OL Organic Letters

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Photoredox–Ni Dual Catalysis: Chelation-Free Hydroacylation of Terminal Alkynes

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Cite This: *Org. Lett.* 2022, 24, 8435–8440 Read Online

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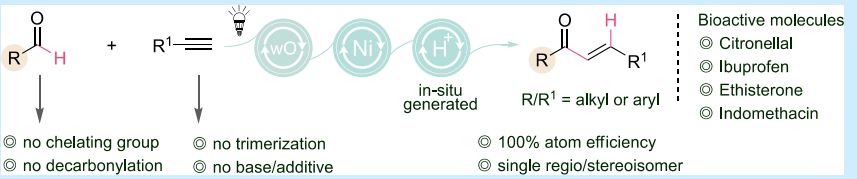


ABSTRACT: Hydroacylation of alkynes is undoubtedly the simplest and most atom-efficient approach for the synthesis of enones with diverse synthetic applications. Despite significant progress in hydroacylations, no hydroacylations exist that make use of aldehydes without a chelating group, especially when combined with terminal alkynes. Here we report a synergistic nickel–photocatalytic system that allows for the highly regio- and stereoselective hydroacylation of unactivated aldehydes and alkynes in milder conditions without the use of chelating groups.

High atom and step economy is a crucial criterion in chemical synthesis,[1] and the hydroacylation of alkenes and alkynes mediated by transition metals has emerged as a highly efficient and atom-economical process (Scheme 1a).[2] Hydroacylation of terminal alkynes with abundant and affordable aldehydes would generate α,β-unsaturated ketones, a ubiquitous structural motif in organic synthesis.[3] Although enones can be synthesized in a variety of ways, traditional protocols are limited by the need for strong bases or higher temperatures in multistep protocols (Scheme 1b).[4] While aldehydes without a chelating group are known to undergo hydroacylations with alkenes,[5] hydroacylation of terminal alkynes is confined to the use of chelating groups on aldehydes,[2d,6] adversely impacting the atom/step economy (Scheme 1c), and it is difficult to incorporate chelating groups for alkyl aldehydes. On the other hand, internal alkynes are known to undergo acylation via acyl radical intermediates (Scheme 1d).[7] There are currently no known methods for accommodating terminal alkynes and aldehydes in hydroacylations without chelating groups.

In the course of our studies on nickel[8] and dual nickel–photoredox[9] catalysis, we sought to address this difficult challenge by employing dual catalysis. Photocatalytic hydrogen atom abstraction (HAT) from an aldehyde can result in an open-shell acyl radical,[10] which can then be coupled with alkyne SOMOphiles in the presence of a nickel catalyst to produce the desired enone (Scheme 1e). Although conceptually appealing, the approach is notoriously problematic because nucleophilic open-shell acyl radicals may react more slowly with alkynes than with alkenes,[11] transitory acylnickel species may suffer decarbonylation, and controlling the regio/stereoselectivity may be challenging. The presence of multiple hydridic C–H bonds such as α-amino and α-oxy C–H bonds may reduce the chemoselectivity of the HAT event.

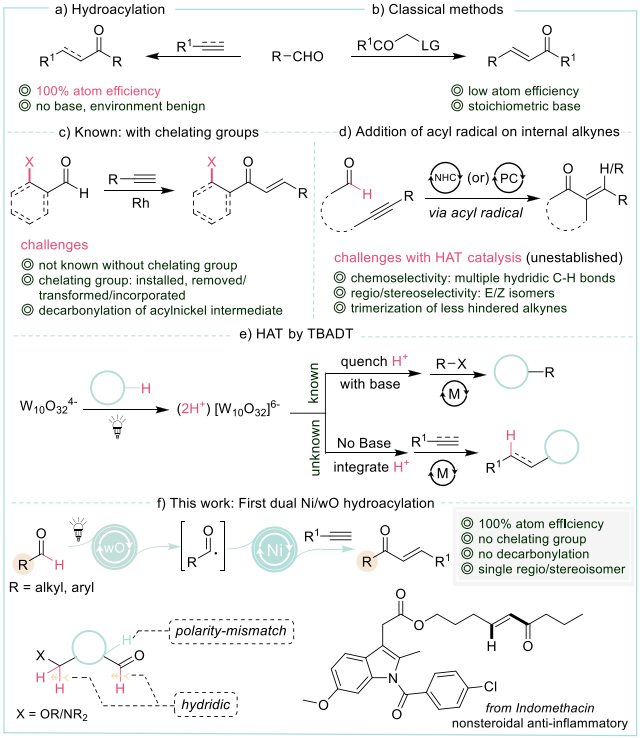
The affordable photocatalyst tetrabutylammonium decatungstate (TBADT) is a remarkable and very appealing photocatalyst that has been utilized in HAT events,[12] but it is typically combined with stoichiometric base to quench in situ-produced HX (X = Cl, Br).[13] A method that can circumvent stoichiometric bases and utilize the in situ-produced proton in the subsequent process has not yet been established. In this context, MacMillan, Rueping, and Wu have over time developed a dual nickel–photoredox catalytic system in which alkyl radicals are generated from carboxylic acids[14] or alkanes[15] and then added to alkynes to produce alkenes. Our group[9] and others have also detailed the photocatalytic generation of acyl radicals from aldehydes.[13a,b,16] Herein, for the first time, we demonstrate the successful realization of this concept by employing a dual catalytic system comprising an economical decatungstate photocatalyst in conjunction with a nickel complex, thereby enabling the highly regio- and stereoselective hydroacylation of alkyl/aryl aldehydes with activated/unactivated alkynes under mild conditions.

At the outset of our studies, we examined the reaction between alkyne **1a** and aldehyde **2a**, and the results are

Received: October 18, 2022
Published: November 7, 2022

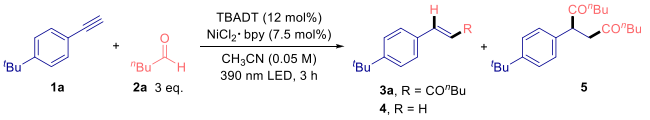
https://doi.org/10.1021/acs.orglett.2c03481
Org. Lett. 2022, 24, 8435–8440

Scheme 1. Hydroacylation of Alkynes



summarized in Table 1. Under the optimized reaction conditions involving 12 mol % TBADT and 7.5 mol % $NiCl_2$·bpy in acetonitrile, we observed a clean reaction with traces of byproduct **5** that were removed by silica chromatography. The use of bipyridine (bpy) proved extremely advantageous in preventing the formation of byproducts **4** and **5**. The ligand dtbpy exhibited poor selectivity, with considerable formation of the diacylated byproduct **5** (entry 2). Similarly, $NiBr_2$·bpy provided a moderate yield of **3a** (entry 3 vs 1), whereas $Ni(OAc)_2$·$4H_2O$ was not suitable (entry 6). The precomplex $NiCl_2$·bpy was superior to the in situ-generated complex: as can be seen from entries 4−6, moderate to poor yields were elicited with the in situ-generated complex derived from $NiCl_2$ or $Ni(OAc)_2$·$4H_2O$ or $NiCl_2$·glyme, and the increased amount of diacylated byproduct **5** indicates that the uncomplexed ligand trapped the in situ-generated HCl that is required to deliver the product **3a** (as discussed later). A change in the solvent concentration had a substantial impact on yield: decreasing the amount of solvent significantly lowered the yield while increasing the yield of byproduct **5**. We attribute this to the ability of acetonitrile to dissolve the in situ-generated HCl,[17] which is required to deliver the product **3a**. Furthermore, reactions were carried out by varying the loading of the catalyst and the ratio of TBADT to $NiCl_2$·bpy. According to entries 8−10, the optimal ratio between the catalysts is 1:1.6. Use of a wavelength greater than 390 nm lowered the reactivity and halted the conversion at 61% (entry 11). Furthermore, rigorous control experiments confirmed the vital roles of $NiCl_2$·bpy, TBADT, and light (entries 12−14). Lowering the amount of aldehyde also lowered the yield, from which we infer that the amount of HCl production was subsequently reduced (entry 15). Increasing the quantity of **2a** increased the amount of diacylated byproduct **5** (SI−S5). In order to study the impact of a protic solvent, we introduced 10

Table 1. Optimization of the Reaction Conditions



entry	deviation from standard conditions[a]	4, 5[b]	3a[b,c]
1	none	T, <5	92 (86[d])
2[e]	$NiCl_2$·dtbpy	<5, 11	63
3[e]	$NiBr_2$·bpy	T, 25	59
4[e]	$NiCl_2$ and bpy	10, 13	45
5[e]	$NiCl_2$·glyme and bpy	T, 19	61
6[e]	$Ni(OAc)_2$·$4H_2O$ and bpy	<5, 33	<5
7	CH_3CN (0.2 M)	<5, 21	27
8[e]	1.0:0.8 $NiCl_2$·bpy:TBADT	<5, T	49
9[e]	1.0:1.3 $NiCl_2$·bpy:TBADT	<5, 13	71
10[e]	1.0:2.0 $NiCl_2$·bpy:TBADT	7, 17	56
11	410 nm LED source	5, ND	61[f]
12	without $NiCl_2$·bpy	ND, ND	ND[f]
13	without TBADT	ND, ND	ND[f]
14	dark conditions	ND, ND	ND[f]
15	2 equiv of **2a**	T, 8	47
16	dry MeOH (10 equiv)	14, 12	46
17	degassed H_2O (5 equiv)	ND, ND	ND[f]
18	Cs_2CO_3 (1 equiv)	ND, ND	ND[f]
19	K_3PO_4 (1 equiv)	ND, ND	ND[f]

[a]Standard reaction conditions: 0.018 mmol of TBADT, 0.0112 mmol of $NiCl_2$·bpy, 0.15 mmol of **1a**, 0.45 mmol of **2a**, CH_3CN (3 mL), 390 nm LEDs. [b]GC yields. [c]>30:1 regioisomeric ratio and *E*/*Z* ratio. [d]Isolated yield. [e]7.5 mol % loading of Ni salt and ligand. [f]Unreacted **1a** was observed. Abbreviations: bpy, 2,2′-bipyridine; TBADT, tetrabutylammonium decatungstate; dtbpy, 4,4′-di-*tert*-butyl-2,2′-dipyridyl; T, traces; ND, not detected.

equiv of MeOH under the optimal conditions. As anticipated, MeOH promoted the formation of byproducts **4** and **5** (entry 16). The reaction was completely quenched by the addition of 5 equiv of degassed water (entry 17). Incorporation of base in the reaction medium resulted in no conversion of **1a** to **3a**, which implies the requirement of HCl in the medium to deliver the desired product (entries 18 and 19). A higher loading of TBADT was required to generate sufficient HCl throughout the reaction.

Having optimized the conditions, we turned our attention to expanding the range of substrates (Scheme 2). A broad spectrum of alkyl aldehydes were screened. Primary alkyl aldehydes **2a−i**, including long-alkyl-chain substrates, generated excellent yields of the cross-coupled products **3a−i**. The secondary alkyl aldehydes **2j−l** were equally effective, delivering the corresponding enones **3j−l** in very good isolated yields. Even the sterically bulkier cyclohexyl aldehyde **2l** produced alkene **3l** in 85% isolated yield. However, the incompatibility of the tertiary alkyl aldehyde pivaldehyde resulted in decarbonylation. As anticipated, aryl aldehydes **2m−q** were compatible, yielding the corresponding alkenes **3m−q** in moderate to good yields. Following the screening of a number of aryl aldehydes, it was determined that in general aryl aldehydes exhibited decreased reactivity compared with alkyl aldehydes. Although aryl bromides are known to undergo oxidative addition with low-valent nickel, we observed a chemoselective reaction with aldehyde **2p** in which bromide remained intact, indicating that HAT from aldehyde **2p** was faster than oxidative addition.

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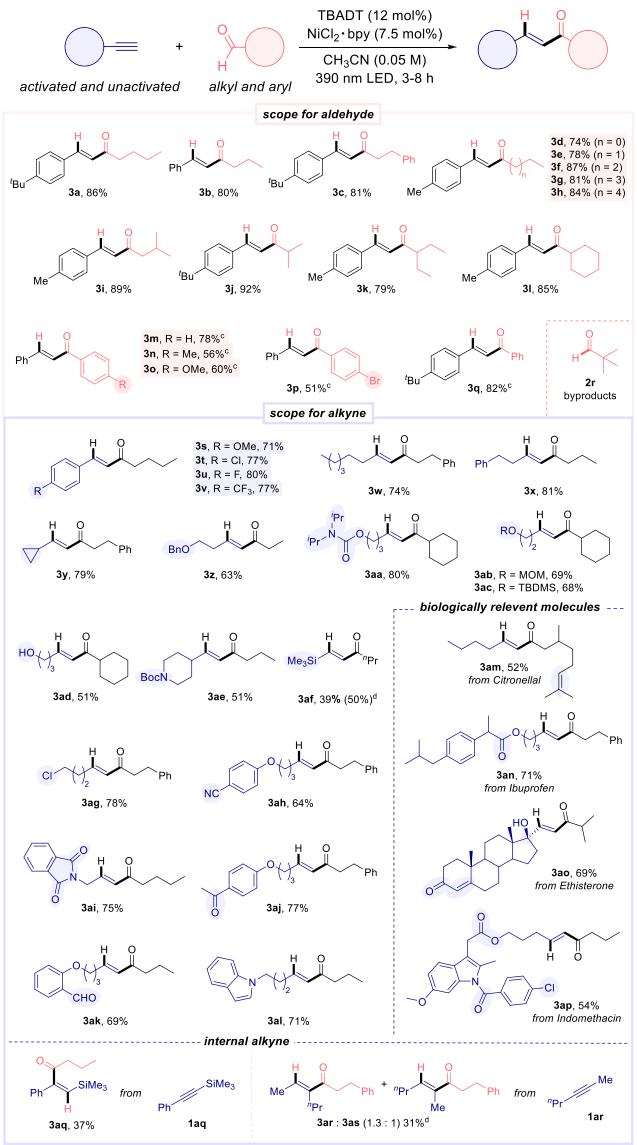
Org. Lett. 2022, 24, 8435−8440

Scheme 2. Substrate Scope[a,b]



[a]Conditions: 0.084 mmol of TBADT, 0.0525 mmol of $NiCl_2$·bpy, 0.7 mmol of **1**, 2.1 mmol of **2**, ACN (14 mL), 390 nm LEDs, 3 h. [b]>30:1 regioisomeric ratio and *E*/*Z* ratio. [c]The reaction time was 8 h. [d]NMR yield.

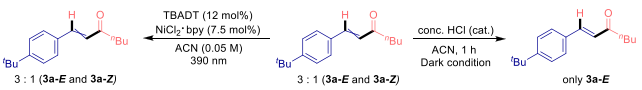
Having demonstrated the scope of aldehydes, we also screened a large library of alkynes. As expected, aryl alkynes **1s**−**v** with electron-withdrawing and -donating groups were compatible and gave good yields of the coupled products **3s**−**v**. Notably, terminal alkynes with sterically less hindered substitutions are prone to undergo cyclotrimerization under metallaphotoredox catalysis.[15] Therefore, hydroacylation of alkynes must be faster than cyclotrimerization. Fortunately, the unactivated and sterically less hindered alkynes were also equally reactive: long-alkyl-chain substrates **3w** and **3x** were isolated in yields of 74% and 81%, respectively. The substrate for a radical clock experiment, ethynylcyclopropane (**1y**), yielded the ring-unopened product **3y** in 79% yield, ruling out the intermediate vinylic radical.[18]

Alkynyl alcohols with various protecting groups, including benzyl (**1z**), carbamate (**1aa**), and TBDMS (**1ac**), were acylated efficiently under the optimized reaction conditions. The acid-sensitive MOM group was stable under the reaction conditions, resulting in a 69% isolated yield of the corresponding product **3ab**. Interestingly, the unprotected alcohol **1ad** did not impede the reaction, although a moderate yield of **3ad** was obtained. Intriguingly, the unstable Boc protecting group proved to be stable under the optimized conditions, and the product **3ae** was isolated in 51% yield. This allows for additional functionalization of the products through a variety of approaches. Functional groups such as trimethylsilyl (**1af**), chloride (**1ag**), nitrile (**1ah**), and imide (**1ai**) were also compatible, resulting in good yields of the products **3af**, **3ag**, **3ah**, and **3ai**, respectively. The compatibility of ketone derivative **1aj** to produce **3aj** in 77% isolated yield was also demonstrated. Interestingly, alkyne **1ak** containing an aldehyde functional group underwent chemoselective acylation to deliver the product **3ak** in 69% isolated yield, while the aryl aldehyde remained intact. We also carried out a competitive experiment that revealed a very high reactivity of alkyl aldehydes over aryl aldehydes (see SI section 6.5). Given the prevalence of indole derivatives in pharmaceuticals, substrates **3al** and **3ap** were synthesized in 71% and 54% yields, respectively. Despite the fact that weaker and polarity-mismatched α-carbonyl C−H bonds (in substrates **2a**−**l**) might be avoided in the kinetically controlled HAT event, hydridic C−H bonds such as α-amino and α-oxy C−H bonds can render the reaction complex. Pleasingly, no competing reactions involving α-amino and α-oxy C−H bonds were observed for substrates **3z**−**ae**. Pyridines and thiophenes are typically incompatible with this approach, resulting in complex mixtures. Structurally complex and bioactive molecules were also compatible, and the strategy was applied to the derivatization of bioactive molecules such as citronellal (**3am**), ibuprofen (**3an**), ethisterone (**3ao**), and indomethacin (**3ap**). To demonstrate the synthetic applicability of this method further, the reaction was conducted on a 3.5 mmol scale for substrate **1b**, and the product **3at** was isolated in 78% yield (p S27 in the SI). In an attempt to include internal alkynes,[19] trimethyl(phenylethynyl)silane (**1aq**) was exposed to the optimal conditions, and **3aq** was isolated as a single regiomer in 37% yield. Hex-2-yne (**1ar**) provided a 1.3:1 mixture of regiomers **3ar** and **3as** in 31% NMR yield. Further study is required to incorporate internal alkynes.

During the development of the strategy, we observed an inconsistent ratio between the *E* and *Z* stereoisomers, **3a-*E*** and **3a-*Z***. Fortunately, we discovered that the addition of HCl at the end of the reaction (after 8 h) produces a single *E* isomer (see SI section 5).[20] In order to confirm the acid-catalyzed isomerization, we subjected a 3:1 mixture of the *E* and *Z* isomers **3a-*E*** and **3a-*Z*** to catalytic concentrated HCl (Scheme 3) and observed complete conversion to **3a-*E*** after 1 h of stirring at room temperature.

We also carried out radical-trapping experiments, which confirmed the presence of acyl radicals in the medium (see SI section 6.4). As illustrated in Scheme 4, deuterium labeling studies revealed the participation of the protic solvent and aldehyde as hydrogen atom sources (see SI section 6.2).

Scheme 3. Acid-Catalyzed Isomerization



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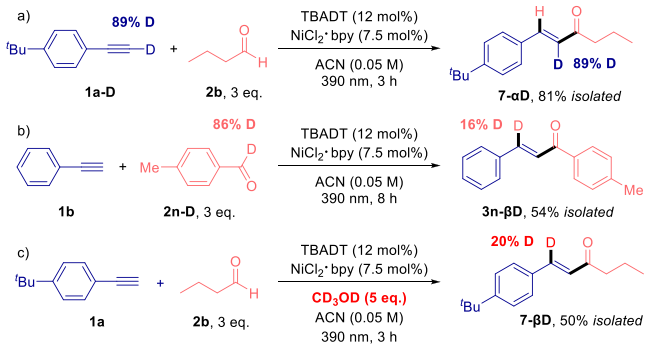
Org. Lett. 2022, 24, 8435−8440

Scheme 4. Deuterium Labeling Studies



On the basis of our observations, we postulated the mechanism shown in Figure 1. The catalytic cycle begins

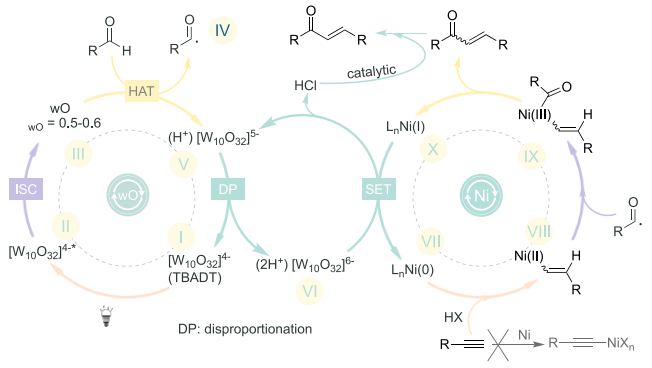


Figure 1. Mechanistic hypothesis.

with the excitation (I → II) of TBADT (LMCT: oxygen → tungsten) by the 390 nm LED, resulting in the formation of the short-lived excited species $[W_{10}O_{32}]^{4-*}$ (**II**). Subsequent intersystem crossing yields the long-lived triplet wO species **III** (II → III), which must be engaged in a HAT event (III → V) to produce transient acyl radical **IV** and $[W_{10}O_{32}]^{5-}$ (**V**). Intermediate **V** undergoes disproportionation to regenerate $[W_{10}O_{32}]^{4-}$ (**I**) and produce the strong reductant $[W_{10}O_{32}]^{6-}$ (**VI**),[9,13g,21] which generates low-valent Ni(0) complex **VII** from Ni(I) complex **X**; similar proposals were made in comparable endeavors. In the presence of HCl,[22] the **VII** can undergo oxidative insertion with the alkyne to generate vinylic nickel intermediate **VIII** (VII → VIII). Since vinylic metal species are expected to be configurationally stable, the insertion of the Ni(0) species into the alkyne (VII → VIII) is not a stereoselective reaction, resulting in the mixture of *E* and *Z* stereoisomers. Two alternate mechanisms cannot be ruled out: (i) oxidative acylation of the intermediate Ni(0) complex **VII** with the acyl radical and (ii) formation of nickel hydride[15,23] and subsequent addition to the alkyne. Oxidative acylation of the intermediate Ni(II) complex **VIII** with the acyl radical (VIII → IX) may produce the intermediate Ni(III) complex **IX**, which then undergoes reductive elimination to produce the final product enone. Although Ni(0) complex **VII** has been proposed as the active species, without further studies we cannot rule out the possibility that the Ni(I) complex is also an active species.

In conclusion, for the first time hydroacylation of terminal alkynes with aldehydes was established without the use of chelating groups. The methodology is completely atom-efficient and highly regio- and stereoselective. A diverse array of unactivated alkyl alkynes, alkyl aldehydes, and particularly aryl aldehydes can be incorporated, and numerous functional groups, including Boc, MOM, and silyl groups, are compatible. In contrast to alkyl aldehydes, aryl aldehydes react more slowly, and active methylene groups like O−CH_2 and N−CH_2 remained intact. The practical utility of the protocol has been demonstrated by conducting the reaction on a large scale and expanding the protocol to the derivatization of bioactive molecules.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03481.

Experimental details, characterization data of compounds, NMR spectra (PDF)

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Author Contributions

V.M., A.M., and G.V.A. performed the experiments. All of the authors contributed to manuscript writing and approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Council of Scientific and Industrial Research (CSIR) (02(0409)/21/EMR-II).

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