Synthesis of α,β -unsaturated ketones through nickel-catalysed aldehyde-free hydroacylation of alkynes

Joon Ho Rhlee

Ulsan National Institute of Science and Technology

Saikat Maiti

Ulsan National Institute of Science and Technology

Ho Seung Lee

Ulsan National Institute of Science and Technology

Soochan Lee

Ulsan National Institute of Science and Technology

Jaehyun Park

Ulsan National Institute of Science and Technology

Seok Ju Kang

Columbia University <https://orcid.org/0000-0002-9921-6674>

Yung Sam Kim

Ulsan National Institute of Science and Technology <https://orcid.org/0000-0001-6306-7438>

Jeong Kon Seo

Ulsan National Institute of Science and Technology

Kyungjae Myung

Institute for Basic Science (IBS)

Wonyoung Choe

Ulsan National Institute of Science and Technology

Sung You Hong (✉ syhong@unist.ac.kr)

Ulsan National Institute of Science and Technology <https://orcid.org/0000-0002-5785-4475>

Article

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Abstract

α,β -Unsaturated ketones are common feedstocks in functional materials, pharmaceuticals and natural compounds. Transition metal-catalysed hydroacylation reactions of alkynes using aldehydes have been widely applied for the atom-economical synthesis of α,β -unsaturated ketones through chemoselective aldehydic C–H activation. However, previous hydroacylation reactions using rhodium, cobalt, or ruthenium catalysts require chelating moiety-bearing aldehydes to prevent undesired decarbonylative product via an unstable acyl-metal-H complex. Herein, we report a nickel-catalysed reductive and anti-Markovnikov selective coupling process to afford non-tethered *E*-enones from terminal alkynes through an acyl-nickel-thiopyridine complex in the presence of zinc metal as a reducing agent. Utilization of a thioester as an acylating agent and water as a hydrogen donor enables this mechanistically distinctive and aldehyde-free hydroacylation of terminal alkynes under mild reaction conditions at room temperature, with a broad substrate scope including versatile functional groups and even simple aryl and alkyl moieties.

Introduction

α,β -Unsaturated ketones have been extensively applied as versatile compounds in synthetic organic chemistry, for example, as key substrates for conjugate addition^{1–4}, Morita–Baylis–Hillman^{5,6}, Diels–Alder^{7,8}, and epoxidation^{9–11} reactions. They have been conventionally prepared through aldol condensation¹², Horner–Wadsworth–Emmons olefination¹³, the dehydrogenation of ketones^{14,15}, or palladium-catalysed carbonylation^{16,17} reactions. However, these methods often require pre-functionalized substrates or operate through multi-step sequences. Alkynes have widely applied as readily available synthetic platforms for catalytic transformations to directly access functionalized cyclic or acyclic products^{18–22}. The catalytic hydroacylation of alkynes using aldehydes inherently provides an atom-economical process leading to the formation of enones. Organocatalytic intramolecular hydroacylation reactions of alkynes using organophosphines or *N*-heterocyclic carbenes have been demonstrated (Fig. 1a)^{23–25}. Metal-catalysed intermolecular hydroacylation has emerged as a prominent method for rapidly accessing *E*-enones through alkyne–aldehyde coupling^{26–31}. This atom-economical method involves the chemoselective activation of an aldehydic C(*sp*²)–H, and chelating moiety-bearing aldehydes have been applied to prevent decarbonylative side pathways (Fig. 1b).

Stabilization of an acyl-metal complex assisted by heteroatom chelation is a powerful strategy for obtaining *E*-enones. However, the installation and removal of the coordinating moieties entailed extra synthetic steps while reducing the step economy of the hydrofunctionalization. Though nondirected hydroacylation methods have been developed for alkenes or dienes^{32–36}, to our knowledge, there is no general hydroacylation method for unactivated terminal alkynes that lead to chelating moiety-free *E*-enones. Recently, the Weix group reported that 2-thiopyridyl esters act as potential acyl donors for cross-electrophile coupling reactions³⁷. We surmised that a thioester may act as both a transient thiopyridyl (SPy) ligand and an acyl component under nickel-catalysed reductive coupling conditions to lead to acyl-

Ni-SPy complex. A consecutive alkyne insertion and subsequent protodemetalation process may lead to hydroacylation product formation (Fig. 1c). However, the challenges of this anticipated reaction process to attain traceless alkyne hydroacylation are fourfold: (i) competition with non-conjunctive cross-electrophile (proton and thioester) coupling, (ii) reduction of substrates, (iii) iterative alkyne additions, and (vi) regio- and stereoselectivity issues. Therefore, precise reactivity and selectivity control is crucial for a general approach to the hydroacylation of unactivated terminal alkynes.

Results

Optimisation studies. To optimize the reaction conditions, *S*-(pyridin-2-yl) 4-methoxybenzothioate (**1**) and 3,3-dimethyl-1-butyne (**2**) were chosen as model substrates, and a thorough screening of catalysts, reducing agents, additives, and solvents was conducted (Table 1, see also the Supplementary Information, Section III). The standard conditions were established on the basis of inexpensive nickel(II) perchlorate hexahydrate, Zn, and ZnCl₂ in 1,2-DME to exclusively afford *E*-enone **3** in 81% isolated yield at room temperature (entry 1). The use of THF resulted in a similar yield (entry 2). Interestingly, coordinated water molecules were also found to be a suitable proton source (entries 3–5). The use of 17 mol% of Ni catalyst was appropriate for providing a stoichiometric 1 equiv of protons to the reaction. No desired product formation was observed in the absence of the nickel catalyst, Zn, or ZnCl₂ (entries 6–8). Mn as the reducing agent instead of Zn also appeared successful; however, this resulted in a diminished yield (entry 9). ZnCl₂ was found to be superior to MgCl₂ (entry 10). Using 1.5 equiv of terminal alkyne **2** was required for better conversion of the thioester (entry 11). The standard optimized reaction conditions were developed under an inert argon atmosphere; however, a significant amount of product formation was observed even under open atmosphere conditions (entry 12). Reduced reaction time or a decreased amount of Ni catalyst led to diminished yields (entries 13, 14). In addition, the employment of acyl chloride or aldehyde as an acyl donor instead of thioester appeared to be completely unproductive (entries 15, 16). Additional ligands in the hydroacylation resulted in slightly diminished yields (entries 17, 18).

Scope of the reaction. With the optimized conditions in hand, we set out to explore the generality of this alkyne hydroacylation by determining the thioester scope (Table 2). Various alkyl substituents worked well to afford *E*-enone products (**5–8**) in moderate to good yields. Hydrogen and phenyl groups, however, led to slightly lower yields (**4, 9**). Generally, electron donating groups gave the products in moderate to good yields (**10–13**). Although yields were low, halide groups were tolerated in the reaction (**14–16**). Electron withdrawing groups such as CO₂Me and CF₃ led to products (**17, 18**) with low yields. *Meta*- and *ortho*-substitution patterns also provided the products in moderate yields (**19–24**). A 2-naphthyl substituent afforded the product in a slightly higher yield (44%) than a 1-naphthyl substituent (32%) (**25, 26**). An electron-rich indole substituent led to product **27** with 82% yield. Both acyclic- and cyclic aliphatic substituents could access the products with moderate yields (**28–32**).

We then examined the scope of a wide range of alkynes. Acyclic- as well as cyclic aliphatic terminal alkynes underwent the reaction to afford the corresponding vinyl ketones (**33–38**) in moderate yields, although cyclopropyl- and cyclopentyl-derived alkynes gave the diminished yields. Aromatic alkynes bearing alkyl, phenyl, and phenoxy substituents worked well to give the desired products (**39–45**) with moderate to good yields. *Ortho*-, *meta*-, and *para*-substituted methoxy groups were also tolerated to obtain the products (**46–48**). Product **49** was isolated in 55% yield by using a disubstituted arylalkyne. Fluoro- and chloro- groups were examined and gave **50** and **51** in 69% and 56% yields, respectively. The strongly electron withdrawing trifluoromethyl group led to product formation (**52, 53**) with diminished yields. 2-Ethynyl-6-methoxy-naphthalene efficiently produced **54** in 76% yield. 2-Ethynylthiophene and 3-ethynylthiophene underwent the reaction smoothly to obtain the corresponding products (**55, 56**) in 39% and 58% yields, respectively. A free hydroxyl group was compatible affording **57** in 62% yield. We were delighted to find that the reaction was feasible with ethisterone, an agent for gynecological disease treatment, to afford **58** in 56% yield. The chemistry was also operative on a 1 mmol scale to give a similar yield. Interestingly, symmetrical as well as unsymmetrical internal alkynes gave hydroacylation products (**59–61**), albeit in low yields. Activated alkenes also underwent the reaction very smoothly to afford **62–64** in good yields.

Mechanistic investigations and deuterium labeling experiments. Control experiments were conducted to gain the insight into the reaction pathway. When TEMPO was added under the standard reaction conditions, the desired hydroacylation completely shut down and an acyl-TEMPO adduct (**65**) was isolated in 70% yield. This study corroborates the involvement of an acyl radical intermediate during the course of the reaction (Fig. 2a). Remarkably, formation of the acyl-TEMPO adduct was also observed by employing Zn and ZnCl₂ in the absence of any nickel catalyst, indicating its role in acyl radical generation from the thioester through single-electron transfer (SET). The formation of hydroacylation product **60** suggests the protodemetalation of nucleophilic vinyl nickel complex **I**³⁸. Interestingly, formation of **66** was also observed verifying an iterative double alkyne insertion (Fig. 2b). In addition to this, cyclic product **67** was isolated illustrating the intermediacy of vinyl nickel species **II**^{39,40}. To identify the proton source of the hydroacylation, deuterium labeling tests were performed (Fig. 2c). First, a reaction conducted using deuterium oxide (3.0 equiv) resulted in formation of the product with 64% and 33% [D] incorporation at the b- and α-positions, respectively, of unsaturated ketone [D]-**3**. Employing deuterated nickel(II) perchlorate hexahydrate resulted in the similar ratio of ~1.9:1 (i.e. 38%:20%, see also the Supplementary Information, Section V). To confirm the non-involvement of solvent molecules, we performed the hydroacylation reaction using deuterated THF, and no D-incorporation was detected in the final product. The employment of terminally deuterated alkyne [D]-**2** for the Ni-catalysed reductive coupling reaction also demonstrated H–D exchange resulting from the weak acidity of the terminal alkyne^{41,42}.

Proposed mechanism. Based on the above mechanistic studies and findings from previous reports^{38–40,43,44}, we proposed a reaction pathway for this reductive hydroacylation as illustrated in Fig. 3. The reaction is initiated by the generation of an acyl radical and a thiopyridyl anion through the single-electron reduction of a redox-active thioester promoted by Zn and ZnCl₂. The SPy anion can undergo a consecutive ligand exchange reaction with the nickel(I)X **A**, which is generated *in-situ* from the reduction of the Ni(II)X₂ pre-catalyst by Zn/ZnCl₂. Engagement of the acyl radical with intermediate **A** directs the formation of acyl-Ni(II)-X complex **B**. Migratory insertion of terminal alkynes gives rise to vinyl nickel complex **D**. Then, protodemetalation of nucleophilic vinyl Ni(II) species **D** with the help of water affords the desired *E*-enone³⁸. The reduction of Ni(II)(OH)X species **E** by zinc regenerates the active Ni(I) species **A**.

Conclusions

In summary, we have demonstrated a nickel-catalysed hydroacylation approach using terminal alkynes to exclusively afford non-tethered *E*-enones. This nondirected and aldehyde-free process proceeds by the single-electron reduction of a redox-active 2-pyridyl thioester to give an acyl radical that is promoted by Zn/ZnCl₂. It requires neither additional steps for removal of the coordinating group, nor use of a nucleophilic hydride source, further enhancing the efficacy of the method. We anticipate that these Ni-catalysed reductive hydroacylation reactions will have an impact on synthesizing important synthetic intermediates, functional materials and pharmaceuticals.

Methods

General experimental procedure for *E*-enones. A 1-dram screw-cap vial equipped with a magnetic stir bar was charged with thioester (0.2 mmol, 1.0 equiv), Zn (33 mg, 0.5 mmol, 2.5 equiv), ZnCl₂ (27 mg, 0.2 mmol, 1.0 equiv), and Ni(ClO₄)₂·6H₂O (12 mg, 0.034 mmol, 17 mol%) inside a glove box. The mixture was dissolved in 1,2-DME (1 mL). Then, alkyne (0.3 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 24 h at room temperature. After completion of the reaction, the mixture was purified by flash column chromatography to afford the desired product.

Data availability

Detailed experimental procedures, HRMS-ESI data and NMR spectra (PDF) for all compounds were provided in the Supplementary Information. Single crystal X-ray data for **27** and **67** (CIF) are available free of charge from the Cambridge Crystallographic Database Centre (CCDC) under reference numbers 2039192 and 2036543.

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Declarations

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Author contributions

J.H.R., S.M., K.M., and S.Y.H. conceived the project. J.H.R., S.M., and H.S.L. prepared substrates, and examined the catalytic reactions. S.L. and W.C. solved single crystal X-ray structures of compounds **27** and **67**. J.H.R., J.P., S.J.K., Y.S.K., and J.K.S. worked on analytical sections for the mechanistic and deuterium labeling experiments. J.H.R., S.M., and S.Y.H. wrote the manuscript. All authors discussed results and provided input on the manuscript.

Competing interests

The authors declare no competing interests.

Tables

Tables 1 and 2 are available in the Supplementary Files.

Figures

a Intramolecular organocatalytic approach

b C–H activation approach

c This Work: **nondirected and aldehyde-free approach**

Figure 1

Hydroacylation of alkynes. Previous works: aldehyde-alkyne coupling. a, Intramolecular organocatalytic approach. b, C–H activation approach. c, this work: non-directed and aldehyde-free approach.

a Trapping of acyl radical

b Iterative alkyne insertion

c Deuterium labeling

Figure 2

Mechanistic and deuterium labeling studies. a, Trapping of acyl radical. b, Iterative alkyne insertion. c, Deuterium labeling.

Figure 3

Proposed mechanism of Ni-catalysed aldehyde-free alkyne hydroacylation

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