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A Dramatic Effect of Lewis-Acid Catalysts on Nickel-Catalyzed Carbocyanation of Alkynes

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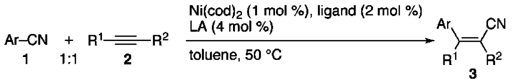
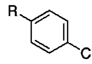
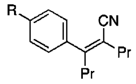
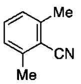
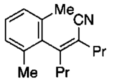
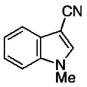
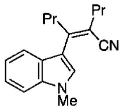
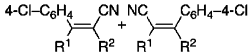
Herein, we report a dramatic effect of Lewis-acid (LA) catalysts on the nickel-catalyzed arylcyanation of alkynes[1] and the first examples of the carbocyanation reactions of alkynes using alkenyl and alkyl cyanides[2] with the aid of Ni−LA dual catalysis. Whereas LA catalysts that are assumed to activate electrophilic centers like carbonyls may further induce the potentials of transition-metal catalysis, such systems have remained relatively unexplored.[3]

As we have recently reported, the arylcyanation of alkynes using electron-rich aryl cyanides is generally sluggish.[1] Since the observed order of reactivity under the catalytic conditions apparently parallels that of the stoichiometric oxidative addition of Ar−CN bonds to Ni(0) with a positive ρ value associated with a para substituent of aryl cyanides as disclosed by Jones and co-workers,[4] we investigated the effect of a LA catalyst on the reaction of 4-methoxybenzonitrile (**1a**) with 4-octyne (**2a**), expecting acceleration of the rate of the oxidative addition.[5] We first assessed various LA catalysts together with Ni(cod)$_2$ (1 mol %) and a ligand at 50 °C to find that moderate LAs like BPh$_3$, AlMe$_3$, and AlMe$_2$Cl significantly promote the reaction and give the arylcyanation product **3aa** in over 90% yields in an exclusive cis fashion (entry 1 of Table 1).[6] In view of practicality, it is worth noting that a similar catalyst prepared in situ from air- and moisture-stable (PhMe$_2$P)$_2$NiCl$_2$ (1 mol %) and AlMe$_3$ (4 mol %) was equally effective to give **3aa** in 96% yield after 19 h.[6] Nucleophilic functionalities such as ester and THP-protected [2-(hydroxymethyl)phenyl]dimethylsilyl groups[7] were also tolerated (entries 2 and 3). Highly electron-rich 4-dimethylamino- (**1d**) and 4-diphenylaminobenzonitrile (**1e**) underwent the arylcyanation to give the corresponding adducts in good yields (entries 4 and 5). Selective activation of the Ar−CN bonds of 4-bromo- (**1f**) and 4-chlorobenzonitrile (**1g**) over the Ar−halogen bonds is highly remarkable (entries 6 and 7). Even the sterically highly demanding Ar−CN bond of 2,6-dimethylbenzonitrile (**1h**) participated in the reaction (entry 8). The selective activation of an Ar−CN bond over an Ar−H bond at C-2 in 1-methyl-3-cyanoindole (**1i**) demonstrates another chemoselective feature of the present Ni−LA catalysis (entry 9), the Ar−H bond being activated exclusively in the absence of LA.[8] Unsymmetrical alkynes underwent the reaction with **1g** to give the corresponding adducts having a larger substituent at the cyano-substituted carbon as major products, although trans adducts were also obtained (entries 10−12). The excellent chemoselectivity of the present Ni−LA catalysis allowed a single step access to **3gb**, which is the synthetic intermediate of P-3622, a squalene synthetase inhibitor (entry 10).[9]

Table 1. Nickel−LA-Catalyzed Arylcyanation of Alkynes



entry	Ar–CN	alkyne	cond.[a]	temp. (°C)	time (h)	product(s), yield (%)[b]
		$Pr-C\equiv C-Pr$				
1	R = MeO: **1a**	**2a**	A	50	16	**3aa**, 96
2	MeO$_2$C: **1b**	**2a**	A	80	25	**3ba**, 93
3	ArMe$_2$Si[c]: **1c**	**2a**	B	50	42	**3ca**, 90
4	Me$_2$N: **1d**	**2a**	A	80	21	**3da**, 87
5	Ph$_2$N: **1e**	**2a**	B	50	47	**3ea**, 91
6[d]	Br: **1f**	**2a**	A	50	27	**3fa**, 72
7	Cl: **1g**	**2a**	B	50	18	**3ga**, 94
8[d]	 **1h**	**2a**	A	100	134	 **3ha**, 78%
9	 **1i**	**2a**	A	50	116	 **3ia**, 58%
		$R^1-C\equiv C-R^2$ R^1, R^2 =				
10[e]	**1g**	Et, *p*-Anis: **2b**	A[f]	60	32	**3gb**, 53%[g] **3'gb**, 27%
11[d]	**1g**	Me, SiMe$_3$: **2c**	A[h]	80	13	**3gc**, 70%[i] **3'gc**, 9%
12[d]	**1g**	*p*-Anis, SiMe$_3$: **2d**	A[h]	60	37	**3gd**, 73%[j] **3'gd**, <5%

[a] Condition A, PPhMe$_2$ and AlMe$_2$Cl; condition B, PPh$_2$Cy and AlMe$_3$. [b] Isolated yields of isomerically pure products, unless otherwise noted. [c] Ar = 2-(THPOCH$_2$)C$_6$H$_4$. [d] The reaction was carried out using Ni(cod)$_2$ (5 mol %), ligand (10 mol %), and AlMe$_2$Cl (20 mol %). [e] The reaction was carried out using 1.2 equiv of the alkyne. [f] PPh$_2$Me was used as a ligand. [g] (*E*)-**3gb** was also obtained in 5% yield. [h] PPh$_2$(*i*-Pr) (10 mol %) was used as a ligand. [i] (*E*)/(*Z*) = 59:41 (78:22 at 5 h). [j] (*E*)/(*Z*) = 47:53 (57:43 at 12 h).

We next turned our attention to the carbocyanation reaction using alkenyl cyanides. After a brief survey of conditions for the reaction of (*E*)-cinnamonitrile (**4a**) with 4-octyne (**2a**), we found that the combination of Ni(cod)$_2$ (2 mol %), PMe$_3$ (4 mol %), and BPh$_3$ (8 mol %) efficiently catalyzed the expected alkenylcyanation reaction to give conjugated dienenitrile **5aa** in 94% yield (entry 1 of Table 2).[10] It is worth noting that the catalyst differentiates precisely the alkenyl−CN bonds of starting alkenyl cyanides from those of products possibly by steric and/or electronic factors. The reaction of (*Z*)-2-pentenenitrile (**4b**) resulted in contamination of 4*E*-isomer because of partial isomerization of **4b** to (*E*)-2-pentenenitrile before the addition took place (entry 2). Disubstituted acrylonitriles gave tetrasubstituted 2,4-pentadienenitriles in good yields (entries 3−5). Especially, selective activation of the cyano group trans to the phenyl group of benzylidenemalononitrile (**4e**) to give dicyano-substituted 1,3-diene (**5ea**) is worth noting. The substituted 2,4-pentadienenitriles thus obtained were readily converted to substituted pyridines via reduction with DIBAL-H, 6π electrocyclization, and oxidation with air as exemplified in eq 1 using **5aa**.

Finally, the Ni−LA catalyst allowed us to achieve even alkylcyanation of alkynes (Table 3). For example, acetonitrile (**7a**) added across 4-octyne (**2a**) in the presence of Ni(cod)$_2$ (5 mol %), PPh$_2$-(*t*-Bu) (10 mol %), and AlMe$_3$ (20 mol %) to give methylcyanation product **8aa** in 71% yield with a 10 mmol scale (entry 1). The fact that the reaction of CH$_3$CN-*d*$_3$ gave **8aa**-*d*$_3$ of 99% deuteriation clearly shows that the methyl group is fully derived from acetonitrile and definitely not from AlMe$_3$ (entry 2). (Trimethylsilyl)acetonitrile (**7b**) also added across **2a** to give highly substituted allylsilane **8ba** under Ni/2-Mes-C$_6$H$_4$-PCy$_2$/AlMe$_2$Cl catalyst albeit in a modest

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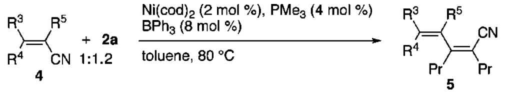
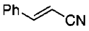
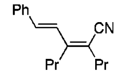
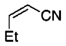
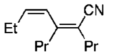
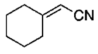
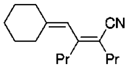
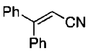
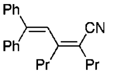
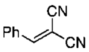
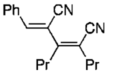
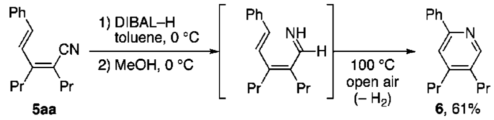
Table 2. Nickel−LA-Catalyzed Alkenylcyanation of 4-Octyne (**2a**)



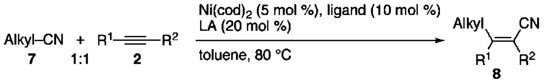
entry	alkenyl–CN		time (h)	product		yield (%)[a]
1		**4a**	20		**5aa**	94
2		**4b**	15		**5ba**	78[b]
3		**4c**	21		**5ca**	91
4		**4d**	46		**5da**	94
5[c]		**4e**	13		**5ea**	81[d]

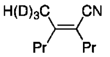
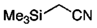
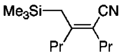
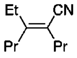
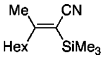
[a] Isolated yields of isomerically pure products, unless otherwise noted. [b] 4Z/4E = 84:16. [c] The reaction was carried out using Ni(cod)$_2$ (4 mol %), dppb (4 mol %), and BPh$_3$ (16 mol %). [d] An isomer was also obtained in ~2% yield.



(1)

Table 3. Nickel−LA-Catalyzed Alkylcyanation of Alkynes



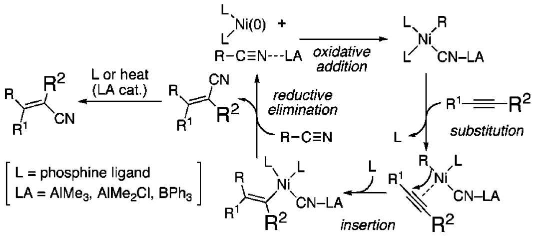
entry	alkyl–CN		alkyne	cond.[a]	time (h)	product		yield (%)[b]
1[c]	Me–CN	**7a**	**2a**	C	4		**8aa**	71
2	CD$_3$–CN	**7a**-d_3	**2a**	C	5		**8aa**-d_3	66[d]
3		**7b**	**2a**	D	17		**8ba**	29
4[c]	Et–CN	**7c**	**2a**	D	20		**8ca**	24
5[e]	**7a**		Hex—≡—SiMe$_3$ **2e**	D[f]	12		**8ae**	74[g]

[a] Condition C, PPh$_2$(t-Bu) and AlMe$_3$; condition D, 2-Mes-C$_6$H$_4$-PCy$_2$ and AlMe$_2$Cl. [b] Isolated yields of isomerically pure products, unless otherwise noted. [c] The reaction was carried with a 10 mmol scale. [d] 99% deuteriation. [e] The reaction was carried out using 2.0 equiv of **7a** and Ni(cod)$_2$ (10 mol %). [f] PPhCy$_2$ (20 mol %) and AlMe$_2$Cl (40 mol %) were used. [g] (Z)/(E) = 91:9 (93:7 at 3 h).

yield (entry 3). Under the identical conditions, propionitrile (**7c**) gave ethylcyanation product (**8ca**) in 24% yield (entry 4). The low yield of **8ca** can be ascribed partly to the formation of (E)-2-propyl-2-hexenenitrile (**9**), which was produced possibly via oxidative addition of Et−CN bond to Ni(0) followed by β-hydride elimination and hydrocyanation of **2a**.[11] Trimethyl(1-octynyl)silane (**2e**) participated in the methylcyanation reaction in a highly regioselective manner (entry 5).

The observed dramatic effects of LA catalysis would be derived primarily from acceleration of the oxidative addition of C−CN bonds by coordination of a cyano group to a LA catalyst as we expected (Scheme 1),[5] but positive effects on the reductive elimination of C−CN bonds[12] and/or other elemental steps could also be operative. Although a rationale for optimum combinations of ligands and LA catalysts remains elusive, electron-donating ligands are generally essential for making the nickel-center electron-rich enough to cleave C−CN bonds. Coordination of an alkyne in the direction avoiding the steric repulsion between bulkier R^2 and an aryl group would be responsible for the observed regioselectivities.[1b] Trans adducts would be derived from phosphine- and/or heat-mediated isomerization of the initial cis adducts, because the ratios between the stereoisomers are variable depending on the conditions. A silyl group tends to further facilitate the isomerization.[1b]

Scheme 1 Plausible Mechanism of the Nickel−LA-Catalyzed Carbocyanation of Alkynes



In conclusion, we have demonstrated that Ni−LA catalysts are significantly effective for carbocyanation of alkynes, and thus not only aryl cyanides but also alkenyl and alkyl cyanides can be employed as substrates for the reaction. Application of this cooperative catalysis to carbocyanation reactions using other nitriles and/or unsaturated compounds as well as novel catalytic reactions involving activation of otherwise inert chemical bonds will be extensively investigated.

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

References

(1) (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (b) Nakao, Y.; Oda, S.; Yada, A.; Hiyama, T. *Tetrahedron* **2006**, *62*, 7567.
(2) For allylcyanation of alkynes, see Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116.
(3) (a) Kamijo, S.; Yamamoto, Y. In *Multimetallic Catalysis in Organic Synthesis*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 22. (b) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903. (c) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174. (d) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598. (e) Tsuchimoto, T.; Kamiyama, S.; Negoro, R.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 852. (f) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440. (g) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818.
(4) Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *125*, 9547.
(5) (a) Starowieyski, K.; Pasynkiewicz, S.; Boleslawski, M. *J. Organomet. Chem.* **1967**, *10*, 393. (b) Tolman, C. A.; Seidel, W. C.; Druliner, J. D.; Domaille, P. J. *Organometallics* **1984**, *3*, 33. (c) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627.
(6) See Supporting Information for details.
(7) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952.
(8) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146.
(9) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380 and references therein.
(10) Acrylonitrile gave a complex mixture under the present conditions.
(11) Garcia, J. J.; Arevalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997.
(12) Huang, J.; Haar, C. M.; Nolan, S. P.; Marcone, J. E.; Moloy, K. G. *Organometallics* **1999**, *18*, 297.

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