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Alkyne Hydroacylation: Switching Regioselectivity by Tandem Ruthenium Catalysis

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Supporting Information

ABSTRACT: By using tandem Ru-catalysis, internal alkynes can be coupled with aldehydes for the synthesis of β,γ-unsaturated ketones. The catalyst promotes alkyne transformations with high regioselectivity, with examples that include the differentiation of a methyl vs ethyl substituent on the alkyne. Mechanistic studies suggest that the regioselectivity results from a selective allene formation that is governed by allylic strain.

In contrast to an enzyme, which is typically specific, a single transition-metal complex can catalyze diverse transformations. This generality can be exploited in *tandem catalysis*, a strategy where one catalyst promotes two or more transformations in a cascade.[1a−c] Ru-complexes are especially versatile in developing efficient *tandem reactions*,[1d−f] including examples that feature olefin metathesis,[2] reductive C−C bond coupling,[3] and amide synthesis.[4] It occurred to us that tandem catalysis[5] could be used to overcome challenges in hydroacylation, the addition of an aldehyde C−H bond across an unsaturated π-bond.[6] Toward expanding ketone hydroacylation, we reported a method involving alcohol oxidation, enantioselective ketone reduction, and lactol oxidation to generate lactones, a process in which all three transformations were promoted by Noyori's Ru-catalyst.[5a] Herein, we apply tandem Ru-catalysis to achieve the hydroacylation of alkynes with unprecedented regiocontrol to afford β,γ-unsaturated ketones.

The coupling of an aldehyde to an alkyne is a promising route to ketones, which has been studied using both transition metal catalysts (e.g., Ni,[7] Rh,[8,9] Ru,[10] Ir,[11] Au,[12] Cu[13]) and organocatalysts[14] (e.g., *N*-heterocyclic carbenes) (Figure 1a). In alkyne hydroacylation, α,β-unsaturated ketones are afforded as the major constitutional isomer for both intra- and intermolecular variants. Most of these methods require terminal or symmetric alkynes to achieve high regioselectivity. Others require aldehydes bearing directing groups to promote C−H bond functionalization in preference to decarbonylation.

In light of these challenges, we proposed using a metal-hydride catalyst to perform a tandem reaction involving (1) alkyne−allene isomerization and (2) allene−aldehyde coupling (Figure 1b). This protocol would tolerate a wider scope of coupling partners and provide access to an alternative ketone isomer. We judged this cascade to be feasible on the basis of literature precedence for metal-hydride catalysis of the independent transformations. Yamamoto demonstrated alkynes as convenient surrogates for allenes in Pd-catalyzed hydroamination.[15] Ishii[16] and Breit[17] achieved alkyne isomerizations

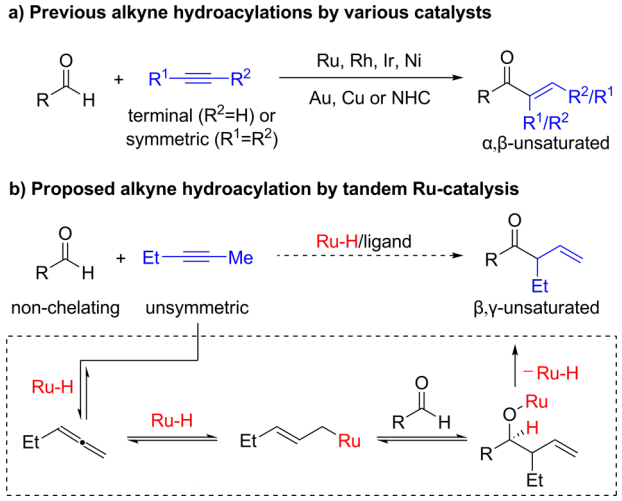

Figure 1. Intermolecular hydroacylation of alkynes.

by Ir and Rh metal-hydride pathways, respectively. Krische proposed that Ru(0) isomerizes alkynes to allenes, albeit by a C−H propargyl activation mechanism.[18] While Willis has reported allene hydroacylations with chelating aldehydes,[19] we envisioned the resulting allene would undergo metal-hydride addition to generate a metal-allyl species that could couple to nonchelating aldehydes (Figure 1b). This mechanistic step has been shown in the coupling of allenes and aldehydes to generate homoallylic alcohols.[20] In our proposal, subsequent β-hydride elimination would generate the desired β,γ-unsaturated ketone and regenerate the metal-hydride catalyst. Thus, we set out to identify a single metal catalyst that could promote both transformations in sequence to afford a novel alkyne hydroacylation.

To test our hypothesis, we chose the coupling of benzaldehyde **1a** and 2-pentyne **2a** as the model. The unsymmetrical alkyne **2a** is a challenging substrate for regioselective transformations due to the similar steric bulk of methyl and ethyl substituents (*A*-values of 1.74 vs 1.79 kcal/mol, respectively).[21] An initial survey of commercially available metal hydride complexes (Rh, Ru, Ir) revealed that $RuHCl(CO)(PPh_3)_3$ was a promising catalyst precursor (Table 1).[22] The regioselectivity for β,γ-unsaturated ketone **3aa** over **4aa** and **5aa** depended on the structure of the ligand chosen (entries 1−7).[23] Only traditional hydroacylation products (α,β-unsaturated ketones) were obtained (**4aa** and **5aa**) using non-ferrocene-based ligands, such as BINAP and Tangphos (entries 1−2). Switching

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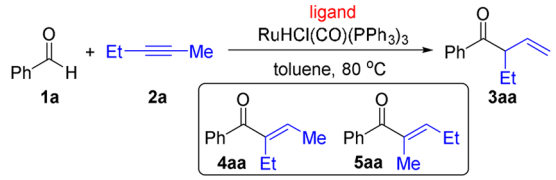
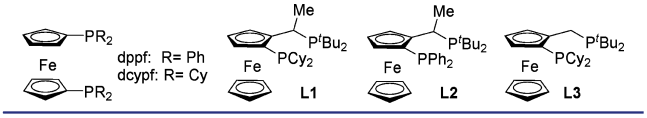
Table 1. Ligand Effects on Hydroacylation of 2-Pentyne[a]



entry	ligand	yield (%)[b] 3aa	4aa	5aa
1	BINAP	0	1	3
2	Tangphos	0	5	18
3	dppf	11	43	40
4	dcypf	30	0	25
5	**L1**	54	0	2
6	**L2**	32	3	58
7	**L3**	41	0	8
8[c]	**L1**	81	1	2

[a]**1a** (0.20 mmol), **2a** (0.60 mmol), $RuHCl(CO)(PPh_3)_3$ (2 mol %), Ligand (2 mol %), toluene (0.5 mL), 80 °C, 18 h. [b]Determined by ^1H NMR or GC-FID with 1,3,5-trimethoxybenzene (0.05 mmol) as the internal standard. [c]$RuHCl(CO)(PPh_3)_3$ (4 mol %), **L1** (4 mol %), 15 h.



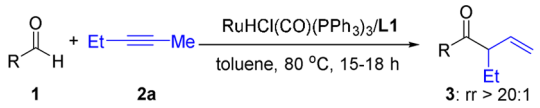
to ferrocene-based ligands gave the desired β,γ-unsaturated product **3aa** (entries 3–6).[24] Josiphos **L1** provided the highest reactivity and regioselectivity (entry 5). Removing the backbone methyl group in Josiphos **L1** resulted in a decrease in regioselectivity (entry 7 vs 5). Increasing the catalyst loading to 4 mol % improved the yield (entry 8). We used racemic **L1** in these initial studies. The stereocenter of Josiphos **L1** has little impact on enantioselectivity[25] but appears essential for both regioselectivity and reactivity.[26]

With this protocol, we explored the hydroacylation of 2-pentyne **2a** with various aldehydes **1** (Table 2). Moderate to good yields (66–85%) and high regioselectivities (>20:1) were obtained with aldehydes **1** possessing varying electronic properties (entries 1–6). The coupling of **2a** tolerated aldehydes **1g–h** with increased steric bulk (78% and 72% yield, entries 7 and 8, respectively). Heteroaromatic β,γ-unsaturated ketones were obtained through the hydroacylation of 2-pentyne **2a** with aldehydes bearing furan (**1i–j**), thiophene (**1k**), and indole (**1l**) rings (entries 9–12). In contrast, under these conditions, aliphatic aldehydes (e.g., cyclohexane carboxyaldehyde, hydrocinnamaldehyde) showed no reactivity.

We next examined the scope of alkynes (Table 3) and found that secondary (Cy) and tertiary (^{t}Bu) alkyl substituted alkynes were suitable coupling partners (entries 1–2). High isolated yields (83–95%) and regioselectivities (>20:1) were observed in the hydroacylation of 1-phenyl-1-propyne with various aldehydes (entries 3–9). Alkynes bearing aryl groups of varying electronic and steric properties could be coupled with aldehyde **1b** with 61–83% yields (entries 10–15). Switching the methyl group to an ethyl group by using 1-phenyl-1-butyne resulted in no desired β,γ-unsaturated ketone product (entry 16). This lack of reactivity may be ascribed to increased allylic strain disfavoring β-hydride elimination to form the allene (Scheme 1).[27]

To support the proposed allene intermediate, we prepared phenylallene **6** independently and then subjected this allene to

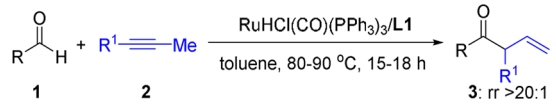
Table 2. Hydroacylation with Various Aldehydes[a]

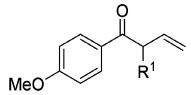
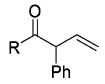
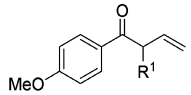
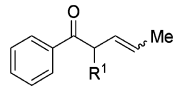


entry	R in **1**	yield (%)[b]
1	Ph (**1a**)	81 (**3aa**)
2	4-$MeOC_6H_4$ (**1b**)	69 (**3ba**)
3	4-MeC_6H_4 (**1c**)	85 (**3ca**)
4	4-FC_6H_4 (**1d**)	79 (**3da**)
5	4-ClC_6H_4 (**1e**)	74 (**3ea**)
6	4-BrC_6H_4 (**1f**)	66 (**3fa**)
7	3-$MeOC_6H_4$ (**1g**)	78 (**3ga**)
8	2-$MeOC_6H_4$ (**1h**)	72 (**3ha**)
9	2-furyl (**1i**)	71 (**3ia**)
10	3-furyl (**1j**)	76 (**3ja**)
11	2-thienyl (**1k**)	87 (**3ka**)
12	3-*N*-Ts-indolyl (**1l**)	83 (**3la**)

[a]**1** (0.20 mmol), **2a** (0.60 mmol), $RuHCl(CO)(PPh_3)_3$ (4 mol %), **L1** (4 mol %), toluene (0.5 mL), 80 °C, 15–18 h. [b]Isolated yields of **3**, >20:1 regioselectivity based on ^1H NMR or GC-FID analysis of the reaction mixtures.

Table 3. Hydroacylation with Various Alkynes[a]



Entry	**3**	R or R^1 in **3**	Yield (%)[b]
1		Cy	68 (**3bb**)
2		^{t}Bu	93 (**3bc**)
3		Ph	95 (**3ad**)
4		4-$MeOC_6H_4$	94 (**3bd**)
5		3-$MeOC_6H_4$	90 (**3gd**)
6		2-Furyl	87 (**3id**)
7		3-Furyl	94 (**3jd**)
8		2-Thienyl	88 (**3kd**)
9		3-*N*-Ts-indolyl	83 (**3ld**)
10		4-ClC_6H_4	77 (**3be**)
11		4-BrC_6H_4	61 (**3bf**)
12		4-$CF_3C_6H_4$	82 (**3bg**)
13		4-$MeOC_6H_4$	82 (**3bh**)
14		3-MeC_6H_4	83 (**3bi**)
15		2-MeC_6H_4	67 (**3bj**)
16		Ph	0 (**3ak**)

[a]**1** (0.20 mmol), **2a** (0.24–0.40 mmol), $RuHCl(CO)(PPh_3)_3$ (4 mol %), **L1** (4 mol %), toluene (0.5–1.0 mL), 80–90 °C, 15–18 h. [b]Isolated yields of **3**, >20:1 regioselectivity based on ^1H NMR or GC-FID analysis of the reaction mixtures.

benzaldehyde **1a** under otherwise standard conditions (eq 1). This control experiment provides the same product **3ad** as that obtained in the hydroacylation of 1-phenyl-1-propyne. While allene **6** was completely consumed, multiple unidentified side products were observed. We propose that tandem catalysis overcomes possible decomposition pathways by forming allenes in

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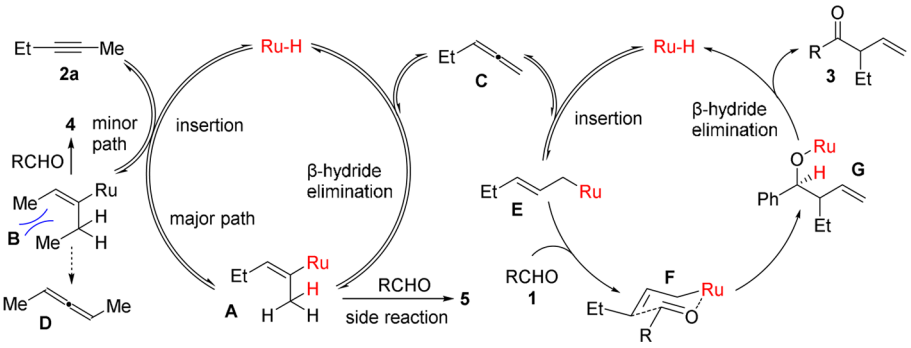
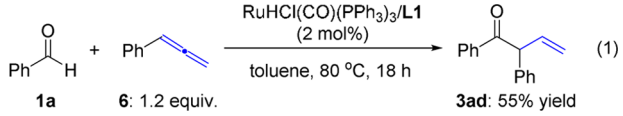
Scheme 1. Tandem Ru-Catalysis: Mechanism for Hydroacylation of Alkynes

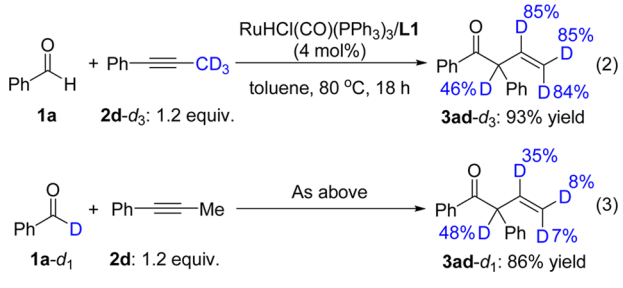




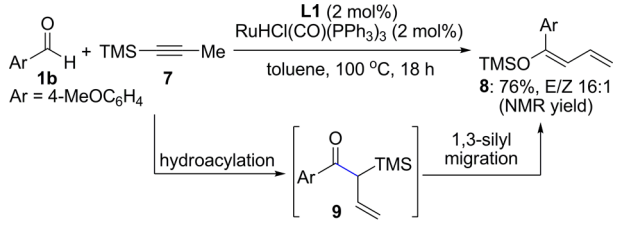
low concentration. A similar phenomenon was observed by Krische in his recent study on the synthesis of homoallylic alcohols.[18]

On the basis of literature and our own observations, we propose the mechanism featuring tandem Ru-catalysis (Scheme 1). The reversible insertion of 2-pentyne **2a** into ruthenium hydride (Ru−H) can yield Ru-vinyl intermediate **A** or **B**. The interception of intermediate **A** with aldehyde **1** generates isomer **5**, whereas interception with **B** generates isomer **4**. Indeed, we observed formation of both **5aa** and **4aa** (~3:1 ratio) when using BINAP or TangPhos (Table 1, entries 1−2). While formation of both **A** and **B** are feasible, we propose that *β*-hydride elimination from **B** to generate the 1,3-disubstituted allene **D** will be disfavored due to higher allylic strain.[28] In contrast, the *β*-hydride elimination of metal−vinyl complex **A** will form 1-substituted allene **C** *in situ* and regenerate a Ru−H species.[29] This mechanistic proposal suggests that the optimal ligand promotes allene formation in preference to conventional hydroacylation (see Table 1). The reinsertion of Ru−H into the terminal allene **C** will occur regioselectively to yield Ru-allyl **E**. Trapping of aldehyde **1** through a six-membered intermediate **F** yields ruthenium alkoxide **G**.[20] A second *β*-hydride elimination from **G** delivers the observed ketone **3** and regenerates the Ru−H.

When the hydroacylation was performed with deutero-alkyne **2d**-d_3, the deuterium label was scrambled into the *α*-, *β*-, and *γ*-positions of ketone **3ad**-d_3 (eq 2). The incorporation of deuterium into both *α*- and *β*- positions of ketone **3ad**-d_3 suggests that the Ru−H species generated from both *β*-H elimination steps (**A** to **C** and **G** to **3**) are indistinguishable (Scheme 1). The observed incorporation of hydrogen at the *γ*-position of product **3ad**-d_3 indicates the reversibility of *β*-hydride elimination in allene formation (Scheme 1). This hypothesis is supported by deuterium scrambling in the isotope-labeling study with aldehyde **1a**-d_1 (eq 3).



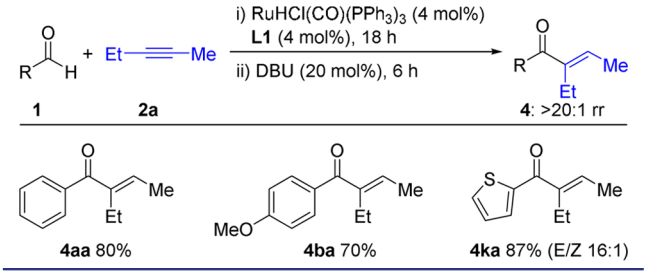
Scheme 2. Silyl Dienol Ether Prepared by Tandem Catalysis



This tandem strategy can be used to access other useful motifs. For example, we investigated the coupling of aldehyde **1b** with 1-(trimethylsilyl)propyne **7** for the formation of silyl dienol ether **8** (Scheme 2). A 1,3-silyl migration[30] of intermediate **9** generates a nucleophile that can be used in asymmetric vinylogous aldol reactions.[31]

In addition, through a procedure involving tandem Ru-catalysis followed by base-catalyzed isomerization, we can generate *α*,*β*-unsaturated ketones **4** with 70−87% yields (Scheme 3). This one-pot protocol allows us to differentiate

Scheme 3. Regioselective Hydroacylation of 2-Pentyne



between the methyl and ethyl groups on 2-pentyne **2a** with high regiocontrol and generate *α*,*β*-unsaturated ketones that would be difficult to access using traditional hydroacylation methods.

We have expanded the power of aldehyde−alkyne cross-couplings by using tandem Ru-catalysis. Due to the formation of a 1-substituted allene intermediate, our protocol differentiates a methyl from an ethyl substituent on 2-pentyne with high regioselectivity. Future studies will focus on stereoselective variants. More importantly, insights from these studies will contribute to the emerging use of alkynes as allene surrogates and guide future developments in tandem catalysis.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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