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Nickel-Catalyzed Oxidative Coupling of Unactivated C(sp^3)−H Bonds in Aliphatic Amides with Terminal Alkynes

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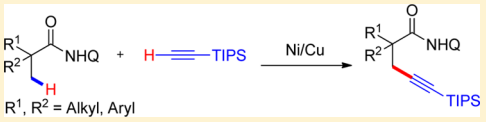
Supporting Information

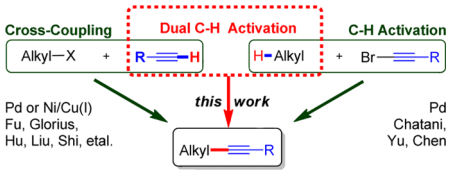
ABSTRACT: In this work, we demonstrated Ni-catalyzed oxidative coupling of unactivated C(sp^3)−H bonds with terminal alkynes for construction of C(sp^3)−C(sp) bonds to synthesize alkyl-substituted internal alkynes. Different amides exhibited good compatibility. Preliminary mechanistic studies were conducted to account for this alkynylation.



Oxidative C−H/C−H coupling is an ideal and environmentally attractive strategy for construction of C−C bonds by avoiding time-consuming prefunctionalization of substrates.[1] The concept of cross dehydrogenative coupling (CDC) was conceived in the late 1990s and applied to construct different types of carbon−carbon bonds. Afterward, pioneering work on oxidative coupling between two different C−H bonds were reported.[1−3] However, those examples mainly involved the oxidative coupling of C(sp^2)−H/C(sp^2)−H bonds.[2] From the viewpoint of C(sp^3)−H bonds, CDC was conducted with at least one relatively active C(sp^3)−H bond in most cases.[1e] Besides, developments on oxidative coupling of an unactivated C(sp^3)−H bond with the other "inert" C−H bond were far behind.[4] In 2008, Li's group reported the Ru-catalyzed oxidative coupling of C(sp^3)−H/C(sp^2)−H between 2-arylpyridines and cycloalkanes.[5] In the same year, Fagnou's group reported the Pd-catalyzed intramolecular coupling of arenes with unactivated alkanes.[4a] Recently, Chatani's group demonstrated an elegant work for direct oxidative coupling of aromatic C(sp^2)−H bonds with C(sp^3)−H bonds of toluene by using a bidentate directing strategy.[6] Later on, they extended this strategy to CDC of unactivated C(sp^3)−H bonds with benzylic C(sp^3)−H bonds of toluene derivatives.[7] Recently, Ge's group reported a protocol for cross dehydrogenative alkylation of substituted arenes.[8] Zhang's group reported a beautiful work on oxidative coupling/cyclization of aliphatic amides and terminal alkynes by using a Co/Ag cocatalyst.[9] However, the reaction failed to give the alkynylated product. When we were preparing this paper, Lei's group developed an elegant work on Cu/Ni/Ag multimetallic catalyzed radical oxidative cross-coupling of unactivated C(sp^3)−H in alkanes with terminal alkynes.[10]

Alkynes are among the most versatile building blocks in organic synthesis and widely applied in chemical biology and material science as precursors.[11] The Sonogashira reaction is a reliable and efficient method for construction of a C(sp^2)−C(sp) bond.[12] In comparison, the construction of C(sp^3)−C(sp) bonds to synthesize alkyl alkynes is more challenging.[13] Continuous efforts have been contributed in this field in the past decades. Radical alkynylation of the C(sp^3) center adjacent to a heteroatom or decarboxylative alkynylation with a nucleophilic or electrophilic alkynyl reagent provided successful tools for construction of C(sp^3)−C(sp) bonds.[14] Transition-metal-catalyzed alkynylation of alkyl halides/pseudohalides with alkynyl reagents is another efficient and direct strategy.[15,16] In 2003, the first example of direct alkynylation of primary alkyl bromides and iodides with terminal alkynes was disclosed by Fu and co-workers (Scheme 1).[17] Subsequently, other groups extended this chemistry with a special ligand set[18] or catalyst[19,20] or to broaden the substrate scope.[21,22] Very recently, Li and co-workers reported an example of performing a photopromoted transition-metal-free coupling between alkyne and alkyl iodide in water.[23] On the other hand, transition-metal-catalyzed coupling of unactivated C(sp^3)−H bonds with alkynyl halides provided another route to synthesize alkyl alkynes.[24−26] From the viewpoint of atom- and step-economy, the oxidative coupling of unactivated C(sp^3)−H bonds with terminal alkynes would be more ideal and attractive. Herein, we disclose the site-selective C(sp^3)−C(sp) bond

Scheme 1. Previous Works and Our Strategy for Alkyl Alkynes Synthesis



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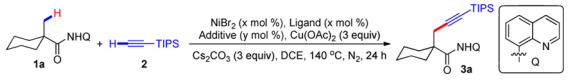
formation to synthesize alkyl alkynes through Ni-catalyzed oxidative coupling of unactivated C(sp^3)−H bonds with terminal alkynes by using the bidentate directing strategy.

To pursue this goal, one of the most challenging points is to avoid the homocoupling of terminal alkynes, which is prone to proceed under oxidative conditions. Thus, a proper oxidant should be intensively investigated to oxidize the low valence of catalytic metal species while suppressing the homocoupling of terminal alkynes. Another challenge is to find a proper transition-metal catalyst, which could efficiently promote both the activation of the unactivated C(sp^3)−H bonds and the reductive elimination to construct the C(sp^3)−C(sp) bond. Inspired by recent exploration of Ni-catalyzed C(sp^3)−H functionalization[27] and the successful bidentate directing strategy in unactivated C(sp^3)−H functionalization,[28] we set out to investigate the oxidative coupling of an unactivated C(sp^3)−H bond with terminal alkynes with a bidentate directing group via Ni catalysis (Table 1). Initial screenings

Table 1. Optimization



entry	[M] (x)	ligand (x)	additive (y)	results[a]
1	$Ni(acac)_2$ (10)	DPPBz (10)	Cu_2O (20)	13%
2	$Ni(acac)_2$ (10)	DPPE (10)	Cu_2O (20)	13%
3	$NiBr_2$ (10)	DPPE (10)	Cu_2O (20)	18%
4	$NiBr_2$ (10)	DPPE (10)	$Me_2S{\cdot}CuBr$ (20)	28%
5	$NiBr_2$ (10)	Davephos (10)	$Me_2S{\cdot}CuBr$ (20)	35%
6	$NiBr_2$ (10)	Davephos (10)	$Me_2S{\cdot}CuBr$ (10)	40%
7	$NiBr_2$ (10)	Davephos (10)	$Me_2S{\cdot}CuBr$ (5)	35%
8	$NiBr_2$ (10)	Davephos (10)	$Me_2S{\cdot}CuBr$ (0)	21%
9	$NiBr_2$ (20)	Davephos (20)	$Me_2S{\cdot}CuBr$ (10)	45%
10[b]	$NiBr_2$ (20)	Davephos (20)	$Me_2S{\cdot}CuBr$ (10)	48%
11[c]	$NiBr_2$ (20)	Davephos (20)	$Me_2S{\cdot}CuBr$ (10)	55% (52%[d])
12	–	Davephos (20)	$Me_2S{\cdot}CuBr$ (10)	<5%
13	$NiBr_2$ (20)	–	$Me_2S{\cdot}CuBr$ (10)	<5%
14[e]	$NiBr_2$ (20)	Davephos (20)	$Me_2S{\cdot}CuBr$ (10)	15%

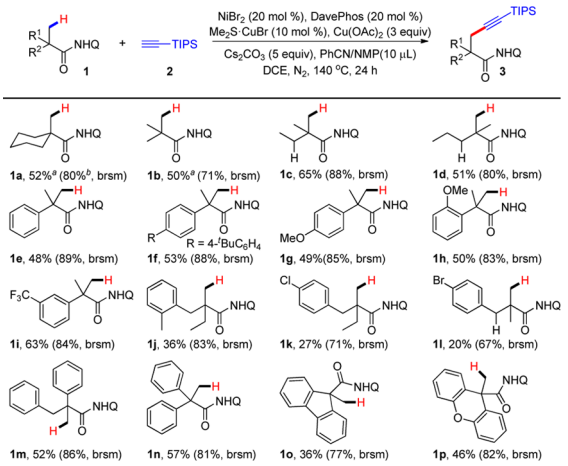
[a]NMR yield, using dibromomethane as the internal standard. [b]PhCN/NMP (10 μL). [c]PhCN/NMP (10 μL), Cs_2CO_3 (5 equiv). [d]Isolated yield. [e]In the absence of $Cu(OAc)_2$.

were carried out with **1a** and ethynyltriisopropylsilane **2**, in combination with $Ni(acac)_2$ as catalyst, DPPBz as ligand, Cu_2O as transmetalating reagent, $Cu(OAc)_2$ as oxidant, and Cs_2CO_3 as base in 1,2-dimethoxyethane (DME) at 140 °C under N_2. To our delight, we observed the desired product in 13% NMR yield with the use of CH_2Br_2 as internal standard (entry 1). More importantly, compared to the previous report,[9] the cascade cyclization of the alkynylated product did not occur. A remarkable solvent effect was observed and only 1,2-dichloroethane (DCE) gave good results; other solvents were not suitable (Table S1). A number of bases were examined. Cs_2CO_3 was found the best choice (Table S2). Notably, only $Cu(OAc)_2$ was workable as an oxidant (Table S3). The phosphine ligands were also tested. DPPE exhibited comparable activity with DPPBz (entry 2), while others gave worse results (Table S4). Further screening on different nickel salts (Table S5) indicated that $NiBr_2$ outperformed the others to give the product in 18% NMR yield (entry 3). Gratifyingly, after intensively screening transmetalating reagent Cu(I) salts (Table S6), $Me_2S{\cdot}CuBr$ significantly improved the efficacy to 28% NMR yield (entry 4). A number of ligands were further extensively tested with $NiBr_2$ and $Me_2S{\cdot}CuBr$ (Table S7). Davephos improved the efficacy significantly with 35% NMR yield (entry 5).

Decreasing the loading of $Me_2S{\cdot}CuBr$ (entry 6) further improved the efficacy and gave the desired product in 40% NMR yield. Gratifyingly, increasing the catalyst and ligand loading also improved the activity (entry 9). Next the cosolvent effect was examined. A trace amount of PhCN and *N*-methylpyrrolidone (NMP) as cosolvent slightly improved the activity (entry 10). Finally, increasing the Cs_2CO_3 amount from 3.0 equiv to 5.0 equiv gave the alkynylated product in 52% isolated yield (entry 11). Notably, other transition-metal salts, such as $Co(acac)_2$, $CoBr_2$, or $Fe(acac)_2$, were not suitable (Table S8). Control experiments indicated that the catalyst (entry 11), ligand (entry 13), transmetalating reagent (entry 8), and oxidant (entry 14) were all necessary. Unfortunately, other efforts could not promote the efficacy at this stage.

With the optimized conditions in hand, we set out to expand the substrate scope of aliphatic acid (Table 2). To our delight,

Table 2. Substrate Scope of Aliphatic Amides



[a]Isolated yield. [b]brsm, based on the recovered starting material.

different alkyl-, phenyl-, or benzyl-substituted amides were tolerated well. Both cyclic amides (**1a**) and acyclic amides (**1b**−**d**) performed well to produce the alkynylated products in moderate to good isolated yields. In addition, the reaction preferred to occur at the methyl group beyond the methylene groups in substrate **1c** and **1d** due to steric hindrance. More importantly, only a monoalkynylated product was observed for substrates **1b**−**d**, which might be attributed to the steric effect of the generated alkynylated products. We further screened phenyl-substituted amides (**1e**−**i**). The amides containing a phenyl ring equipped with electron-donating substituents, for example, *tert*-butylphenyl (**1f**) and a methoxy group (**1g** and **1h**), proceeded well and delivered the corresponding alkynylated products in moderate yields. To our interest, substrate **1i**, with an electron-withdrawing trifluoromethyl group, exhibited better activity, and the desired product was isolated in 63% yield. The structure of **1i** was further confirmed by X-ray crystallography data (Figure 1). This result unambiguously solidified the success of oxidative coupling of unactivated C(sp^3)−H bonds with terminal alkynes. It should be mentioned that the reaction showed a predominant preference for the C(sp^3)−H bonds of the methyl group over the C(sp^2)−H bonds of the phenyl group (**1e**−**i**), indicating

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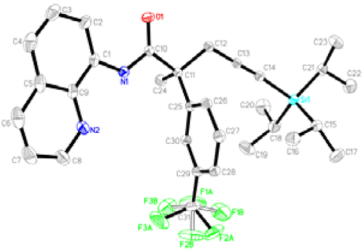
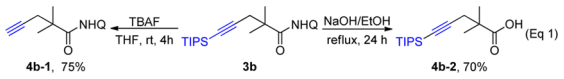


Figure 1. ORTEP of drawing of internal alkyne **3i**.

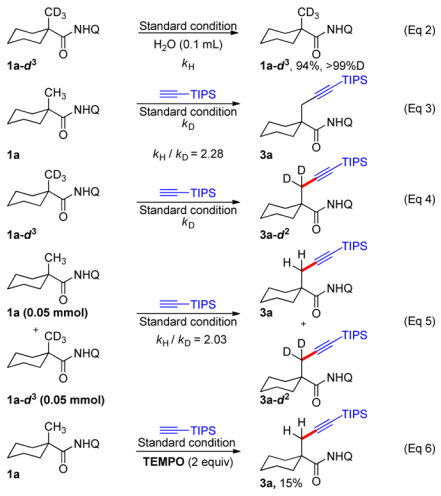
that in the metalation step a 5/5-membered fused ring intermediate was favored over a 5/6-membered intermediate.

For benzyl-substituted substrates (**1j**−**m**), the regioselectivity preferred to proceed at the β-methyl group over the more active β-benzyl group, arising from steric effects. Gratifyingly, the chloro (**1k**) or bromo (**1l**) functional group survived well, albeit in low yields. Finally, diphenyl acids (**1n**−**p**) can be smoothly converted to the alkynylated product in acceptable yields. This reaction exhibited good mass balance, and the starting materials were recovered in all cases. It is noteworthy that only triisopropylsilyl acetylene **2** can serve as the alkynyl reagent in this reaction, which is consistent with a previous report.[29]

Removing the protecting silyl group afforded the terminal alkyne **4b-1** in 75% isolated yield, which can be used to conduct diverse transformations (eq 1). The amide **3b** can easily remove the 8-aminoquinoline directing group in refluxing EtOH with the base NaOH to give alkynyl acid **4b-2** in 70% isolated yield.



To unveil the catalytic pathway, preliminary mechanistic studies were conducted. The deuterated **1a**-d_3 was submitted to standard reaction conditions in the absence of terminal alkynes, and the scrambling of proton−deuterium was not observed in the recovered starting material **1a**-d_3 (eq 2). This observation

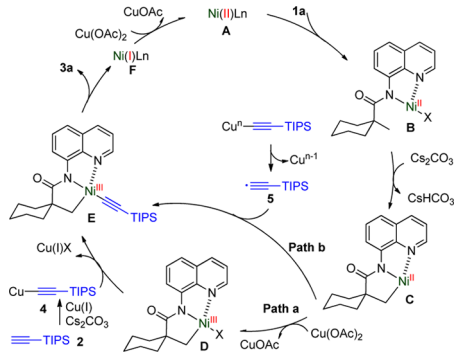


indicated that the C−H activation step was irreversible. An intermolecular kinetic isotope effect (KIE) experiment was conducted independently to calculate their initial rate constant (k_H for **1a** and k_D for **1a**-d_3) to determine the intermolecular KIE (2.28) (eq 3 and eq 4). A competition KIE was performed by the treatment of equivalent amide **1a** and **1a**-d_3 in a vessel (2.03) (eq 5).

Both of them (KIE > 2.0) are large, suggesting that the cleavage of the C−H bond was involved in the rate-determining step. Moreover, when we added TEMPO in our standard reaction to determine potential radical species (eq 6), the reaction efficacy decreased significantly, and 15% isolated yield of desired product was obtained, suggesting that the radical might be involved.

On the basis of current results, we proposed a plausible catalytic cycle as shown in Scheme 2. The substrate **1a**

Scheme 2. Plausible Catalytic Cycle



coordinated to Ni(II) species **A** through a ligand exchange under alkaline condition to generate **B**, which gave the intermediate **C** through C−H activation with the assistance of base. Subsequently, a single-electron oxidation of **C** by oxidant $Cu(OAc)_2$ afforded Ni(III) complex **D** (path a),[27,30] which was further converted to **E** with an alkynyl ligand through a transmetalation process with alkynyl Cu(I) species **4**, which was *in situ* generated from a Cu(I) complex and alkynyl reagent. Finally, reductive elimination of **E** generated the alkynylated product **3a** with the release of Ni(I) complex **F**, which was further oxidized to the Ni(II)species **A** to fulfill the catalytic cycle. In addition, an alternative pathway (path b) to generate the species **E** from **C** through oxidative addition of alkynyl radical **5**, which would be generated from the alkynyl-copper species, cannot be ruled out.[10,31]

In conclusion, we disclosed the oxidative coupling of unactivated C(sp^3)−H bonds with terminal alkynes by using a synergetic Ni/Cu cocatalyst. Different amides exhibited good compatibility in this reaction. The reaction preferred to occur at the methyl group over the secondary C(sp^3)−H bond and benzyl methylene group. Confirmation of the crystal structure of alkynylated product **3i** further confirmed the success of this direct alkynylation. From the preliminary mechanistic studies, a plausible pathway was proposed. Further studies to completely understand the reaction mechanism, to promote the reaction efficacy, and to expand the substrate scope are under way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00529.

Experimental procedures, detailed optimization data, and characterization data of all compounds (PDF)

Crystallographic data for **3i** (CCDC-1432770) (CIF)

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Notes

The authors declare no competing financial interest.

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