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Dehydrogenative [4 + 2] Cycloaddition of Formamides with Alkynes through Double C−H Activation

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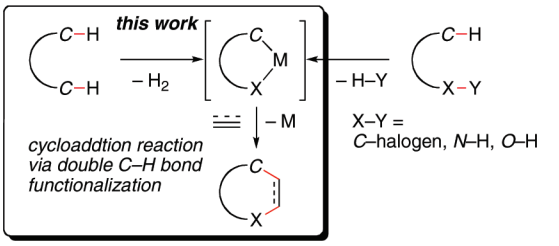
Supporting Information

ABSTRACT: Formamides having 1-arylalkyl groups on nitrogen undergo an unprecedented dehydrogenative [4 + 2] cycloaddition reaction with alkynes via nickel/$AlMe_3$ cooperative catalysis to give highly substituted dihydropyridone derivatives in good yields. Notably, the transformation proceeds through double functionalization of C(sp^2)−H and C(sp^3)−H bonds in the formamides.

Cycloaddition reactions represent one of the most important class of transformations in organic synthesis. A diverse range of ring structures can be constructed by these transformations in a single operation starting with two or more compounds.[1] A number of transition-metal complexes have been investigated as mediators or catalysts for cycloaddition reactions,[2] many of which provide cyclic molecules that are inaccessible by classical concerted cycloaddition reactions such as the Diels−Alder reaction. A key common feature of transition-metal-mediated cycloaddition reactions is a metallacycle intermediate, which is typically formed through the reaction of a metal center with unsaturated C−C or C−heteroatom bonds. Recent studies have shown that the key metallacycle intermediates can also be formed through metalation of unreactive C−H bonds. For example, the reaction of reactive C−halogen, O−H, or N−H bonds at a metal center followed by that of unreactive C−H bonds in an intramolecular manner leads to a metallacycle species (Scheme 1).[3] Subsequent reactions with unsaturated compounds give cycloadducts, allowing direct functionalization of C−H bonds to afford synthetically useful cyclic products. Ultimately, the metallacycle intermediates could also be generated by sequential activation of two C−H bonds. Cycloaddition reactions involving such double C−H functionalization allow the use of less-oxidized starting materials and thus should be of great synthetic potential in terms of atom[4] and redox economy.[5] Only a limited number of examples that proceed through activation of C(sp^2)−H bonds have been reported,[6] whereas no precedents involving unreactive C(sp^3)−H functionalization[7] are available.[8] We report herein the oxidative cycloaddition reaction of *N*,*N*-bis(1-arylalkyl)formamides with alkynes via functionalization of formyl C(sp^2)−H and alkyl C(sp^3)−H bonds. A catalytic cycle involving oxidative addition of the formyl C(sp^2)−H bond followed by hydronickelation of the alkyne and intramolecular C(sp^3)−H activation by the resultant alkenyl group bound to the nickel center to form a key nickelacycle intermediate is proposed.

Scheme 1. Strategies for Metallacycle Formation through C−H Activation



We recently reported that the C(sp^2)−H bond of various formamides can be functionalized by cooperative nickel/Lewis acid (LA) catalysis to allow hydrocarbamoylation of unsaturated compounds.[9] The reaction of (*R*,*R*)-*N*,*N*-bis(1-phenylethyl)formamide [(*R*,*R*)-**1a**] having over 99% enantiomeric excess (ee) with 4-octyne (**2a**) in the presence of bis(1,5-cyclooctadiene)nickel [Ni(cod)$_2$, 1 mol %], tri(*tert*-butyl)phosphine [P(*t*-Bu)$_3$, 4 mol %], and trimethylaluminum ($AlMe_3$, 20 mol %) in toluene at 80 °C for 21 h (conditions similar to those for the hydrocarbamoylation reaction[9]) gave the expected α,β-unsaturated amide **4aa** in only 4% yield, and dihydropyridone **3aa** was obtained instead in 91% yield (Table 1, entry 1). Use of P(*t*-Bu)$_3$ as a ligand was crucial: use of PCy_3 resulted in ∼10% yield of **3aa**, and other ligands gave not even trace amounts of the products. The ee value for **3aa** was found to be over 99%, showing that no loss of the stereochemical information in (*R*,*R*)-**1a** was observed under the reaction conditions. Lack of either of the catalyst components resulted in no formation of **3aa** and **4aa**. The reaction of 7-tetradecyne (**2b**) gave a stereoisomeric mixture of tetradec-7-ene (70% yield) and the corresponding cycloadduct **3ab** (entry 2), suggesting that excess alkyne serves as a hydrogen acceptor. (*E*)-Tetradec-7-ene was formed gradually under the reaction conditions, probably through isomerization of the initially formed (*Z*)-alkene on the basis of the reaction profile monitored by GC. Formamides with other bulky *N*-substituents [e.g., *N*,*N*-diisopropylformamide[9] and *N*-isopropyl-*N*-(1-phenylethyl)formamide] resulted in either preferential hydrocarbamoylation of alkynes or no reaction. Curiously, *meso*-**1a** showed a lower reaction rate and gave the corresponding adduct in 66% yield under identical conditions after 21 h (entry 3). Therefore, two 1-phenylethyl groups having the same configuration are crucial for this transformation, presumably because they allow a

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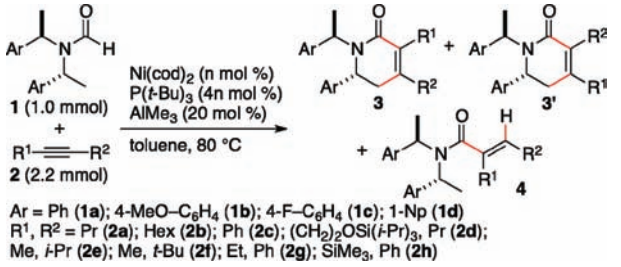
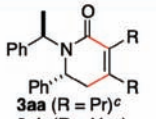
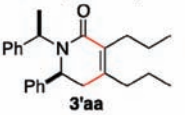
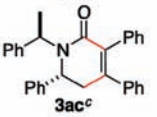
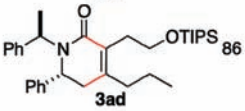
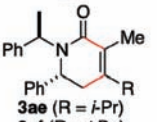
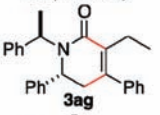
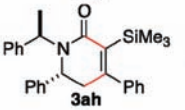
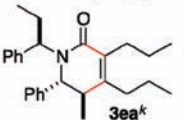
Table 1. Dehydrogenative [4 + 2] Cycloaddition of Formamides with Alkynes Catalyzed by Ni/AlMe$_3$



Ar = Ph (**1a**); 4-MeO–C_6H_4 (**1b**); 4-F–C_6H_4 (**1c**); 1-Np (**1d**)
R^1, R^2 = Pr (**2a**); Hex (**2b**); Ph (**2c**); $(CH_2)_2OSi(i\text{-}Pr)_3$, Pr (**2d**); Me, *i*-Pr (**2e**); Me, *t*-Bu (**2f**); Et, Ph (**2g**); $SiMe_3$, Ph (**2h**)

entry	1	2	n	time (h)	major product	yield of 3+3'+4 (%)[a]	3/3'[b]	3+3'/4[b]
1	1a[c]	2a	1	21		95	—	96:4
2	1a	2b	1	21		85[d]	—	93:7
					3aa (R = Pr)[c] **3ab** (R = Hex)			
3	1'a[e]	2a	1	21		66	—	97:3
					3'aa			
4	1a[c]	2c[f]	10	7		79	—	>95:5
					3ac[c]			
5	1a	2d[f]	10	36		86	76:24	96:4
					3ad			
6	1a	2e	10	1		79	62:38	80:20
7[g]	1a	2f	10	21		63	>95:5	80:20
					3ae (R = *i*-Pr) **3af** (R = *t*-Bu)			
8	1a	2g[f,h]	10	1		80	57:43	>95:5
					3ag			
9[g]	1a	2h[f]	10	24		23	>95:5	>95:5
					3ah			
10	1b	2a	5	2		99	—	86:14
11	1c	2a	5	4		97	—	92:8
12	1d	2a[i]	5	89		74	—	>95:5
					3ba (Ar = 4-MeO–C_6H_4) **3ca** (Ar = 4-F–C_6H_4) **3da** (Ar = 1-naphthyl)			
13	1e[j]	2a	5	23		85	—	>95:5
					3ea[k]			

[a] Isolated yields based on **1**. [b] Estimated by GC and/or ^{1}H NMR analysis of the crude products. [c] >99% ee as estimated by chiral HPLC. [d] Tetradec-7-ene (*E*/*Z* = 19:81) was also isolated in 70% yield. [e] Meso isomer of **1a**. [f] 4.4 mmol was used. [g] The reaction was run at 100 °C. [h] Slow addition over 1 h (**2g**) or 5 h (**2h**). [i] 6.6 mmol was used. [j] (*R**,*R**)-*N*,*N*-bis(1-phenylpropyl)formamide. [k] Diastereoselectivity = 96:4.

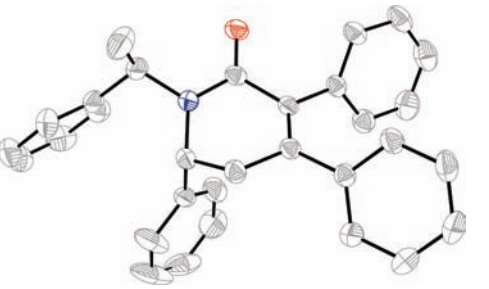
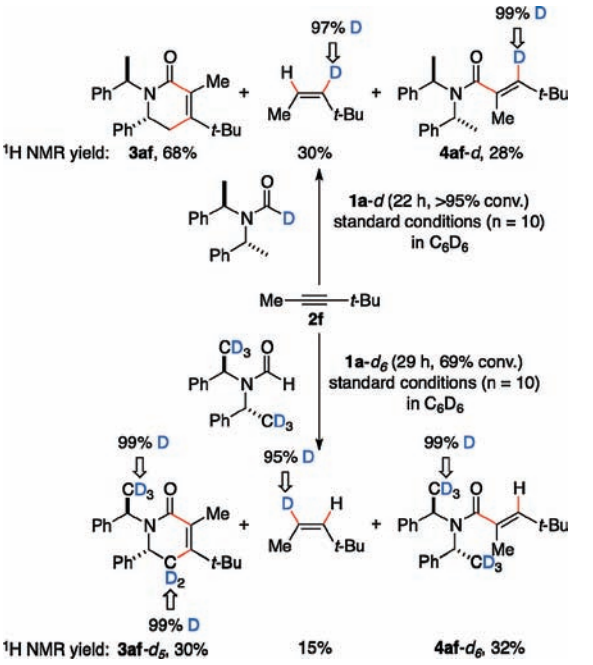


Figure 1. Molecular structure of **3ac**.

Scheme 2. Reactions of Deuterated 1a with 2f



conformation suitable for the C(sp^3)−H functionalization. The reaction of (*R*,*R*)-**1a** with diphenylacetylene (**2c**) exclusively gave cycloadduct **3ac** in 79% yield (entry 4), whose structure was unambiguously confirmed by X-ray crystallography (Figure 1). Alkynes having sterically biased substituents also reacted with racemic **1a** (entries 5−9). Whereas modest regioselectivity was observed with alkynes **2d**, **2e**, and **2g**, 4,4-dimethylpent-2-yne (**2f**) and phenyl(trimethylsilyl)acetylene (**2h**) gave a single cycloadduct. Generally, a smaller substituent was introduced at the α-position of the carbonyl in **3**, except for **3ad** and **3ah**. The attempted cycloaddition reactions with terminal alkynes were futile because of rapid tri- and/or oligomerization of the alkynes. Both electron-donating and -withdrawing groups on the phenyl ring of **1a** were tolerated, giving the corresponding adducts **3ba** and **3ca** in good yields (entries 10 and 11). On the other hand, the reaction of 1-naphthyl variant **1d** with **2a** was sluggish, presumably as a result of steric repulsion induced by the aryl group (entry 12). (*R**,*R**)-*N*,*N*-Bis(1-phenylpropyl)formamide (**1e**) also gave six-membered-ring product **3ea** through functionalization of its methylene C(sp^3)−H bond rather than the terminal methyl group (entry 13). Notably, the C(sp^3)−H bond functionalization took place highly diastereoselectively.

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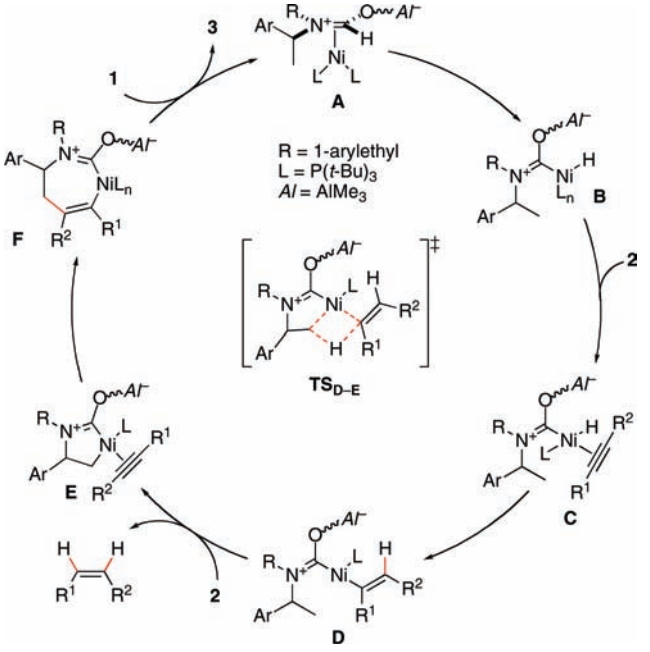
Scheme 3. Plausible Catalytic Cycle



Some additional experiments were performed to gain mechanistic insights into the present cycloaddition reaction. First, the reaction of isolated hydrocarbamoylation product **4aa** under the reaction conditions gave no trace amount of **3aa**, suggesting that the present cycloaddition reaction is independent of the hydrocarbamoylation. Second, the reaction of **1a**-*d*, which was deuterated at the formyl C−H bond, with **2f** in C_6D_6 showed the formation of **3af** and **4af**-*d* as well as (*Z*)-3-deuterio-4,4-dimethyl-2-pentene[10] by ^{1}H NMR analysis of the crude product (Scheme 2). On the other hand, the identical reaction using **1a**-d_6 labeled on both methyl groups of **1a** gave **3af**-d_5, **4af**-d_6, and (*Z*)-2-deuterio-4,4-dimethyl-2-pentene[10] (Scheme 2). These results indicate that hydrogenation of the alkyne takes place in a manner distinct from simple addition of free H_2 across alkynes, which would have led to the formation of identically deuterated (*Z*)-4,4-dimethyl-2-pentene.

On the basis of these observations, the following catalytic cycle is proposed (Scheme 3). The formamide coordinated to $AlMe_3$ at the carbonyl oxygen interacts with an electron-rich nickel(0) species through η^2-coordination to give **A**, which undergoes oxidative addition of the formyl C−H bond to give **B**. Coordination followed by migratory insertion of the alkyne takes place, giving **D** via **C**. While C−C bond-forming reductive elimination from **D** gives the hydrocarbamoylation product **4**,[9] the sterically demanding 1-arylalkyl group retards this pathway and induces C(sp^3)−H activation through a concerted cyclometalation, presumably through a transition state like $\mathbf{TS_{D-E}}$, to give five-membered nickelacycle **E**.[11] A second migratory insertion of a coordinating alkyne takes place at the sp-carbon bearing the bulkier substituent R^2 to give seven-membered nickelacycle **F**, which reductively eliminates the cycloadduct **3**. Decomplexation of $AlMe_3$ from **3** and its recomplexation with **1** are followed by the formation of η^2-nickel complex **A**, which reenters the proposed catalytic cycle. The observed difference in the **3af**/**4af**-*d* and **3af**-d_5/**4af**-d_6 ratios (Scheme 2) possibly suggests that the functionalization of the C(sp^3)−H bond may be rate-determining. Highly electron-donating, bulky P(*t*-Bu)$_3$ may facilitate both of the C−H activation steps in terms of electron density and steric environment of the nickel center.

In conclusion, we have demonstrated that *N*,*N*-bis(1-arylalkyl)formamides undergo an unprecedented dehydrogenative [4 + 2] cycloaddition reaction with alkynes via nickel/$AlMe_3$ cooperative catalysis through double functionalization of otherwise unreactive C(sp^2)−H and C(sp^3)−H bonds to give highly substituted dihydropyridone derivatives, which can serve as versatile synthetic precursors for nitrogen-containing six-membered heterocycles.[12] Current efforts are being directed toward understanding in detail the reaction mechanisms for the two C−H activation steps and further development of this class of novel cycloaddition reactions.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, spectroscopic and analytical data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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