

Letter

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Transition-Metal-Free Catalytic Formal Hydroacylation of Terminal Alkynes

Takafumi Yatabe,[†] Noritaka Mizuno,[†] and Kazuya Yamaguchi^{*,†}

[†]Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

ABSTRACT: Although hydroacylation is a very useful reaction for producing ketones from aldehydes with 100% atom efficiency, classical Rh-catalyzed hydroacylation presents several problems, including the need for transition metal catalysts, unwanted decarbonylation of aldehydes, and difficulty in regioselectivity control. However, formal hydroacylation utilizing the nucleophilicity of terminal alkynes can avoid these problems. In this work, we have achieved transition-metal-free formal hydroacylation of terminal alkynes using an Mg₃Al–CO₃-layered double hydroxide as a heterogeneous catalyst. This system was applicable to the efficient synthesis of α , β -unsaturated ketones with various substituents, and the catalyst can be reused without a significant loss of catalytic performance.

KEYWORDS: Hydroacylation • Alkynes • Layered double hydroxide • Transition-metal-free • Heterogeneous catalysis

Hydroacylation, which is the transformation of aldehydes into ketones without any byproducts, is an extremely important, efficient, and environmentally friendly method of C–C bond formation from C–H bonds.¹ Particularly, many examples of alkynes/alkenes hydroacylation using transition metals, mainly Rh, as catalysts have been reported (Figure 1a).^{1–3} However, this system still presents several problems, especially for intermolecular hydroacylation, owing to the intrinsic mechanism of Rh-catalyzed hydroacylation; a) competing decarbonylation of acylrhodium intermediates and b) difficulty in controlling the regioselectivity of insertion into alkynes/alkenes.¹ Accordingly, the development of alternative catalytic hydroacylation systems is required to avoid these problems.^{1d}

Recently, Hashmi et al. pioneered formal hydroacylation⁴ terminal alkynes catalyzed by Au utilizing their of nucleophilicity through aldehyde-alkyne-amine coupling (A³coupling) and hydration (work-up), which is completely different from classical Rh-catalyzed hydroacylation (Figure 1b).^{5,6} Since this formal hydroacylation does not involve an oxidative addition step or an insertion step, no decarbonylation or regioselectivity problems are observed. Since then, precious-metal-free formal hydroacylation reactions using Cu catalysts have been developed.⁷ However. these A³-coupling systems require the use of transition-metal catalysts and (super)stoichiometric amounts of amines. Interestingly, when the Favorskii reaction,⁸ *i.e.*, the addition of terminal alkynes to carbonyl compounds to afford propargylic alcohols using strong bases, e.g., KOH,^{8a,b} 'BuOK,^{8c,e} and Bu₄NOH,^{8f} is performed using an aromatic aldehyde as the substrate, the side reaction to produce an α , β -unsaturated carbonyl compound occurs.⁹ This side reaction can be regarded as a transition-metal-free formal hydroacylation; however, these systems require strong basic conditions, and the substrate scopes are quite limited.

In the present study, we successfully achieved, for the first time, transition-metal-free formal hydroacylation of

terminal alkynes catalyzed by a commercially available Mg₃Al–CO₃-layered double hydroxide $(Mg_6Al_2(OH)_{16}(CO_3) \cdot 4H_2O,$ hereafter termed Mg₃Al-CO₃ LDH) through nucleophilic addition/prototropy utilizing the unique basicity and ionicity of Mg₃Al-CO₃ LDH (Figure 1c). Mg₃Al-CO₃ LDH is well known as a solid base catalyst and is composed of cationic metal hydroxide layers $([Mg_6Al_2(OH)_{16}]^{2+})$ and hydrated anion lavers ([(CO₃)·4H₂O]²⁻).¹⁰ However, to the best of our knowledge, nucleophilic addition of alkynes or prototropy in propargylic alcohols promoted by Mg₃Al-CO₃ LDH has not been reported. Mg₃Al-CO₃ LDH shows moderate basicity¹⁰ compared to the strong bases typically used for the Favorskii reaction. This indicates a broad substrate scope in this system, which we have demonstrated using 22 examples. In this method, products possessing substituent patterns opposite to those obtained condensation,4a-c through hydration/aldol nucleophilic addtion/Meyer-Schuster rearrangement,4d,e or aldehyde-alkyne metathesis^{4f-i} are produced (Figure S1). In addition, the present catalysis is truly heterogeneous and the LDH catalyst can be reused without severe loss of its catalytic activity; thus, the system is also environmentally friendly.

Initially, the synthesis of (E)-4'-methoxychalcone (**3aa**) from *p*-anisaldehyde (**1a**) and phenylacetylene (**2a**), *i.e.*, the formal hydroacylation of **2a** using **1a**, was carried out in the presence of various solid base catalysts in toluene at 100 °C under an Ar atmosphere (Table 1). Surprisingly, of the catalysts examined, namely Mg₃Al–CO₃ LDH (Mg/Al = 3), HAP, Mg(OH)₂, Ca(OH)₂, MgO, CaO, ZnO, Al₂O₃, CeO₂, ZrO₂, and TiO₂, **3aa** was afforded only when Mg₃Al–CO₃ LDH was used (Table 1, entries 1 and 3–12). An LDH with an Mg/Al ratio of 2 also showed the catalytic activity whereas the use of an LDH with an Mg/Al ratio of 4 or Mg₃Al–CO₃ LDH calcined at 200, 300, or 400 °C hardly afforded **3aa**, indicating that

starting from 1a and 2a^a



(c) This Work: Transition-Metal-Free Formal Hydroacylation of Terminal Alkynes



Figure 1. Hydroacylation of alkynes/alkenes. (a) Classical hydroacylation catalyzed by Rh. (b) Formal hydroacylation of terminal alkynes *via* A³-coupling. (c) This work: Transition-metal-free formal hydroacylation of terminal alkynes catalyzed by an Mg₃Al–CO₃-layered double hydroxide.

the ionic layered structure of the LDH is important for the present formal hydroacylation (Table S1, entries 1–5, XRD patterns presented in Figure S2). The partial exchange of interlayer anions from CO_3^{2-} to CI^- decreased the yield of **3aa**, indicating that the basicity of the interlayer anion also affected the catalytic activity (Table S1, entry 6). Moreover, in the presence of K₂CO₃, Na₂CO₃, or *i*Pr₂EtN, the formal hydroacylation did not proceed at all (Table S1, entries 7–9). The effect of solvents on the formal hydroacylation was found to be remarkable, with low-polarity solvents such as methoxycyclopentane, PhCF₃, and toluene being effective (Table S2, entries 1–15). Once the temperature, the amount of the catalyst, and the reaction time had been optimized, the yield of **3aa** reached 87% (Table 1, entry 2 and Table S2, entries 16–18).

To investigate the notable effect of catalysts on **3aa** synthesis, the interaction between the solid bases and **2a** was

- 1a	н + н – - 2а	Catalyst Toluene, 100 °C 5 h, Ar (1 atm)		Jaa Jaa
entry	catalyst	conv. (%)		yield (%)
		1a	2a	3aa
1	Mg ₃ Al-CO ₃ LDH	55	52	42
2^b	Mg ₃ Al–CO ₃ LDH	99	96	87
3	HAP	<1	1	<1
4	Mg(OH) ₂	<1	3	<1
5	Ca(OH) ₂	4	8	<1
6	MgO	1	5	<1
7	CaO	<1	2	<1
8	ZnO	<1	<1	<1
9	Al ₂ O ₃	10	6	<1
10	CeO ₂	6	1	<1
11	ZrO ₂	5	<1	<1
12	TiO ₂	<1	3	<1

Table 1. The effect of solid catalysts on the synthesis of 3aa

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base catalyst (100 mg), toluene (2 mL), Ar balloon (1 atm), 100 °C, 5 h. Yields and conversions were determined by GC using biphenyl as an internal standard. ^bCatalyst (130 mg), 120 °C, 15 h. HAP = hydroxyapatite.

examined (Scheme 1 and Figure S3). When the solid bases were stirred with 2a under the optimal reaction conditions for 2 h, those that exhibited the catalytic activity became colored, whereas the others exhibited no apparent change (except for CeO₂). Conversely, when diphenylacetylene, an internal alkyne, was stirred with Mg₃Al-CO₃ LDH or CeO₂, the color of Mg₃Al-CO₃ LDH did not change, whereas that of CeO₂ became almost the same as when CeO₂ interacted with 2a, demonstrating the interaction between CeO_2 and the C=Cbond of alkynes (Figure S4).¹¹ Therefore, the coloring interaction of Mg₃Al-CO₃ LDH with 2a likely occurred through alkynyl species generated by deprotonation of terminal alkynes. When Mg₃Al-CO₃ LDH (100 mg) was stirred with 2a (0.5 mmol) for 16 h (termed LDH-2a, colored reddish),¹² the amount of **2a** incorporated into the LDH was *ca*. $3 \,\mu mol$ (determined by GC analysis after dissolution of LDH– 2a with 1 M HCl followed by extraction of 2a with CHCl₃). When the reaction of 1a and LDH-2a was conducted under the optimized conditions, 3aa was formed in 67% yield based on the amount of 2a contained in LDH-2a (Figure S8). In addition, ¹H NMR analysis indicated that H/D exchange

Scheme 1. H/D exchange of 2a with D_2O using Mg₃Al-CO₃ LDH or Al₂O_{3^{*a*}} and their images before/after stirring with 2a.

"Reaction conditions: **2a** (0.5 mmol), base catalyst (100 mg), toluene-d₈ (2 mL), D₂O (50 μ L), Ar (1 atm), 100 °C, 2 h.



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59 60 between **2a** and D₂O occurred using either Mg₃Al–CO₃ LDH or Al₂O₃, regardless of their catalytic activities for **3aa** synthesis (Scheme 1 and Figure S9). Considering these results, catalytic amounts of alkynyl nucleophilic species are probably formed by the basicity and stabilized by the ionicity of Mg₃Al–CO₃ LDH, which promotes the nucleophilic addition of alkynes to aldehydes unlike other solid catalysts¹³.

To establish whether the observed catalysis occurred heterogeneously on Mg₃Al-CO₃ LDH or arose from leached species in the solution, the catalyst was removed by hot filtration during the reaction, and the reaction was restarted with the filtrate under the same conditions. As expected, the production of 3aa immediately ceased upon removing the catalyst (Figure S11). Additionally, after the reaction, the filtrate was analyzed using inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and Mg and Al species were hardly detected (Mg < 4 × 10⁻⁶%, Al < 4 × 10⁻³%). Thus, the observed catalysis for the present formal hydroacylation is truly heterogeneous. Furthermore, the Mg₃Al-CO₃ LDH can be easily retrieved from the reaction mixture by simple filtration. The retrieved Mg₃Al-CO₃ LDH can be reused after washing the catalyst with acetone for the reaction of 1a and 2a at least three times without significant loss of catalytic activity (Table S4).14

Table 2. Substrate scope under the optimized conditions^a



^{*a*}Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Mg₃Al–CO₃ LDH (130 mg), toluene (2 mL), Ar balloon (1 atm), 120 °C, 15 h. GC Yields of the (*E*) isomers are displayed below chemical structures without parentheses. The values in parentheses are isolated yields. ^{*b*}The average value of two or three runs is displayed. ^c16 h. ^{*d*}24 h. ^{*c*}Mg₃Al–CO₃ LDH (200 mg). ^{*f*}The isolated yield includes the (*Z*) isomer (2–6%).



Figure 2. Mechanistic studies on the present formal hydroacylation. Reaction conditions are indicated, and yields were determined by GC. (a) Nucleophilic addition of 2a to 1n. (b) Rearrangement from 4da. (c) LDH-catalyzed formal hydroacylation using D-2a. (d) LDH-catalyzed formal hydroacylation using D-1d.

Next, the substrate scope of the present system was investigated. Under the optimized reaction conditions, the formal hydroacylation using various aromatic aldehydes (1) and aromatic alkynes (2) proceeded efficiently to produce α , β unsaturated ketones (3) in an (E)-selective fashion (Table 2).¹⁵ The desired products were isolated by simple column chromatography on silica gel (see Supporting Information).¹⁶ When benzaldehydes substituted with a methoxy group at the o-, m-, or p-position were used as the substrates, the formal hydroacylation proceeded efficiently to give the corresponding chalcones in high yields (3aa-3ca). Naturally, benzaldehyde can also be used as the substrate (3da). The use of benzaldehydes with different substituents, including methyl, trifluoromethyl, chloro, bromo, and amino groups, was also possible with this system (3ea-3ia). Moreover, owing to the mild basicity of Mg₃Al-CO₃ LDH,¹⁰ benzaldehydes possessing cyano or ester groups, for which it is difficult to react efficiently in strongly basic media, can be utilized (3ja and 3ka). When furfural was used as the substrate, the corresponding enone was obtained (31a). As well as 2a, a range of aromatic terminal alkynes can also be used for the present formal hydroacylation. Phenylacetylenes with a chloro group at the o-, m-, or p-position and benzaldehyde were successfully converted into the corresponding chalcones (3db-3dd). The formal hydroacylation proceeded efficiently even when using phenylacetylenes bearing a bromo, fluoro, methoxy, or pentyl group as the substrates Furthermore, 2-ethynylpyridine (3de-3dh). or 3ethynylthiophene can be formally hydroacylated by benzaldehyde (3di and 3dj). Using 4-formylbenzonitrile and 1-ethynyl-4-methoxybenzene, the corresponding multi-substituted chalcone can be synthesized (3jg). However, this system could not be applied to aliphatic aldehydes or aliphatic alkynes (3ma and 3dk).17

The most likely reaction mechanism of the present formal hydroacylation is the nucleophilic addition of the alkyne to the aldehyde to produce a propargylic alcohol followed by the

alcohol's rearrangement into an α , β -unsaturated carbonyl compound. However, no propargylic alcohol was detected during any of these formal hydroacylations. Thus, to investireaction path, the reaction of 2,2,2gate the trifluoroacetophenone (1n) and 2a was carried out under the optimized conditions (Figure 2a). Consequently, the corresponding propargylic alcohol (4na) was produced in moderate yield because the final rearrangement did not occur as it is a tertiary propargylic alcohol. In addition, using 1,3diphenylprop-2-yn-1-ol (4da) as the substrate, the corresponding α , β -unsaturated carbonyl compound (3da) was obtained in 59% yield less than 10 min after the reaction started (Figure 2b).^{18,19} At the same time, 4da was quantitatively converted (i.e., it was undetectable by GC), and the Mg₃Al-CO₃ LDH became colored, suggesting that 4da was rapidly deprotonated and adsorbed onto the Mg₃Al-CO₃ LDH. These results are consistent with the fact that propargylic alcohols cannot be observed when the present formal hydroacylation is conducted. Thus, the nucleophilic addition/rearrangement mechanism was strongly supported. Furthermore, when the reaction of 1a and phenylacetylene-d₁ (D-2a) was carried out under the optimized conditions, no deuterated 3aa was produced (Figure 2c and ¹H NMR spectra in Figure S14); when the reaction of benzaldehyde- α -d₁ (**D-1d**) and **2b** was carried out under the optimized conditions, α -deuterated **3db** was produced, for which the H/D ratio determined by ¹H NMR was 60:40 (Figure 2d and Figure S15). Thus, the rearrangement of propargylic alcohols catalyzed by Mg₃Al-CO₃ LDH most likely occurred through prototropy^{9b,c,20} rather than hydride transfer.⁹⁴

Given previous reports^{9b,c,20} and the results above, we propose a plausible reaction mechanism of the present Mg₃Al– CO₃ LDH-catalyzed formal hydroacylation as follows (Figure S16). Nucleophilic addition of the alkynyl species catalytically produced owing to the basicity and ionicity²¹ of Mg₃Al– CO₃ LDH to the aldehyde affords a propargylic alcohol. Then, a delocalized carbanion species is produced through deprotonation of the propargylic alcohol by Mg₃Al–CO₃ LDH. Subsequently, this species is protonated to produce an allenol, which immediately tautomerizes to give the formally hydroacylated product.

In summary, we have developed the first transition-metalfree/additive-free formal hydroacylation of terminal alkynes catalyzed by a commercially available Mg₃Al-CO₃ LDH. This efficient transformation is enabled by the unique ionicity and basicity of Mg₃Al-CO₃ LDH, which promotes both the nucleophilic addition of terminal alkynes and prototropy of propargylic alcohols effectively. This system is applicable to various combinations of substrates, even including those with cyano or ester groups, to produce a range of substituted α , β -unsaturated ketones. The present catalysis was confirmed to be truly heterogeneous, and the catalyst can be reused several times without loss of its catalytic activity. Considering the fact that hydroacylation is highly atomically economical, the present formal hydroacylation is clearly environmentally friendly. In addition, we believe that this novel catalysis that exploits the unique properties of Mg₃Al-CO₃ LDH will allow the development of novel organic reactions that utilize the specific properties of solid catalysts.

AUTHOR INFORMATION

Corresponding Author

*E-mail: kyama@appchem.t.u-tokyo.ac.jp

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Fax: +81-3-5841-7220

Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publication website: experimental details and compound characterization, aldehyde–alkyne coupling schemes, XRD patterns, photo images, NMR spectra, DR UV-vis spectra, FT-IR spectra, reaction using LDH–**2a**, reaction profiles, the proposed mechanism, tables presenting the effect of catalysts, solvents, and temperatures as well as results of reuse tests (PDF).

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(12) XRD patterns, DR UV-Vis spectra, and FT-IR spectra of LDH-2a (stirred for 15 h) and Mg₃Al-CO₃ LDH were shown in Figure S5-S7.

(13) When the reaction from **1a** and **2a** with benzoic acid was conducted under the conditions where 3aa yield reached 87% as of 24 h without benzoic acid, an induction period was observed, which was likely derived from the formation of alkynyl nucleophilic species on Mg₃Al-CO₃ LDH (Figure S10a). Also, when the amount of benzoic acid was increased from 20 mol% to 40 mol%, the initial rate after the induction period decreased linearly (Figure S10b,c). With 50 mol% of benzoic acid, the initial rate became close to zero, and the yield of 3aa was only 5% after 50 h, which was the same as that as of 24 h (Table S3), indicating that this system is catalytic.

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(14) The change of XRD patterns and appearances through the repeating use of Mg₃Al–CO₃ LDH indicated that the slight decrease of the catalytic performance was possibly caused by the adsorption of organic compounds (Figure S12).

(15) A larger scale (5 mmol) α , β -unsaturated ketone synthesis was also effective to produce **3aa** in 67% yield from **1a** and **2a** under the conditions described in Figure S13.

(16) The isolation of (*E*)-4'-(methoxycarbonyl)chalcone (**3ka**) as the sole compound was unsuccessful because the separation of **3ka** and methyl 4-formylbenzoate (**1k**) was quite difficult.

(17) When using cyclohexanecarboxaldehyde (1m) as the substrate, a
byproduct that seemed to be the corresponding propargylic alcohol
was obtained in 38% GC yield. When using 1-octyne (2k) as the substrate, 2k was hardly converted and no byproducts were also detected.
(18) The *E*/*Z* ratio of 3da was 86/14 as of 10 min. After 3 h, the *E*/*Z*

15 ratio became >99/<1 as with the present formal hydroacylation from aldehydes and alkynes (the yield of 3da also increased from 59% to 77%).
17 (10) Without any activity paiter the pusheaphilia addition of 2a to

(19) Without any catalysts, neither the nucleophilic addition of **2a** to **1n** nor the rearrangement of **4da** proceeded at all.

(20) For the reports on base-catalyzed isomerization of propargylic alcohols with electron withdrawing groups to enones, see: (a) Nine-ham, A. W.; Raphael, R. A. J. Chem. Soc. 1949, 0, 118-121. (b) Sonye, J. P.; Koide, K. Organic Base-Catalyzed Stereoselective Isom-erizations of 4-Hydroxy-4-phenyl-but-2-ynoic Acid Methyl Ester to (E)-and (Z)-4-Oxo-4-phenyl-but-2-enoic Acid Methyl Esters. Synth. Commun. 2006, 36, 599-602. (c) Sonye, P.; Koide, K. Base-Catalyzed Stereoselective Isomerization of Electron-Deficient Pro-pargylic Alcohols to E-Enones. J. Org. Chem. 2006, 71, 6254-6257. (d) Sonye, P.; Koide, K. Sodium Bicarbonate-Catalyzed Stereoselective Isomerizations of Electron-Deficient Propargylic Alcohols to (Z)-Enones. J. Org. Chem. 2007, 72, 1846-1848.

(21) The basicity necessary for the deprotonation of alkynes is derived from the metal hydroxide cationic layer ($[Mg_6Al_2(OH)_{16}]^{2+}$) and/or the anionic hydrated layer ($[(CO_3) \cdot 4H_2O]^{2-}$). The ionicity necessary for the stabilization of nucleophilic alkynyl anionic species is also derived from the metal hydroxide cationic layer ($[Mg_6Al_2(OH)_{16}]^{2+}$) and/or the anionic hydrated layer protonated from alkynes ($[(HCO_3) \cdot 4H_2O]^{-}$).

TOC graphic



✓ Good Regioselectivity ✓ Reusable Heterogeneous Catalyst