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Nickel-Catalyzed Stereoselective Alkenylation of C(sp^3)−H Bonds with Terminal Alkynes

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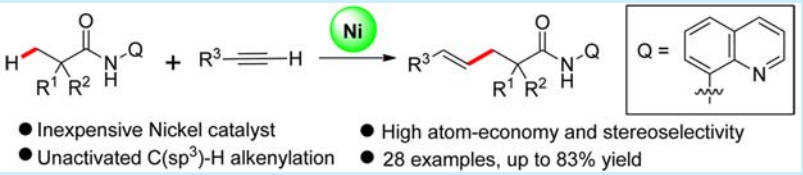
Supporting Information



ABSTRACT: A nickel-catalyzed stereoselective alkenylation of an unactivated β-C(sp^3)−H bond in aliphatic amide with terminal alkynes using 8-aminoquinoline auxiliary is reported for the first time. This reaction displays excellent functional group tolerance with respect to both aliphatic amides and terminal alkynes and features a cheap nickel catalytic system. The 8-aminoquinolyl directing group could be smoothly removed, and the resultant β-styrylcarboxylic acid derivatives could serve as versatile building blocks for further transformation.

Functionalized alkene derivatives are powerful building blocks in organic synthesis, as exemplified by their frequent application in diverse cross-coupling reactions, cycloaddition, and metathesis reactions.[1] Traditional approaches to build an alkene moiety usually involved prefunctionalized starting materials such as the Mizoroki−Heck, Suzuki, Negishi, and Stille reactions, resulting in operational complexity and metal waste.[2] From the point of step- and atom-economic strategy, transition-metal-catalyzed direct functionalization of C−H bonds represents an ideal and appealing tool for the construction of structurally diverse alkenes.[3] Over the past few years, several pioneering works for the efficient synthesis of alkene derivatives though different transition-metal-catalyzed direct C(sp^2)−H bond functionalization have been demonstrated.[4] However, the synthetic protocol involving the direct cleavage of inert C(sp^3)−H bonds remains quite limited owing to the low reactivity of C(sp^3)−H bonds. For instance, in 2016, Yu and co-workers reported the first example of palladium-catalyzed pyrazole-directed alkenylation of C(sp^3)−H bonds,[5] whereas the transformation was limited to the utilization of electron-deficient alkenes as coupling partners and the irremovable directing group. The alkenylation of unactivated C(sp^3)−H bonds by the employment of vinyl iodide has been developed by Chen,[6] Shi,[7] and Baran,[8] respectively. Recently, the addition-type alkenylation of unreactive C(sp^3)−H bonds with internal alkynes was achieved by You, Maiti, and others,[9] resulting in the formation of trisubstituted alkene products, which had relatively narrow applications in organic synthesis. Despite these significant advancements, the exploration and development of efficient approach to the alkenylation of C(sp^3)−H bonds with readily accessible terminal alkynes to afford synthetically useful disubstituted alkene derivatives remains a challenge.[9d] In particular, the involvement of terminal alkynes into unreactive C(sp^3)−H activation reaction has been underdeveloped due to the relatively high reactivity and the tendency of self-di- or trimerizations of terminal alkynes.

Nickel is an inexpensive and sustainable transition metal that has been considerably exploited in various C−H bond functionalizations. Much progress has been attained in terms of nickel-catalyzed C(sp^2)−H bond transformations, which was pioneered by Chatani, Ge, and others.[10] More recently, the initial achievement related to C(sp^3)−H bond cleavage, including nickel-catalyzed arylation,[11] alkylation,[12] intramolecular amidation,[13] and C−S bond formation[14] of aliphatic amides, has been disclosed herein, further highlighting the formidable catalytic ability of nickel catalyst. Our groups also demonstrated a nickel-catalyzed unactivated C(sp^3)−H bond functionalization of aliphatic amides for the efficient construction of C−S bonds.[14a] Inspired by the above encouraging works and our continuous investigations on C(sp^3)−H bond functionalizations,[15] we envisioned that the strategy of nickel-catalyzed alkenylation of unactivated β-C(sp^3)−H bonds of aliphatic amides and terminal alkynes with the assistance of an 8-aminoquinolyl auxiliary was feasible to lead to a wide range of disubstituted alkene derivatives.

We chose the amide **1b** and phenylacetylene **2a** as model substrates to initiate our investigation. The reaction was performed in the presence of 20 mol % of Ni(OAc)$_2$ and 50 mol % of NaOAc in DMF at 160 °C under N_2 atmosphere. Unfortunately, the desired product **3b** was not observed (Table 1, entry 1). When HOAc was used as an additive to add to the

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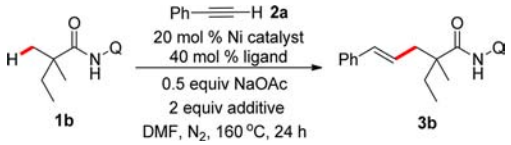
Table 1. Optimization of Reaction Conditions[a]



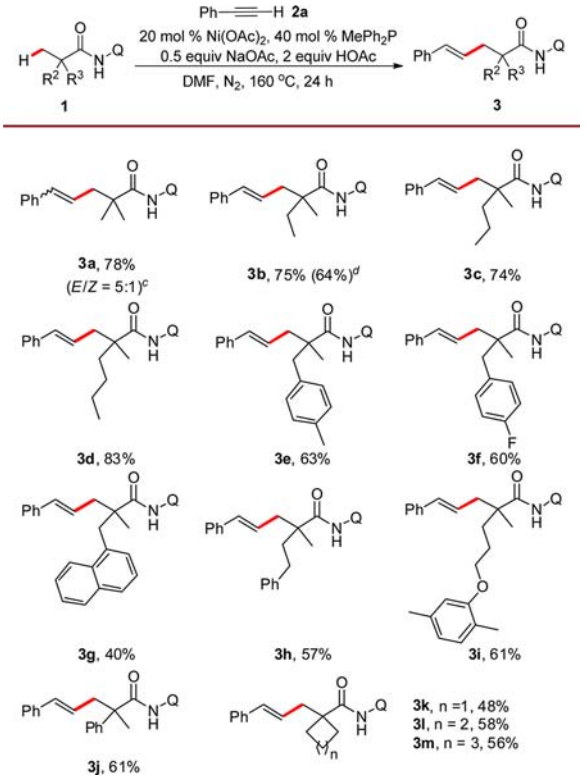
entry	catalyst	ligand	additive	yield[b] (%)
1	$Ni(OAc)_2$			0
2	$Ni(OAc)_2$		HOAc	35
3	$Ni(OAc)_2$		CF_3COOH	trace
4	$Ni(OAc)_2$		PhCOOH	25
5	$Ni(OAc)_2$	Ph_3P	HOAc	40
6	$Ni(OAc)_2$	Cy_3P	HOAc	trace
7	**$Ni(OAc)_2$**	**$MePh_2P$**	**HOAc**	**75**
8	$Ni(OAc)_2$	$PrPh_2P$	HOAc	65
9	$Ni(OTf)_2$	$MePh_2P$	HOAc	68
10	$NiBr_2$	$MePh_2P$	HOAc	50
11	$NiCl_2$	$MePh_2P$	HOAc	51
12	NiI_2	$MePh_2P$	HOAc	48
13	$(Cy_3P)_2NiCl_2$	$MePh_2P$	HOAc	15
14	$(Ph_3P)_2NiCl_2$	$MePh_2P$	HOAc	15
15		$MePh_2P$	HOAc	0

[a]Reaction conditions: **1b** (0.1 mmol), **2a** (0.4 mmol), Ni catalyst (20 mol %), ligand (40 mol %), NaOAc (0.05 mmol), additive (0.2 mmol), DMF (0.5 mL), under N_2, 160 °C, 24 h. Q = 8-quinolinyl. [b]Isolated yield by flash column chromatography.

reaction, the alkenylated product **3b** was isolated in 35% yield (Table 1, entry 2). Other acidic additives, such as CF_3COOH and PhCOOH, were tested, and the results were inferior to that of HOAc (Table 1, entries 3 and 4). We also examined the ligand effect of the transformation, and various phosphine ligands were employed in the reaction. Noteworthy was that $MePh_2P$ was identified as the optimal candidate to deliver the target product **3b** in 75% yield (Table 1, entries 5−8). The replacement of $Ni(OAc)_2$ with other nickel catalysts, including $Ni(OTf)_2$, $NiBr_2$, $NiCl_2$, NiI_2, $(Cy_3P)_2NiCl_2$, and $(Ph_3P)_2NiCl_2$, led to the obvious decrease in the reactivity (Table 1, entries 9−14). No reaction occurred in the absence of nickel catalyst (Table 1, entry 15). Among other basic additives, NaOAc turned out to be the most efficient in the formation of desired product **3b** (see the Supporting Information). Further optimization toward the solvents revealed that DMF was superior to other solvents (see the Supporting Information).

Having established the optimized reaction conditions, the generality and limitation of this new alkenylation protocol with regard to the aliphatic amides were examined (Scheme 1). Gratifyingly, the diverse aliphatic amides bearing β-methyl group smoothly participated in the alkenylation reaction to provide the corresponding products with *E*-configuration selectivity in moderate to good yields (**3b−j**). The different kinds of substituents located at the α-carbon of the aliphatic amides, such as long-chain alkyl, benzyl, and even phenyl, all could be tolerated in the transformation. Noteworthy was that a 5:1 ratio of *E*/*Z*-configuration was observed with regard to the product **3a**, presumably due to the minor steric hindrance of α-carbon of the pivalamide **1a**. It was worth mentioning that the site of C(sp^3)−H alkenylation exclusively occurred at the β-methyl group instead of the β-methylene or γ-methyl groups of the amides, exhibiting the high regioselectivity of the protocol. The inertness of the CH_2 group might be attributed to the steric hindrance of methylene C(sp^3)−H bonds. Some α-cyclic amides were also

Scheme 1. Substrate Scope of Aliphatic Amides[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.4 mmol), $Ni(OAc)_2$ (20 mol %), $MePh_2P$ (40 mol %), NaOAc (0.05 mmol), HOAc (0.2 mmol), DMF (0.5 mL), under N_2, 160 °C, 24 h. Q = 8-quinolinyl. [b]Isolated yield by flash column chromatography. [c]The ratio of *E*/*Z* in parentheses was determined by ^{1}H NMR. [d]1 mmol scale

compatible with the reaction system with moderate efficiency to lead to structurally interesting α-cyclic substituted amide derivatives (**3k−m**).

After examining the compatibility of the alkenylation reaction with a variety of the amide substrates, our attention was turned toward the reactivity of terminal alkynes (Scheme 2). It was observed that a wide range of terminal alkynes could be well tolerated in the reaction (**4a−o**). The aryl acetylenes bearing electron-withdrawing substituents gave the only *E*-configuration alkenylated products (**4a−c**) in moderate yields, whereas the electron-rich aryl acetylenes could give rise to a mixture of *E*- and *Z*-configuration alkenylated products with *E*-isomer as major products (**4f−j**), which possibly depends on the thermodynamic stability of *E*-isomer. The *ortho*- and *meta*-substituted phenylacetylenes showed comparative reactivity compared with *para*-substituted phenylacetylene, revealing that the orientation of the substituents attached in the aromatic ring had a negligible influence on the reaction (**4h−j**). Several heterocyclic alkynes, including thiophene-yl group, could serve as viable substrates in the reaction for the successful production of the corresponding alkenylated products (**4k,l**). We tested the reactivity of other heteroaryl acetylenes such as 3-ethynylpyridine and 2-ethynylpyridine, but no products were observed. More significantly, the aliphatic alkynes were also applicable under the current reaction conditions, affording the desired products in acceptable yields (**4m−o**, 44−64%). As for product **4o**, the shifting of the double bond occurred during the reaction.

Interestingly, the alkenylation reaction proceeded with the replacement of nickel catalyst by cobalt catalyst, producing the

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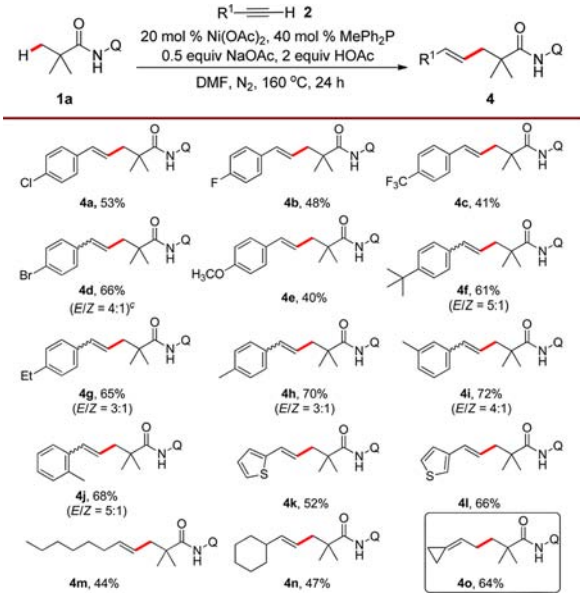
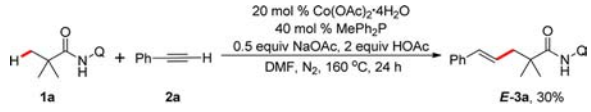
Scheme 2. Substrate Scope of Terminal Alkynes[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.4 mmol), $Ni(OAc)_2$ (20 mol %), $MePh_2P$ (40 mol %), NaOAc (0.05 mmol), HOAc (0.2 mmol), DMF (0.5 mL), under N_2, 160 °C, 24 h. Q = 8-quinolinyl. [b]Isolated yield by flash column chromatography. [c]The ratio of *E*/*Z* in the parentheses was determined by ^1H NMR.

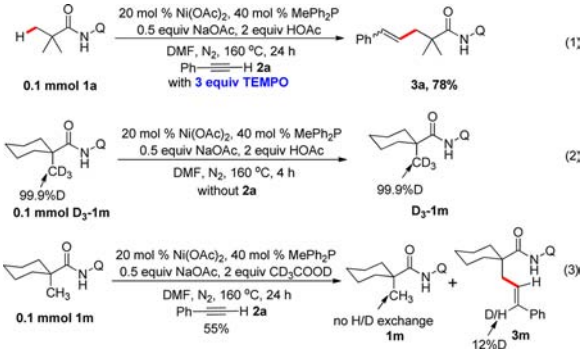
alkenylated product in 30% yield (Scheme 3). The reaction constituted the first example of Co-catalyzed alkenylation of the C(sp^3)−H bond in aliphatic amides with terminal alkynes.

Scheme 3. Co-Catalyzed Alkenylation of 1a with 2a



To gain insight into the mechanism, we performed radical and deuterium-labeling experiments (Scheme 4). The addition of

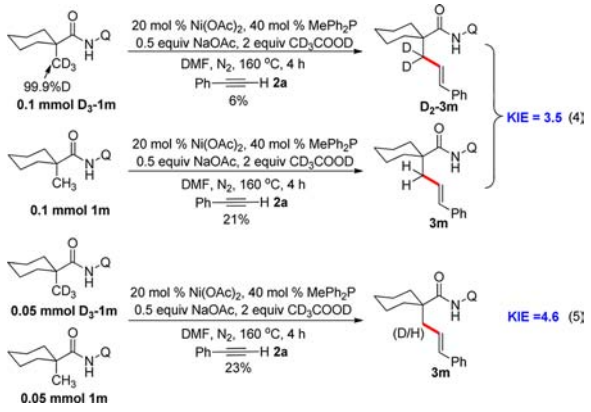
Scheme 4. Radical and Deuterium-Labeling Experiments



radical scavenging reagents such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) into the reaction had no influence on the reaction efficiency, indicating that a radical pathway may not be involved in the reaction process (Scheme 4, eq 1). The reaction with the deuterium labeled compound **D_3-1m** in the absence of phenylacetylene under the standard reaction conditions was performed, and the deuterium−proton exchange was not observed (Scheme 4, eq 2). This result clearly illustrated that the C−H cleavage step was irreversible. The deuterium-labeled product on the alkenyl carbon was detected in the presence of deuterated acetic acid, which was indicative of the involvement of deuteration process during the final protonation of C−M bond of the cyclometalation intermediate (Scheme 4, eq 3).

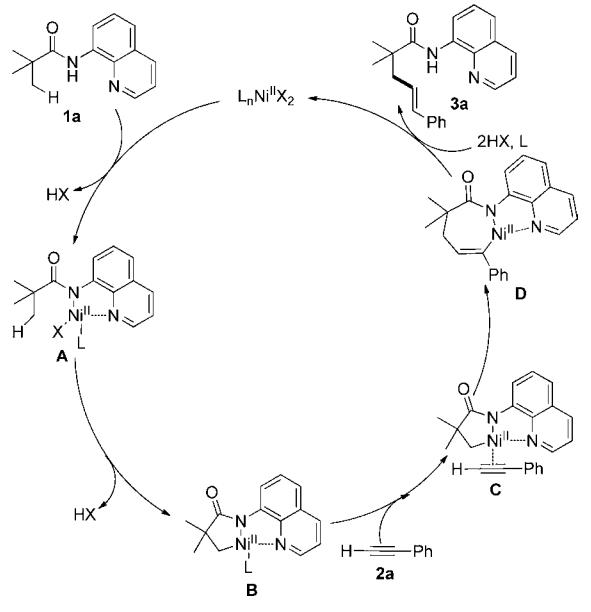
The parallel intermolecular kinetic isotopic experiments were conducted (Scheme 5), and the KIE value was determined to be

Scheme 5. Intermolecular Kinetic Isotopic Effects



3.5 and 4.6, respectively, thus implying that C−H cleavage was involved in the rate-determining step. Based on the preliminary mechanistic results and previous reports,[11,14,15c] a plausible reaction pathway was proposed as depicted in Scheme 6. First,

Scheme 6. Proposed Reaction Mechanism



the Ni(II) center coordinated with the nitrogen in 8-amino-quinoline auxiliary followed by ligand exchange under basic conditions to form the intermediate **A**. The cleavage of the C(sp^3)−H bond of intermediate **A** attaching to the Ni(II) center generated the cyclometalated intermediate **B**. Subsequently, the coordination of alkyne **2a** with intermediate **B** formed the complex **C**, followed by the migratory insertion of the alkyne to give intermediate **D**. Finally, the protonation of **D** with AcOH

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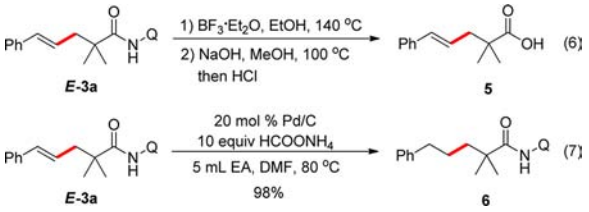
could deliver the alkenylated product **3a**, and the Ni(II) species was regenerated to accomplish a catalytic cycle.

The 8-aminoquinolyl auxiliary could be readily removed in good yield upon treatment with $BF_3{\cdot}OEt_2$ and sodium hydroxide (Scheme 7, eq 6). Notably, the resultant β-styrylcarboxylic acid **5**

Scheme 7. Removal of Directing Group and Further Application



can act as a versatile building block for further transformation. The catalytic hydrogenation of product *E*-**3a** also proceeded smoothly to give saturated compound **6** in 98% yield (Scheme 7, eq 7).

In conclusion, we have developed for the first time the nickel-catalyzed direct alkenylation of unactivated C(sp^3)−H bonds with terminal alkynes by the assistance of a bidentate directing group. The transformation features inexpensive and stable catalyst, high efficiency, good regio- and stereoselectivity, and broad substrate scope. The preliminary mechanistic investigation was conducted, and a tentative reaction pathway was proposed. The pendent 8-aminoquinoline directing group can be easily removed, and the obtained alkenylated products can be applied as versatile intermediates for various useful transformations. Further studies to illuminate the reaction mechanism and extend the application of this methodology are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03856.

General procdures and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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