

# Nickel-Catalyzed Addition-Type Alkenylation of Unactivated, Aliphatic C–H Bonds with Alkynes: A Concise Route to Polysubstituted $\gamma$ -Butyrolactones

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**Supporting Information** 

**ABSTRACT:** Through the nickel-catalyzed chelation-assisted C–H bond activation strategy, the addition-type alkenylation of unreactive  $\beta$ -C(sp<sup>3</sup>)–H bonds of aliphatic amides with internal alkynes is developed for the first time to produce  $\gamma$ , $\delta$ -



unsaturated carboxylic amide derivatives. The resulting alkenylated products can further be transformed into polysubstituted  $\gamma$ butyrolactones with pyridinium chlorochromate (PCC).

Recently, transition-metal-catalyzed C–H bond activation has emerged as a highly effective strategy for the construction of synthetically enabling synthons and richly functionalized molecules.<sup>1–3</sup> The synthesis of  $\gamma$ , $\delta$ -unsaturated aliphatic carboxylic acids has been attracting much attention due to their versatility in organic transformations.<sup>4</sup> Both transition-metal-catalyzed  $\beta$ -C(sp<sup>3</sup>)–H addition of aliphatic acid derivatives with alkynes and olefination with alkenes would be ideal methods to enrich the diversity of structurally limited  $\beta$ -alkenyl carboxylic acid derivatives (Scheme 1a). In addition to step economy and simplicity, the addition-type alkenylation is also a highly atom-economical process because every atom of two substrates remains in the targeted molecule. Over the past

# Scheme 1. Transition-Metal-Catalyzed Chelation-Assisted $C(sp^3)$ -H Alkenylation

a) synthesis of  $\beta$ -alkenyl carboxylic acids by transition metal-catalyzed unreactive C(sp<sup>3</sup>)-H alkenylation with alkenes or alkynes





good functional group compatibility

- relatively broad ranges of aliphatic amides and internal alkynes
- removable directing group

few years, it was determined that the unactivated  $C(sp^3)$ -H bonds of aliphatic amides can efficiently couple with electrondeficient alkenes through the palladium-catalyzed chelationassisted C-H activation, albeit the resulting  $\beta$ - or  $\gamma$ -alkenyl carboxylic amides inevitably undergo tandem intramolecular hetero-Michael addition to result in lactams.<sup>5</sup> In contrast, the addition of  $C(sp^3)$ -H bonds of aliphatic acid derivatives with alkynes is still underrepresented. This is not surprising considering the following possible reasons. First, an alkyne can compete with a carboxylic acid derivative for access to the coordination sites at the metal center, which disturbs the cleavage of an unreactive  $C(sp^3)$ -H bond.<sup>6</sup> Second, the relatively strong  $\pi$ -coordination interaction of alkyne to the metal center may result in a higher barrier to migratory insertion of alkyne into cyclometalated species.<sup>7</sup> Although the addition of (hetero)aryl  $C(sp^2)$ -H bonds with alkynes has been well explored in recent years,<sup>8</sup> expansion this chemistry to  $C(sp^3)$ -H sites is doubtless a conceptual and practical challenging task. To the best of our knowledge, there is only one example describing the rhodium-catalyzed alkenylation of  $C(sp^3)$ –H bonds with internal alkynes, but the transformation is limited to the reactive benzylic  $\alpha$ -C(sp<sup>3</sup>)-H bond of 8methylquinoline.<sup>9</sup> The alkenylation of unreactive remote  $C(sp^3)$ -H bonds with alkynes still remains unsolved (Scheme 1b).

Nickel, an abundant and inexpensive transition metal, has shown potential in direct C–H bond functionalization.<sup>10</sup> Recent reports have demonstrated that nickel can efficiently catalyze the addition reactions of  $C(sp^2)$ –H bonds of electrondeficient heteroarenes and fluoroarenes with internal alkynes via a hydronickelation.<sup>8c,11</sup> In 2011, Chatani reported the Nicatalyzed chelation-assisted oxidative cycloaddition of  $C(sp^2)$ – H bonds of aromatic amides with alkynes via the formation of a bicyclic nickelacyle intermediate.<sup>12</sup> Recently, the nickel-





inexpensive metal catalyst system

catalyzed direct functionalization of unactivated  $C(sp^3)$ -H bonds has also achieved initial progress, including the dehydrogenative [4 + 2] cyclization of formamides with alkynes, and the arylation, alkylation, and intramolecular amidation of aliphatic amides.<sup>13</sup> Inspired by the above works, we surmised that addition-type alkenylation of unactivated  $C(sp^3)$ -H bonds with internal alkynes could be feasible with the assistance of a suitable bidentate directing group to form a bicyclic nickelacyle species (Scheme 1c).

Considering that 8-aminoquinoline is a highly efficient bidentate directing group in transition-metal-catalyzed C–H bond activation,<sup>10b,14</sup> our study was initiated with the reaction of 2,2-dimethyl-3-phenyl-N-(quinolin-8-yl)propanamide **1a** and 1,2-diphenylethyne **2a** (eq 1). To our delight, the desired



product 3a was obtained in 28% yield (E/Z = 1/2.8) in the presence of  $Ni(cod)_2$  and PPh<sub>3</sub> in toluene (Table S1, entry 1). The yield was decreased to less than 10% in the absence of PPh<sub>3</sub> (Table S1, entry 6). Other phosphine ligands proved to be less efficient (Table S1, entries 10-13). The addition of *i*-PrOH as cosolvent could improve the yield to 54% when  $Ni(OAc)_2$  was used instead of  $Ni(cod)_2$  (Table S1, entry 21).<sup>15</sup> Other nickel(II) sources such as  $Ni(acac)_2$  and  $Ni(OTf)_2$  gave diminished yields, and no desired product was afforded when NiCl<sub>2</sub> and Ni(dppe)Cl<sub>2</sub> were used (Table S1, entries 16-19). Finally, the alkenylated product could be obtained in 78% yield in the presence of  $Ni(OAc)_2$  (30 mol %) and PPh<sub>3</sub> (60 mol %) in a mixture of i-PrOH and toluene (1:5). Efforts to improve the yield proved fruitless by using other bidentate directing groups, such as pyridin-2-yl methanamine and 2-(methylthio)aniline (Table S1, entries 25-26). With the optimized conditions in hand, we next screened the substrate scope (Scheme 2). A range of 2,2-disubstituted propanamides bearing linear or cyclic chains were transformed into the alkenylated products in moderate to high yields (3a-d). It is noteworthy that the alkenylation only occurred at the  $C(sp^3)$ -H bond and the C(sp<sup>2</sup>)–H bond functionalization was not detected when 2phenyl substituted amides were attempted (3e and 3f). In addition to the methyl group adjacent to an  $\alpha$ -quaternary carbon center, the methyl adjacent to an  $\alpha$ -tertiary carbon center could also undergo the  $C(sp^3)$ -H bond alkenylation with an internal alkyne (3f). The reaction conditions exhibited good alkyne compatibility, and an E/Z value of up to 1:20 could be obtained (3g-r). The alkynes with both electrondonating and -withdrawing groups on the aromatic rings worked well, giving the corresponding products in moderate to high yields (3g-n). No obvious steric effect was found even with 1,2-di(naphthalen-2-yl)ethyne (30). The internal alkyne with a heteroaromatic moiety could also furnish the corresponding product in a high yield (3p). The reactions with unsymmetrical alkynes delivered the desired products in good yields (3q and 3r).

To gain insight into the reaction mechanism, H/D exchange reactions were carried out. When the reaction was performed with  $D_2O$  instead of an alkyne, 12% of the methyl hydrogen in **1c** was deuterated, thus indicating the C–H bond activation is reversible (Scheme 3, eq 2). When  $[D_3]$ -**1c** was subjected to the reaction conditions, 13% of the hydrogen on the resulting



<sup>*a*</sup>Reactions were carried out with Ni(OAc)<sub>2</sub> (30 mol %), PPh<sub>3</sub> (60 mol %), amide **1** (0.6 mmol), and internal alkyne **2** (0.2 mmol) in a mixture of *i*-PrOH (0.1 mL) and toluene (0.5 mL) at 170 °C for 24 h. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>The ratio of E/Z was determined by <sup>1</sup>H NMR. Q = 8-quinolinyl.

#### Scheme 3. Mechanistic Experiments



C=C bond was deuterated, which implied that the hydrogen source in protonolysis might come from the generated AcOH in the reaction system (eq 3). KIE (kinetic isotope effect) experiments were carried out with two independent reactions. The KIE value was found to be  $k_{\rm H}/k_{\rm D} = 1.0$ , indicating that the cleavage of the methyl C–H bond with a nickel species was not involved in the rate-determining step (eq 4). Based on the above results, a tentative mechanism of alkenylation was proposed in Scheme 4. Initially, a bidentate chelation process of

### Scheme 4. Plausible Mechanism of Alkenylation



amide 1 with a Ni(II) species forms complex IM1. The following  $C(sp^3)$ -H nickelation delivers the cyclometallic intermediate IM2, followed by a coordination of internal alkyne 2 to the nickel(II) center. The resulting intermediate IM3 undergoes a migratory insertion of the alkyne to lead to a seven-member metallacycle IM4. The sterically congested structure of IM3 is supposed to render the migratory insertion at higher temperature. After a protonation with AcOH (or *i*-PrOH if it exists), the product 3 is released, and the Ni(II) species is regenerated to accomplish a catalytic cycle.

The  $\gamma$ -butyrolactone framework is prevalent in naturally occurring products that often exhibit a diverse array of biological activities.<sup>16</sup> Despite significant progress made in the synthesis of such structures,<sup>17</sup> exploring an effective and concise synthetic alternative to construct polysubstituted  $\gamma$ -butyrolactones from the abundant, yet less functionalized molecules is still very attractive and desirable. Based on the alkenylation of the  $C(sp^3)$ -H bond of aliphatic amides, our effort was next devoted to the synthesis of polysubstituted  $\gamma$ -butyrolactones. A logical synthetic route to  $\gamma$ -butyrolactones should involve removal of the 8-aminoquinoline directing group/intramolecular annulation sequence. This tedious route prompted us to explore a more efficient and concise method. Inspired by PCCpromoted intramolecular alkoxyhydroxylation of alkenes to form cyclic ethers,<sup>18</sup> we deemed that a similar oxidative cyclization could occur with imidic acids, which are tautomerized from the corresponding amides, to furnish the lactone structure. Gratifyingly, when amide 3b reacted with PCC in CH<sub>2</sub>Cl<sub>2</sub> at 100 °C,  $\gamma$ -butyrolactone 4 was obtained in 78% yield in concomitance with the removal of the 8aminoquinoline moiety (eq 5). No desired product was



afforded when other oxidants, including ceric ammonium nitrate (CAN), 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ), phenyliodine diacetate (PIDA), and Dess-Martin periodinane, were employed (Table S2, entries 1-4).

After the feasibility of the synthetic approach to  $\gamma$ butyrolactones was evaluated, we investigated the substrate scope in the sequential  $C(sp^3)$ —H alkenylation/lactonization reactions (Scheme 5). It was found that electron-rich, -neutral, and -poor symmetrical diarylacetylenes all proceeded well to





<sup>*a*</sup>Reactions conditions: (1) Ni(OAc)<sub>2</sub> (30 mol %), PPh<sub>3</sub> (60 mol %), amide **1** (0.6 mmol, 1 M), internal alkyne **2** (0.2 mmol), *i*-PrOH/ toluene (1:5), 170 °C, 24 h. (2) PCC (5.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 100 °C, 48 h. <sup>*b*</sup>Two-step overall yields. The *dr* value was determined by <sup>1</sup>H NMR. <sup>*c*</sup>48 h were required in the alkenylation.

provide the desired products in satisfactory yields (5a-o). The structure of **5o** was confirmed by single crystal X-ray analysis. It is noteworthy that an array of functional groups including OCH<sub>3</sub>, Ac, and CO<sub>2</sub>Me were compatible with the reaction conditions, which could offer the opportunity for further transformations. The spiro  $\gamma$ -butyrolactone **5n**, a feature which often occurs in biologically active molecules, could also be formed in a moderate yield. Unsymmetrical alkynes were also investigated, and the corresponding products **5p** and **5q** were obtained in synthetically useful yields.<sup>19</sup>

Furthermore,  $\gamma$ , $\delta$ -unsaturated carboxylic amides have proven to be versatile synthons for organic transformations. Besides  $\gamma$ butyrolactones, the alkenylated products **3b** could also be converted into  $\gamma$ -carbonyl ester **6** and  $\gamma$ -lactam **7**. Meanwhile, the  $\gamma$ -butyrolactones **4** could also be obtained via the hydrolysis and subsequent oxidation of  $\gamma$ , $\delta$ -unsaturated ester **3b-1** (Scheme 6).

In conclusion, we have developed for the first time the nickel-catalyzed addition of unactivated  $C(sp^3)$ –H bonds with both symmetrical and unsymmetrical alkynes. A broad set of aliphatic amides can be readily alkenylated in moderate to good yields. A sequential  $C(sp^3)$ –H alkenylation/lactonization procedure has been developed to afford a complementary method to construct polysubstituted  $\gamma$ -butyrolactones from the less functionalized aliphatic carboxylic acid derivatives. For the first time, PCC has proven to be an efficient reagent in the formation of  $\gamma$ -butyrolactones from  $\beta$ -alkenylated amides. Removal of the 8-aminoquinoline directing group is not indispensable for lactonization. In addition, the alkenylated

#### Scheme 6. Transformations of Alkenylated Amide



products can also serve as versatile intermediates for further transformations. Further studies to extend the reaction scope are ongoing in our laboratory.

# ASSOCIATED CONTENT

# **Supporting Information**

Experimental procedures, characterization data, X-ray crystallographic data, copy of  ${}^{1}H-{}^{1}H$  NOESY spectra of **3b**, and copies of  ${}^{1}H$ ,  ${}^{13}C$  NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01128.

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Notes

The authors declare no competing financial interest.

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(19) For the plausible mechanism of the PCC-promoted lactonization, see the Supporting Information (SI), Part IV.