts generated from complexes **8**, **17**, and **18** all possess similar steric properties. From these results we can conclude the incorporation of electron-withdrawing groups on the β-diketonate is detrimental to the rate of the reaction. Also supporting this trend is the comparison between catalysts **3** (R = Me) and **8** (R = Ph), with the greater electronegativity of the phenyl ring decreasing the reaction rate. These results support the necessity of an electron-rich rhodium catalyst similar to the results observed in the phosphine screen preformed earlier.[10]

Table 2. Relative rates of the formation of product **20**

Entry	Rh Catalyst	k_{rel}
1	R = Me (**3**)	1
2	R = *t*-Bu (**7**)	1.51
4	R = Ph (**8**)	0.81
5	R = 4-Cl–Ph (**17**)	0.45
6	R = 4-OMe–Ph (**18**)	1.13

Variation of the β-diketonate ligand on the rhodium has small but significant effects on the addition reaction of

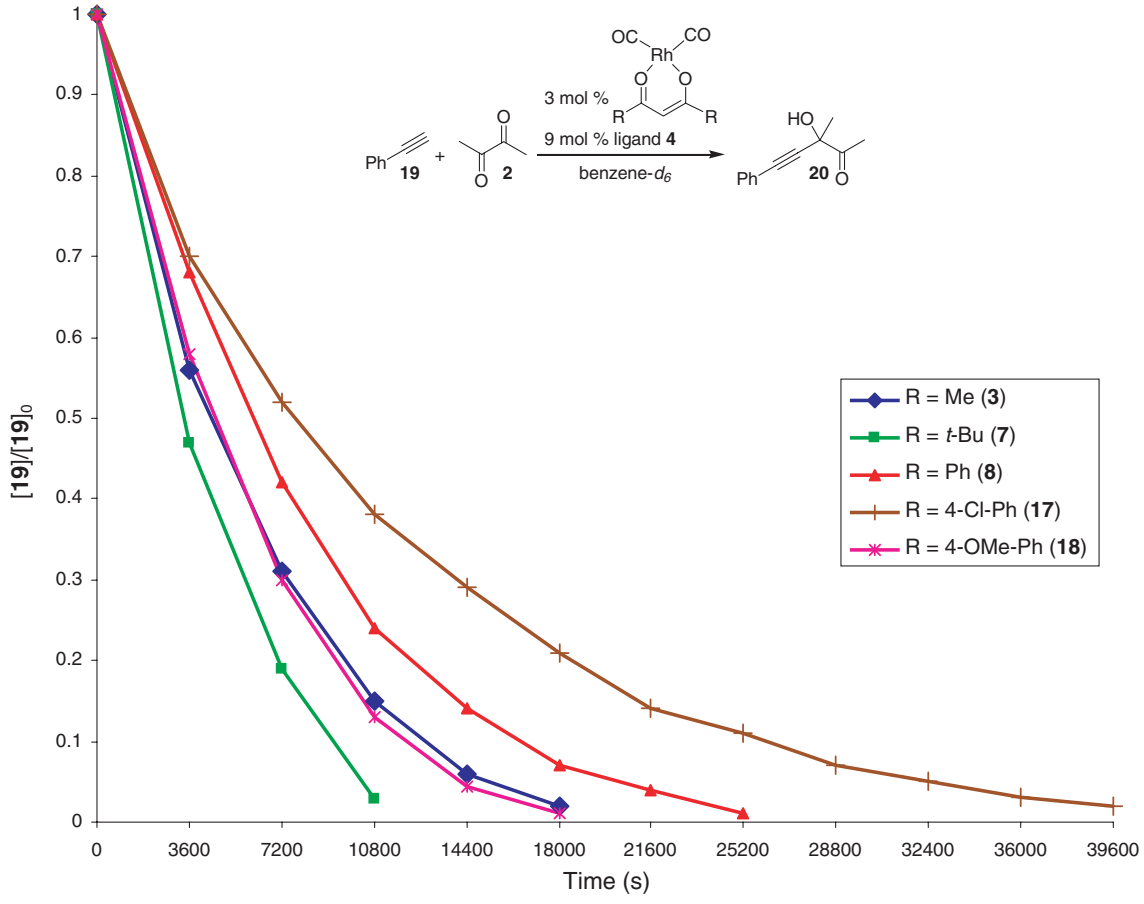


Figure 1. Rate comparison on the disappearance of alkyne **19**.

alkynes to 1,2-diketones. The incorporation of electron-withdrawing substituents on the β-diketonate ligand slows the alkyne addition reaction leading to lower yields, while the use of electron-donating substituents provides higher yields and faster reaction rates. The reaction tolerates the incorporation of bulky groups on the β-diketonate ligand, which should facilitate the incorporation of chiral groups. This may control the enantioselectivity of the addition reaction. Further developments in this area will be reported in due course.

Acknowledgment

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

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27. *Characterization data for new compounds*: **17**: IR (KBr): 3054, 2082, 2013, 1589, 1533, 1479, 1477 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 4H, $J = 8.6$ Hz), 7.42 (d, 4H, $J = 8.6$ Hz), 6.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 183.1, 180.8, 138.3, 136.8, 129.1, 129.0, 95.3. Anal. Calcd for $C_{17}H_9Cl_2O_2Rh$: C, 45.27; H, 2.01. Found: C, 45.20; H, 1.88. Compound **18**: IR (KBr): 3054, 2930, 2080, 2010, 1603, 1587, 1532 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J = 8.9$ Hz, 4H), 6.94 (d, $J = 8.9$ Hz, 4H), 6.84 (s, 1H), 3.88 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 183.7, 180.3, 162.6, 131.2, 129.6, 113.9, 94.1, 55.6. Anal. Calcd for $C_{19}H_{15}O_6Rh$: C, 51.60; H, 3.42. Found: C, 52.09; H, 3.52.