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Heteroatom-Directed Alkylcyanation of Alkynes

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Abstract: Alkanenitriles having a heteroatom such as nitrogen, oxygen, and sulfur at the γ-position are found to add across alkynes stereo- and regioselectively by nickel/Lewis acid catalysis to give highly substituted acrylonitriles. The heteroatom functionalities likely coordinate to the nickel center to make oxidative addition of the C−CN bonds of the alkyl cyanides kinetically favorable, forming a five-membered nickelacycle intermediate and, thus, preventing β-hydride elimination to allow the alkylcyanation reaction.

Introduction

Stereoselective construction of acyclic tri- and tetra-substituted ethenes is a major challenge in modern organic synthesis, because they are ubiquitous in many natural products and materials and serve as a building block for branched alkanes with vicinal stereocenters through hydrogenation, epoxidation, and cyclopropanation of the substituted double bond.[1] Classical approaches to such structures involve the Wittig, Honer−Wadsworth−Emmons, Julia, and Peterson reactions, that often result in low stereoselectivity with substituents of a small steric and/or electronic difference.[2] Representative alternative protocols to address this issue are stereo- and regioselective addition reactions across alkynes. Especially, carbometalation followed by trapping with carbon electrophiles has been a reliable method to access stereochemically well-defined olefins.[1b] Nevertheless, use of prefunctionalized organometallic reagents and electrophiles as well as stoichiometric metal residues as a byproduct limits the potential of the protocols, particularly for large-scale production.

We have developed insertion reactions of alkynes into the C−CN bonds of nitriles, namely, carbocyanation reaction, as a novel strategy to access substituted ethenes.[3] While many nitriles have been found to participate in the transformation with high stereo- and regioselectivity, use of alkanenitriles has been severely limited due to relatively low reactivity of their C(sp^3)−CN bonds toward oxidative addition and competitive β-hydride elimination of an alkylnickel intermediate, resulting in contamination of hydrocyanation products.[4] We envisaged that coordinating functionalities in alkyl cyanides could suppress the unwanted β-hydride elimination by forming a chelate intermediate. This strategy to facilitate otherwise challenging activation of C−C bonds other than C−CN bonds by transition metals[5] has been demonstrated in both stoichiometric[6] and catalytic[7] reactions. We report herein chelation-assisted C−CN bond activation to realize the addition reactions of γ-aza(oxa or thia)alkanenitriles across alkynes in the presence of a nickel/Lewis acid (LA) cocatalyst to give highly substituted and functionalized acrylonitriles with high stereo- and regioselectivity and atom economy.

Results and Discussion

The problem associated with β-hydride elimination was previously solved in part by employing highly bulky ligands such as SPhos[8] in the reaction of propionitrile to improve the yield of the cis-ethylcyanation product,[4a,c] whereas butyronitrile still suffered from competitive hydrocyanation products afforded propylcyanation product in low yield.[4c] A dramatic improvement of the product selectivity was observed by introducing a secondary amino group at the γ-position of butyronitrile. Thus, the reaction of aminobutyronitrile **1a** (1.0 mmol) with 4-octyne (**2a**, 2.0 mmol) in the presence of $Ni(cod)_2$ (10 mol %), SPhos (20 mol %), and $AlMe_3$ (40 mol %) in toluene at 50 °C for 9 h gave the corresponding cis-alkylcyanation product **3aa** in 86% yield and no trace amount of hydrocyanation products (entry 1 of Table 1). The observed effect of the amino group, however,

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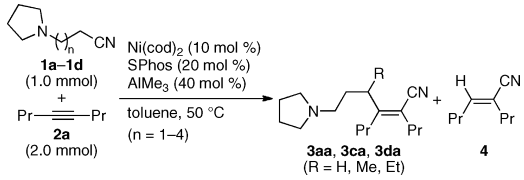
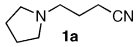
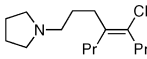
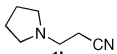
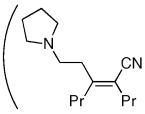
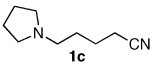
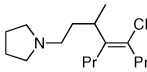
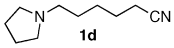
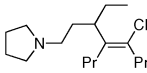
Table 1. Nickel/$AlMe_3$-Catalyzed Alkylcyanation of 4-Octyne



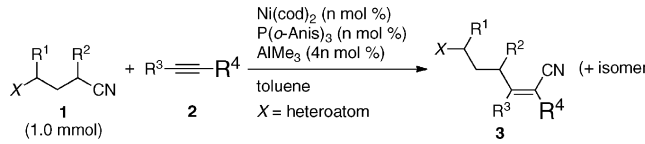
entry	1	time (h)	product(s), yield[a]
1	 **1a**	9	 **3aa**, 86%
2[b]	 **1b**	21	 **3ba**, <5%
3[b]	 **1c**	11	 **3ca**, 77%
4[b,c]	 **1d**	45	 **3da**, 45% + **4**, 9%[d]
5[b,e]	**1a** + Et–CN (1:1)	6	ethylcyanation, <5%[d] + **3aa**, 57%[d]

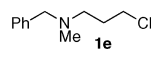
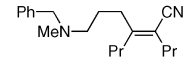
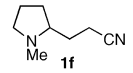
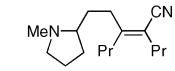
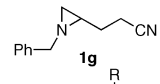
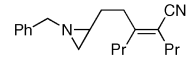
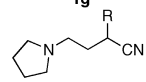
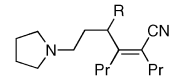
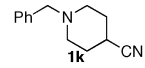
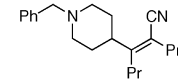
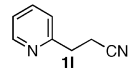
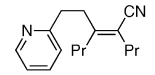
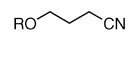
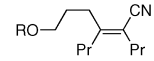
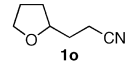
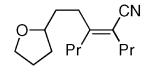
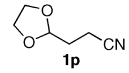
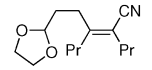
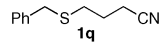
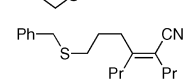
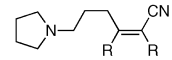
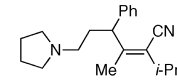
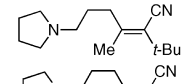
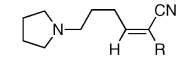
[a] Isolated yields based on **1**. [b] Run at 80 °C. [c] Run with 60 mol % of $AlMe_3$. [d] Estimated by GC using *n*-dodecane as an internal standard. [e] Run with 0.50 mmol of **2a**.

did not work at all with aminopropionitrile **1b** (entry 2), whereas the addition of amino-substituted valeronitrile **1c** and hexanenitrile **1d** across **2a** took place exclusively at the γ-position of the pyrrolidyl group to allow addition of secondary alkyl groups (entries 3 and 4). We observed that γ-aminonitrile **1a** reacted much faster than propionitrile based on the results from their competitive reactions with **2a** (entry 5).

The amino effect for promotion of the alkylcyanation reaction was further tested under slightly modified conditions using P(2-MeO-C_6H_4)$_3$ as a ligand (Table 2). Use of this ligand gave **3aa** in 88% yield with 1.4 mmol of **2a**, 3 mol % of $Ni(cod)_2$, and 12 mol % of $AlMe_3$ at 80 °C for 9 h. Other cyclic and acyclic amino moieties were equally effective (entries 1 and 2) even with strained and thus labile[9] aziridine-containing substrate **1g** (entry 3). The formation of **3ca** and **3da** (Table 1) prompted us to examine secondary alkyl cyanides, challenging substrates for the alkylcyanation.[4b,c] To our delight, a range of α-substituents in **1a** tolerated to give branched carbocyanation products in modest to good yields (entries 4−7). Nevertheless, attempted addition of optically active (*S*)-**1i** of 86% ee[10] resulted in **3ia** of 34% ee due to background racemization of (*S*)-**1i**, and that of tertiary alkyl cyanides was futile even with the aid of an amino group. The pyridyl sp^2-nitrogen of **1l** also served as a directing group (entry 8), whereas the corresponding 4-pyridyl variant did not participate in the reaction (Figure 1). These results prove that the effect of the heteroatom is derived primarily from its coordination to nickel but not from its inductive influence. Moreover, ether, thioether, and acetal functionalities assisted the reaction to give the corresponding alkylcyanation products (entries 9−13), whereas alkyl cyanides having arylamine, sp^2-nitrogen-containing five-membered heterocycles, epoxide, ester, amide carbonyl oxygens, and thioacetal did not give the corresponding adduct due to either no reaction or decomposition of the nitriles, or apparent catalyst decomposition observed with the thioacetal substrate (Figure 1). The scope of alkynes was examined briefly with **1a** and **1i** as nitrile substrates. In addition to other symmetrical dialkylacetylenes (entries 14 and 15), internal alkynes with sterically biased substituents reacted successfully with stereo- and regioselectivities similar to common alkyne-carbocyanation reactions,[3] and adducts are produced having a larger alkyne-substituent and the cyano group bound to the same sp^2-carbon (entries 16 and 17). Use of less electron-donating triphenylarsine as a ligand was

Table 2. Carbocyanation of Alkynes with Alkanenitriles Having a Coordinating Group



entry	1	2 (mmol)	n	temp (°C)	time (h)	(major) product	yield (%)[a]
1	 **1e**	**2a** (1.4)	5	80	20		88 (**3ea**)
2	 **1f**	**2a** (1.4)	5	80	9		82 (**3fa**)
3	 **1g**	**2a** (1.4)	5	80	3		79 (**3ga**)
4	R = Et: **1h** 	**2a** (2.0)	10	60	8	R = Et: **3ha** 	89
5	Ph: **1i**	**2a** (2.0)	10	60	31	Ph: **3ia**	90
6	$OSiMe_2$*t*-Bu: **1j**	**2a** (2.0)	10	60	3	$OSiMe_2$*t*-Bu: **3ja**	90
7	 **1k**	**2a** (2.0)	10	60	111		49 (**3ka**)
8	 **1l**	**2a** (1.1)	5	50	4		94 (**3la**)
9	R = Bn: **1m** 	**2a** (2.0)	10	50	20	R = Bn: **3ma** 	64
10	*t*-$BuMe_2Si$: **1n**	**2a** (2.0)	10	50	40	*t*-$BuMe_2Si$: **3na**	65
11	 **1o**	**2a** (2.0)	10	50	40		47 (**3oa**)
12	 **1p**	**2a** (2.0)	10	50	22		66 (**3pa**)
13[b]	 **1q**	**2a** (1.4)	5	50	24		79 (**3qa**)
14[c]	**1a** R = Me: **2b** (2.0)	10	50	10	R = Me: **3ab** 	72
15	**1a** CH_2SiMe_3: **2c** (1.4)	3	80	5	CH_2SiMe_3: **3ac**	94
16	**1i** Me—≡—*i*-Pr **2d** (2.0)	10	60	14		87 (**3id**)[d]
17	**1a** Me—≡—*t*-Bu **2e** (1.4)	3	80	13		88 (**3ae**)[e]
	H—≡—R					
18[f]	**1a** R = *t*-Bu: **2f** (1.4)	3	50	26	R = *t*-Bu: **3af**	74[e]
19[f,g]	**1a** Ph: **2g** (2.0)	3	50	10	Ph: **3ag**	73[e]

[a] Isolated yields based on **1**. [b] Run with P(*t*-Bu)$_3$ as a ligand. [c] Run with 60 mol % of $AlMe_3$. [d] Contaminated with 9% of regioisomer **3′id**. [e] Contaminated with <5% of regio- and/or stereoisomers. [f] Run with $AsPh_3$ (6 mol %) and B(C_6F_5)$_3$ (12 mol %). [g] Run with slow addition of **2g** over 7.5 h and additional stirring for 2.5 h.

(9) Aziridines undergo oxidative addition to nickel(0), see: Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.
(10) See Supporting Information for the synthesis of (*S*)-**1i**.

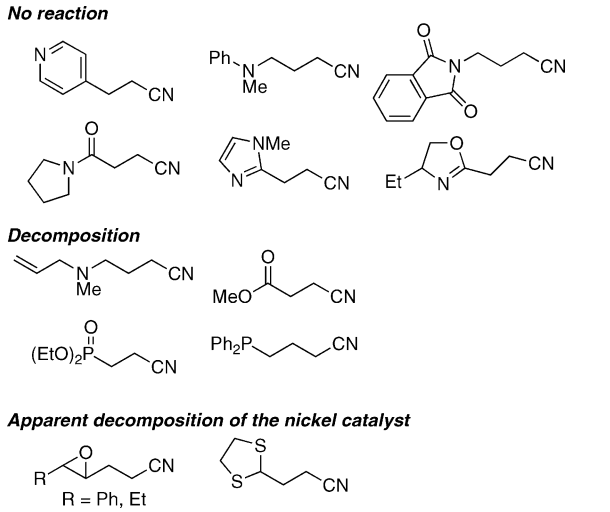
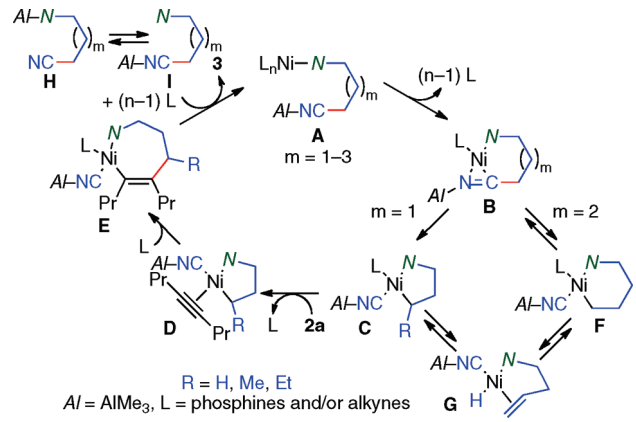


Figure 1. Nitriles inapplicable to the alkylcyanation reaction.

found to be effective for the addition across terminal alkynes (entries 18 and 19); nickel catalysts with an electron-donating phosphine were prone to induce trimerization and/or oligomerization of terminal alkynes.

All the data described above suggest a catalytic cycle involving 5-membered azanickelacycle **C** as a key intermediate generated by rapid oxidative addition of the C−CN bond of **1a** to nickel(0) through coordination of the amino group to nickel(0) (**A**) and intramolecular η^2-coordination of the cyano group (**B**), wherein the cyano nitrogen is bound to $AlMe_3$ (Scheme 1).[11] Subsequent ligand exchange (**D**), alkylnickelation (**E**), and reductive elimination afford **3aa** and regenerate **A**. No observed adduct derived from **1b** may be attributed to lack of the possibility of a 5-membered chelate, while a possible 6-membered nickelacycle **F** derived from **1c** would be reluctant to proceed through the subsequent elemental steps and undergo β-hydride elimination (**G**) followed by hydronickelation in an opposite direction to give 5-membered intermediate **C** (R = Me), which appears to be responsible for the formation of **3ca**. Similar rearrangement of nickelacycles was reported by Rovis and co-workers.[12] This isomerization would also be operative

Scheme 1. Plausible Mechanism



with **1d** through multiple β-hydride elimination−hydronickelation sequences to finally give **3da** through **C** (R = Et). The amino group can also interact with $AlMe_3$, but the resulting species **H** would not be involved in the present catalytic cycle and in equilibrium with cyano-coordinating one **I**, which can participate in the catalysis.

Conclusion

In conclusion, we have demonstrated that regio- and stereoselective alkylcyanation of alkynes is achieved by introducing a coordinating heteroatom in alkanenitriles and using nickel/LA catalysts. Accordingly, the scope of the alkylcyanation reaction is broadened significantly to allow stereoselective synthesis of various tri- and tetra-substituted ethenes having an alkyl group containing various heteroatom functionalities that allow further elaboration of the adducts. The concept to suppress β-hydride elimination presented herein will be applicable to other carbocyanation reactions especially across alkenes.

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

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