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Communication

Rhodium-catalyzed intermolecular hydroacylation of 1-alkynes: Effect of phosphines and MK-10 on the reaction selectivity

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Abstract

The use of bulky ligands in the rhodium-catalyzed reaction of aldehydes **7** (R^1 = Ph) and **18** with 1-octyne increased the selectivity for ketones **13** and **20**, to the detriment of ketones **12** and **19**. Bulky phosphines reduced the hydroacylation reaction rate, leading to competition from the addition of the benzoic acid co-catalyst to the alkynes. This competing reaction can be suppressed by using the clay Montmorillonite K 10 (MK-10) as the co-catalyst instead of benzoic acid.

Keywords: Hydroacylation; Alkynes; Rhodium; Catalysis; Selectivity; Montmorillonite MK-10

1. Introduction

The intermolecular hydroacylation of alkynes often requires the presence of coordinating heteroatoms in the aldehyde moiety in order to avoid the competing decarboxylation reaction. For example, benzaldehyde bearing PPh_2 [1] (**1**) or OH [2] (**2**) groups in the *ortho* position has been successfully used in the hydroacylation of terminal as well as disubstituted alkynes, providing the α,β-unsaturated ketones **3** and **4** of *E* configuration, respectively (Scheme 1) [3]. Compounds **3** were reduced *in situ* to the saturated ketone except when a bulky substituent was present (R^1 = H, R^2 = ^{t}Bu). In a similar approach, alkyl aldehydes **5**, react with alkynes in the presence of a rhodium catalyst to yield 1,2-disubstituted alkenes **6** with an *E* configuration (Scheme 2) [4].

Jun et al. reported the rhodium-catalyzed intermolecular hydroacylation of alkynes [5,6] by transforming *in situ* the aldehyde into a piridyl-aldimine [7]. Specifically, the process starts with the transformation of the aldehyde **7** into the aldimine **8** by reaction with 2-amino-3-picoline in the presence of benzoic acid as a co-catalyst. The aldimine then reacts with the alkyne in the presence of Wilkinson's catalyst to give the ketimine **9**, which is hydrolyzed under these conditions to the α,β-unsaturated ketone **10** (Scheme 3). The regioselectivity of this reaction differs from that obtained by reacting aldehydes **1** and **2**.

Using the aldimine approach, it was found that when R^1 was an alkyl group, a small percentage of the product was the *E* isomer **11**. By contrast, **11** was exclusively obtained when R^2 was a bulky substituent such as a *tert*-butyl group. This indicates that the regioselectivity of the reaction is very sensitive to steric hindrance of the substituents.

The strategy based on the use of aldimine derivatives is synthetically more flexible than the other approaches, although compounds of general structure **10** are usually favored. In the present work, we show that the selectivity in the final ketone can be modified to give increasing amounts of ketones **11**, by varying the steric hindrance induced by the phosphines and that Montmorillonite MK-10 can advantageously replace the benzoic acid in order to avoid secondary reactions.

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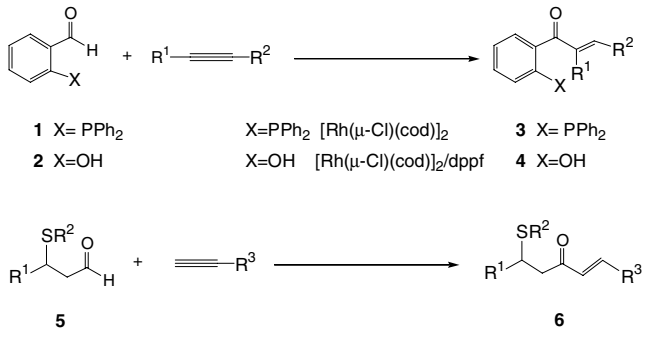
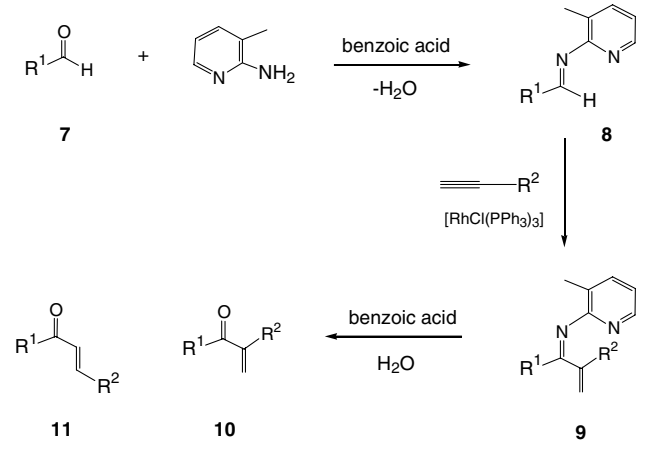
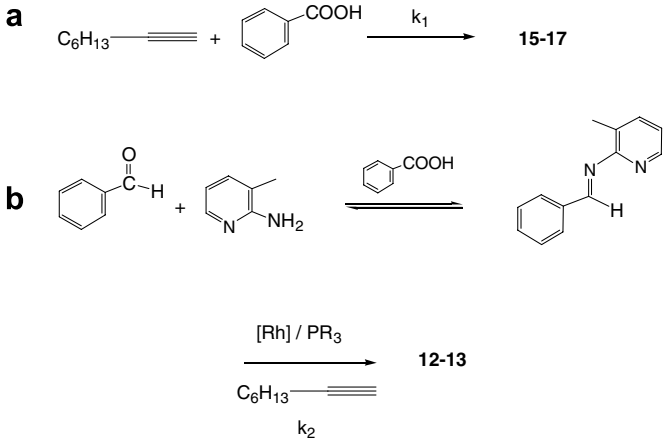


Scheme 1.



Scheme 2.



Scheme 3.

2. Results and discussion

Initially, benzaldehyde was reacted with 1-octyne in the presence of 2-amino-3-picoline and benzoic acid, using $[Rh(\mu\text{-}Cl)(cod)]_2$ /PPh_3 as a catalyst [5]. After 12 h at 80 °C, 90% conversion was obtained with 80% selectivity for the ketone **12** (entry 1, Table 1). The by-products of the reaction were identified as the α,β-unsaturated esters **15**–**17**, on the basis of IR (band at 1735 cm^{-1}) and NMR data. The esters **15**–**17** resulted from the addition of benzoic acid to octyne. The results were found to be reproducible under these conditions.

We additionally tested the use of phosphine ligands with cone angles [8] larger than that of PPh_3. The results, summarized in Table 1, showed that when the cone angle of the ligand increased from 145° (triphenylphosphine) to 194° (tri-*o*-tolylphosphine) the selectivity for ketone **12** decreased from 80% to 8%, while higher amounts of the *E* isomer **13** was produced under these conditions (entries 1–6, Table 1).

This finding can be explained by phosphine ligands with larger cone angles inducing greater steric hindrance. Significantly, when the bulky ligands tri-*tert*-butylphosphine or tri-*o*-tolylphosphine were used, the formation of ketone **13** was favored over ketone **12** (entries 5 and 6, Table 1). In all cases, esters **15**–**17** were obtained and the *cis* isomer **14** was not detected. Furthermore, when the ketone conversion was low, the percentage of ester increased. Thus, when the phosphine ligand was P^tBuPh_2 or PCy_3 (entries 3 and 4, Table 1), esters constituted over 50% of the products generated by the reaction, and when $P(o\text{-tolyl})_3$ was used, this percentage reached 75%.

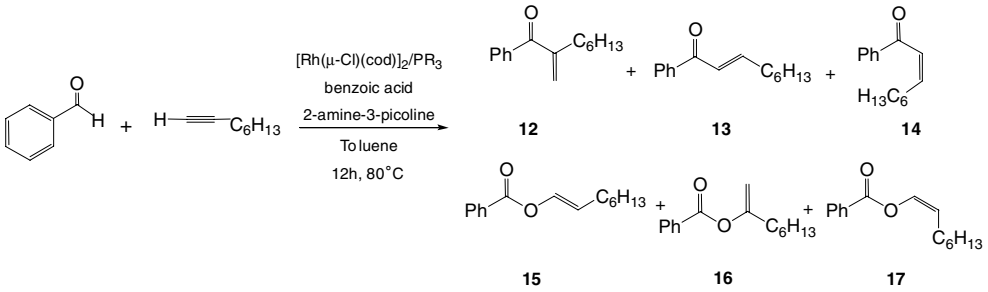
The use of a bulky phosphine decreases the value of k_2, making the addition of benzoic acid to the alkyne more competitive (Scheme 3). As a consequence, the concentrations of benzoic acid and alkyne are lowered, further decreasing the overall reaction rate of the hydroacylation process.

The above results indicate that the use of phosphine ligands with larger cone angles favors the formation of ketone **13** with respect to ketone **12**, and leads to decreased conversion as well as increased formation of the unsaturated esters such that, when the phosphine cone angle exceeds 160°, the esters are the major reaction products.

Recently we developed a novel catalytic system using Montmorillonite K-10 (MK-10) as a co-catalyst in chelation-assisted intermolecular hydroacylation [9]. MK-10 can be employed as a reusable acid co-catalyst, instead of benzoic acid, for the condensation of aldehydes and aminopyridines to provide the intermediate aldimine (Scheme 2). In addition, we hypothesized that, unlike benzoic acid, MK-10 would not undergo an addition reaction with the alkynes.

When MK-10 was used in the intermolecular catalytic hydroacylation of benzaldehyde and 1-octyne with $[RhCl(PPh_3)_3]$ as the catalyst, under conditions similar to those used previously [9], 85% conversion was achieved (entry 7, Table 1); unexpectedly, however, the α-β-unsaturated ketones **12** and **13** were obtained in a ratio of 75:25. Finally, when tricyclohexylphosphine was used in the presence of MK-10 at 80 °C for 12 h (entry 8, Table 1), the conversion was found to be 20%, and the enones **12** and **13** were obtained in a 60:40 ratio. Notably, none of the previously described reactions produced esters **15**–**17** or the *cis*-ketone **14** at detectable levels, indicating that the use of MK-10 in the Rh-catalyzed intermolecular hydroacylation of alkynes avoids the formation of ester by-products.

Table 1
Influence of the ligand cone-angle on the selectivity of the rhodium-catalyzed intermolecular hydroacylation of 1-octyne with benzaldehyde[a]



Entry	PR_3	(°)[b]	Conv.[c](%)	Products (%)[c]					
				12	**13**	**14**	**15**	**16**	**17**
1[d]	PPh_3	145	90	80	–	–	10	5	5
2	$P(m\text{-}OMeC_6H_4)_3$	150	85	75	–	–	15	10	–
3	P^tBuPh_2	164	40	35	15	–	35	10	5
4	PCy_3	170	45	35	10	–	40	15	–
5	P^tBu_3	182	60	20	30	–	30	20	–
6	$P(o\text{-tolyl})_3$	194	20	8	17	–	40	25	10
7[d,e]	PPh_3	145	85	75	25	–	–	–	–
8[f]	PCy_3	170	20	60	40	–	–	–	–

[a] Standard conditions: benzaldehyde (2 mmol), 1-octyne (4 mmol), 2-amino-3-picoline (0.8 mmol), benzoic acid (0.4 mmol), $[Rh(\mu\text{-Cl})(cod)]_2$ (5 mol %), ratio $Rh/PR_3 = 1{:}3$, 2 ml of toluene, 12 h, 80 °C.
[b] Cone angle [8].
[c] Determined by GC.
[d] $[RhCl(PPh_3)_3]$ was used as catalyst.
[e] MK-10 (83 mg) was used instead of benzoic acid, 110 °C, 2 h.
[f] MK-10 (83 mg) was used instead of benzoic acid, 80 °C, 12 h.

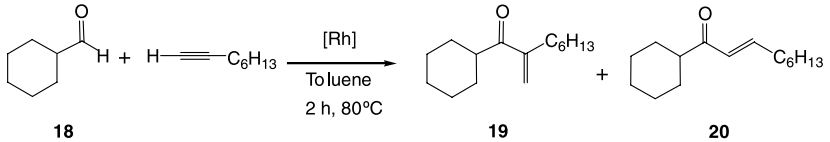
The intermolecular hydroacylation reaction of non-aromatic aldehydes such as cyclohexanecarbaldehyde (**18**) and 1-hexyne in the presence of 2-amino-3-picoline and benzoic acid using Wilkinson's catalyst has been investigated previously. When we performed this reaction under the conditions used in the previous study, 100% conversion and a ratio of **19/20** = 81:19 were obtained in 2 h of reaction to 80 °C, consistent with the previous report (entry 1, Table 2). No ester by-products were detected in this case. When MK-10 was used instead of benzoic acid, the conversion decreased to 70%, and in agreement to the observed in Table 1 *E* isomer **20** increased slightly (entry 3, Table 2).

The effect of sterically demanding ligands was also explored. The reaction was carried out with PCy_3 in the presence of benzoic acid or MK-10. The conversions were found to be 50% and 40%, respectively, whereas the selectivity of the *trans* α,β-unsaturated ketone **20** increased to 30% and 35%, respectively (entries 3 and 4, Table 2). When P^tBu_3 was used, the conversion was 40% and the percentage of ketone **20** was 40%. The *cis* isomer was not detected among the products of any of the reactions (entry 5, Table 2).

3. Conclusions

In summary, we have shown here that the use of sterically demanding ligands in the rhodium-catalyzed intermolecular hydroacylation of alkynes increases the selectivity

Table 2
Rhodium-catalyzed intermolecular hydroacylation of 1-octyne with cyclohexanecarbaldehyde[a]



Entry	Catalytic system	PR_3	Co-catalyst	Conv. (%)	**19**	**20**
1	$[RhCl(PR_3)_3]$	PPh_3	Benzoic acid	100	81	19
2	$[RhCl(PR_3)_3]$	PPh_3	MK-10[b]	70	75	25
3	$[Rh(\mu Cl)(cod)]_2$	PCy_3	Benzoic acid	50	70	30
4	$[Rh(\mu Cl)(cod)]_2$	PCy_3	MK-10b	40	65	35
5	$[Rh(\mu Cl)(cod)]_2$	P^tBu_3	Benzoic acid	40	60	40

[a] Standard conditions: **18** (2 mmol), 1-octyne (4 mmol, 600 μl), 2-amino-3-picoline (0.8 mmol), catalytic system (5 mol%), benzoic acid (0.4 mmol) or MK-10 (83 mg), toluene (2 ml), 2 h, 80 °C.
[b] Temperature 110 °C.

for ketones **13** and **20** with an *E* configuration with respect to ketones **12** and **18**, respectively. We found that the use of sterically demanding ligands reduced the hydroacylation rate, leading to competitive addition of the benzoic acid co-catalyst to the alkynes to give esters. This secondary reaction could, however, be suppressed by using MK-10 as the co-catalyst for the formation of the imine and the hydrolysis of ketimine.

4. Experimental

All of the starting materials, reagents, MK-10 and phosphines used in this work were purchased and used without further purification except the aldehydes, which were distilled prior to use. All solvents were distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded using a 300 MHz and 400 MHz apparatus, with $CDCl_3$ as the solvent and Me_4Si as the internal reference. Flash column chromatography was performed using silica gel 60 A CC (230–400 mesh). The catalytic reactions were monitored by GC on a Hewlett–Packard 5890A. Conversion was measured in an HP-5 column (25 m × 0.2 mm ∅).

4.1. General procedure for the intermolecular hydroacylation of alkynes

A mixture of aldehyde (2 mmol), 1-octyne (4 mmol, 600 μl), 2-amino-3-picoline (0.8 mmol), benzoic acid (0.4 mmol), $[Rh(\mu\text{-}Cl)(cod)]_2$ (0.054 mmol), and PR_3 (0.162 mmol), or alternatively 0.05 mmol of $[RhCl(PPh_3)_3]$, was heated at 80 °C for 12 h in 3 ml of toluene. The reaction mixture was allowed to cool to room temperature and then purified by flash chromatography with hexane–AcOEt 98:2. The structures of the isolated compounds were determined from their ^{1}H and ^{13}C NMR spectra.

4.2. General procedure for the intermolecular hydroacylation of alkynes using $[Rh(\mu\text{-}Cl)(cod)]_2/PR_3$/Montmorillonite (MK-10)

A mixture of aldehyde (2 mmol), 1-octyne (4 mmol, 600 μl), 2-amino-3-picoline (0.8 mmol), MK-10 (83 mg), $[Rh(\mu\text{-}Cl)(cod)]_2$ (0.054 mmol), and PR_3 (0.162 mmol) was heated at 110 °C for 2 h in 3 ml of toluene. The reaction mixture was allowed to cool to room temperature and then purified by flash chromatography with hexane–AcOEt 98:2.

Main spectroscopic data of ketones **12**, **13**, **19** and **20**, and of esters **15**–**17**.

2-Hexyl-1-phenyl-2-propenone (**12**). IR: 1685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.80 (dd, $J = 7.2$, 1.5 Hz, 2H), 7.55 (tt, $J = 7.1$, 1.5 Hz, 1H), 7.43 (t, $J = 7.3$ Hz, 2H), 5.82 (s, 1H), 5.60 (s, 1H), 2.56 (t, $J = 7.4$ Hz, 2H), 1.5–1.2 (m, 8H), 0.90 (t, $J = 5.9$ Hz, 3H, –CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 198.5, 148.5, 137.9, 132.1, 129.5, 128.1, 125.1, 32.2, 31.5, 29.0, 28.1, 22.5, 14.0.

(E)-1-Phenyl-non-2-en-1-one (**13**). Obtained from the mixture with **12**. ^{1}H NMR (400 MHz, $CDCl_3$) δ in ppm: 7.80 (d, $J = 6.9$ Hz, 2H), 7.55 (d, $J = 6.2$ Hz, 1H), 7.42 (t, $J = 7.3$ Hz, 2H), 6.82 (dt, $J = 15.6$ and 6.9 Hz, 1Hα), 6.10 (dt, $J = 15.9$, 1.6 Hz, 1Hβ). 2.2 (qd, $J = 6.9$, 1.6 Hz, 2H), 1.5–1.2 (m, 8H), 0.91 (t, $J = 7.6$ Hz, 3H, CH_3).

(E)-Oct-1-enyl benzoate (**15**). Obtained from the mixture with **16**. ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ in ppm: 8.11 (dd, $J = 7.2$, 1.1 Hz, 2H), 7.59 (tt, $J = 7.2$, 1.1 Hz, 1H), 7.49 (t, $J = 7.3$ Hz, 2H), 7.31 (dt, $J = 12.4$ and 1.6 Hz, 1Hα), 5.61 (dt, $J = 12.4$ and 7.2 Hz, 1Hβ), 2.07 (qd, $J = 7.6$, 1.2 Hz, 2H, –CH_2), 1.50–1.20 (m, 8H), 0.90 (t, $J = 5.9$ Hz, 3H, –CH_3).

1-Pentyl-vinyl benzoate (**16**). IR 1735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ ppm 8.05 (dd, $J = 7.2$, 1.5 Hz, 2H), 7.60 (tt, $J = 7.5$, 1.5 Hz, 1H), 7.47 (t, $J = 7.3$ Hz, 2H), 4.85 (d, $J = 1.4$ Hz, 1H), 4.83 (d, $J = 1.4$ Hz, 1H), 2.57 (t, $J = 7.6$ Hz, 2H, –CH_2), 1.50–1.20 (m, 8H), 0.88 (t, $J = 7.2$ Hz, 3H, –CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 164.8, 156.8, 133.3, 129.9, 128.5, 101.3, 33.4, 31.6, 28.7, 26.5, 22.5, 14.0.

(E)-Oct-1-enyl benzoate (**17**). IR (CH_2Cl_2) 1733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ ppm 8.10 (d, $J = 6.9$ Hz, 2 H, Ph), 7.61 (d, $J = 6.2$ Hz, 1H, Ph), 7.50 (t, $J = 7.3$ Hz, 2H, Ph), 7.26 (dt, $J = 6.4$ and 1.6 Hz, 1Hα), 5.01 (dt, $J = 7.4$, 6.4 Hz, 1Hβ), 2.28 (qd, $J = 7.4$, 1.6 Hz, 2H, –CH_2), 1.50–1.20 (m, 8H), 0.90 (t, $J = 7.4$ Hz, 3H, –CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 163.6, 134.1, 133.4, 129.9, 128.5, 115.0, 31.6, 29.2, 28.8, 24.6, 22.6, 14.0.

1-Cyclohexyl-2-hexyl-propenone (**19**). ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ in ppm: 5.9 (s, 1H), 5.7 (s, 1H), 2.5 (t, $J = 7.4$ Hz, 2H), 1.5–1.2 (m, 8H), 0.9 (t, $J = 5.9$ Hz, 3H, –CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ in ppm: 203.5, 148.0, 123.2, 42.0, 32.3, 31.6, 29.1, 28.5–27.1 (5C), 22.6, 14.0.

(E)-1-Cyclohexyl-2-nonenone (**20**). Spectroscopic data obtained from the mixture with **18**. ^{1}H NMR (400 MHz, $CDCl_3$,TMS) δ ppm 6.8 (d, $J = 15.9$ and 6.9 Hz, 1Hα), 6.1 (d, $J = 15.9$ Hz, 1Hβ). 2.2 (q, $J = 6.9$ Hz, 2H), 1.5–1.2 (m, 8H), 0.91 (t, $J = 5.9$ Hz, 3H, CH_3).

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