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Nickel/$AlMe_2Cl$-catalysed carbocyanation of alkynes using arylacetonitriles†‡

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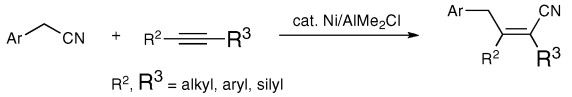
Nickel/Lewis acid dual catalysis was found to effect the carbocyanation reaction of alkynes using arylacetonitriles, giving a range of triply substituted acrylonitriles; the reaction of optically active α-phenylpropionitrile suggested a reaction mechanism that involves oxidative addition of a C–CN bond with retention of its absolute configuration.

The stereoselective synthesis of polysubstituted alkenes has been a major subject in organic synthesis.[1] To this end, we[2] and others[3] have demonstrated the carbocyanation reaction[4] of alkynes as a new entry to stereochemically well-defined and atom economical protocols for the synthesis of tri- or disubstituted acrylonitriles, versatile synthetic intermediates for polysubstituted alkenes. While we have recently disclosed that the use of Lewis acid (LA) cocatalysts significantly promotes the carbocyanation reaction of alkynes to allow the addition of acetonitrile, the attempted addition of propionitrile resulted in a low yield of the corresponding ethylcyanation product due to β-hydride elimination.[2d] In this communication, we report the carbocyanation reaction of alkynes with arylacetonitriles to give a wide variety of tri- and disubstituted acrylonitriles with a functional group regio- and stereoselectively (eqn (1)).



(1)

Initially, we examined the reaction of benzyl cyanide (**1a**, 1.0 mmol) with 4-octyne (**2a**, 1.0 mmol) in toluene in the presence of $Ni(cod)_2$ (2 mol%), 2-Mes–C_6H_4–PCy_2[5] (**L1**, 4 mol%), and $AlMe_2Cl$ (8 mol%) as a Lewis acid, an optimized set of catalysts for the reaction of propionitrile.[2d] The reaction proceeded smoothly at 35 °C to afford the corresponding *cis*-benzylcyanation product, **3aa**, in 90% yield after 8 h (entry 1 of Table 1). We further studied the scope of benzyl cyanides with substituents on the phenyl ring, and found that a range of functional groups, such as chloro, acetal and ester moieties, were compatible with both electron-rich nickel(0) and LA catalysis, with the C–CN bonds being activated exclusively to give various (*Z*)-3-arylmethyl-2,3-dipropylacrylonitriles (entries 2–8). Naphthyl and heteroaryl derivatives also participated in the reaction (entries 9–12). Notably, no *N*-protecting group was necessary for pyrrole (**1k**) and indole (**1l**) substrates (entries 11–12). Even the sterically hindered C–CN bond of diphenylacetonitrile (**1m**) was activated to give the corresponding adduct with a tertiary carbon, albeit in a low yield (entry 13).

The scope of alkynes with benzyl cyanide (**1a**) is shown in Table 2. As a symmetrical alkyne, 1,4-bis(trimethylsilyl)-2-butyne (**2b**) participated in the benzylcyanation reaction to afford **3ab** in 93% yield in an exclusive *cis*-fashion (entry 1), whereas the addition reaction across diphenylacetylene (**2c**) gave a mixture of stereoisomers (entry 2). The stereochemistry of (*Z*)-**3ac** was unambiguously confirmed by X-ray crystallography (Fig. 1).‡ Internal unsymmetrical alkynes with sterically biased substituents reacted with modest to excellent regio- and stereoselectivities (entries 3–6). While the regioselectivity across 2-pentyne (**2d**) was modest because of small steric differences in the substituents (entry 3), 4,4-dimethyl-2-pentyne (**2e**), 1-phenyl-1-propyne (**2f**) and trimethyl(1-propynyl)silane (**2g**) all reacted regioselectively to afford an isomer with a lager substituent at the cyano-substituted carbon as a major product (entries 3, 5 and 6).[6]

To gain a mechanistic insight, (*S*)-α-phenylpropionitrile [(*S*)-**1n**][7] of 85% ee was reacted with **2a** under slightly modified conditions using $Ni(cod)_2$ (20 mol%), 2-(2,4,6-*i*-Pr_3–C_6H_2)–C_6H_4–PCy_2 (**L2**, 40 mol%),[5] and $AlMe_2Cl$ (20 mol%) (eqn (2)). The corresponding adduct, (*S*)-**3na**, of 41% ee was obtained in 22% yield, the absolute configuration being determined based on the reported optical rotation of (*R*)-2-phenyl-3-hexanone[8] after oxidative cleavage of the double bond. Also obtained were hydrocyanation product **4**, styrene **5** and hydrocinnamonitrile **6** in 35, 44 and 3% yields, respectively, as estimated by GC. Recovered **1n** showed 80% ee, suggesting that background racemization of **1n** under these conditions appears to be slower than the carbocyanation event. We also confirmed that no further racemization of **3na** took place under the present conditions. Accordingly, these results clearly suggest the mechanism shown in Scheme 1, which should start with oxidative addition of a C–CN bond with *retention* of configuration through the LA adduct of η^2-nitrile nickel species **A**[4g] to give **B**.[9] The oxidative addition of acetonitrile to nickel(0) has also been suggested to proceed in a similar manner by theoretical calculations.[10] This

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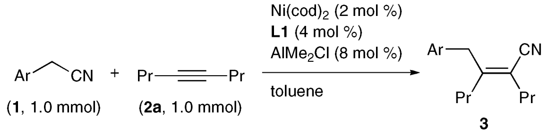
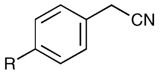
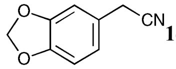
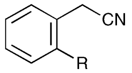
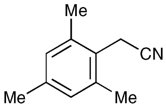
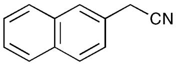
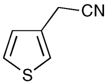
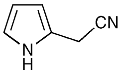
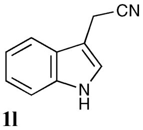
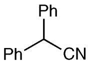
‡ Electronic supplementary information (ESI) available: General experimental information, spectral data and crystallographic data (excluding structure factors) for the structure of (*Z*)-**3ac**. CCDC 727199. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b907290j

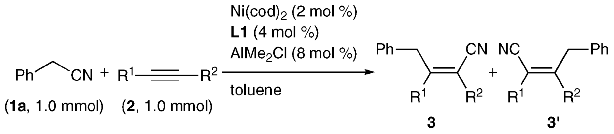
Table 1 Nickel/AlMe$_2$Cl-catalysed carbocyanation of 4-octyne using arylacetonitriles

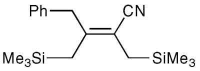
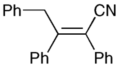
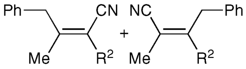


Entry	Arylacetonitrile	Temp/°C	Time/h	Product	Yield (%)[a]
					
1	R = H: **1a**	35	8	**3aa**	90
2	Ph: **1b**	35	8	**3ba**	90
3	Cl: **1c**	80	18	**3ca**	74
4	MeO: **1d**	35	8	**3da**	93
5	 **1e**	35	24	**3ea**	96
					
6[b]	R = CO$_2$Me: **1f**	80	5	**3fa**	56
7	MeO: **1g**	35	24	**3ga**	83
8	 **1h**	80	2	**3ha**	85
9	 **1i**	35	96	**3ia**	85
10	 **1j**	80	2	**3ja**	95
11[b]	 **1k**	35	10	**3ka**	54
12[b]	 **1l**	35	48	**3la**	69
13[b]	 **1m**	100	12	**3ma**	22

[a] Isolated yields. [b] The reaction was carried out using Ni(cod)$_2$ (10 mol%), **L1** (20 mol%), and AlMe$_2$Cl (40 mol%).

Table 2 Nickel/AlMe$_2$Cl-catalysed carbocyanation of alkynes using phenylacetonitrile



Entry	R^1, R^2	Temp/°C	Time/h	Product(s), yield (%),[a] ratio[b]
1	CH$_2$SiMe$_3$ (**2b**)	80	70	 **3ab**, 93
2	Ph (**2c**)	80	73	 **3ac**, 86[c]
				
3	Me, Et (**2d**)	35	24	**3ad**, **3′ad**, 69, 59 : 41
4	Me, *t*-Bu (**2e**)	35	8	**3ae**, **3′ae**, 94, >99 : 1
5	Me, Ph (**2f**)	35	21	**3af**, **3′af**, 85, 92 : 8
6[d]	Me, SiMe$_3$ (**2g**)	35	53	**3ag**, **3′ag**, 56, 81 : 19

[a] Isolated yields. [b] Estimated by ^{1}H NMR of the crude product. [c] *E* : *Z* = 79 : 21 (82 : 18 at 1.5 h). [d] The reaction was carried out using Ni(cod)$_2$ (10 mol%), **L1** (20 mol%), and AlMe$_2$Cl (40 mol%).

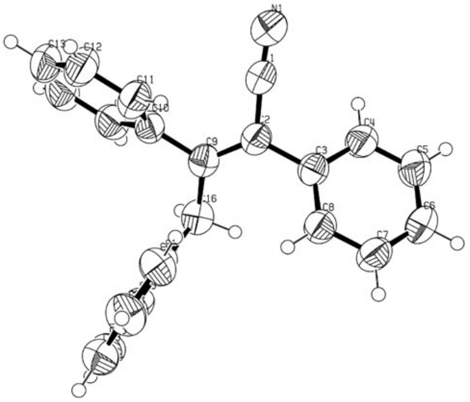
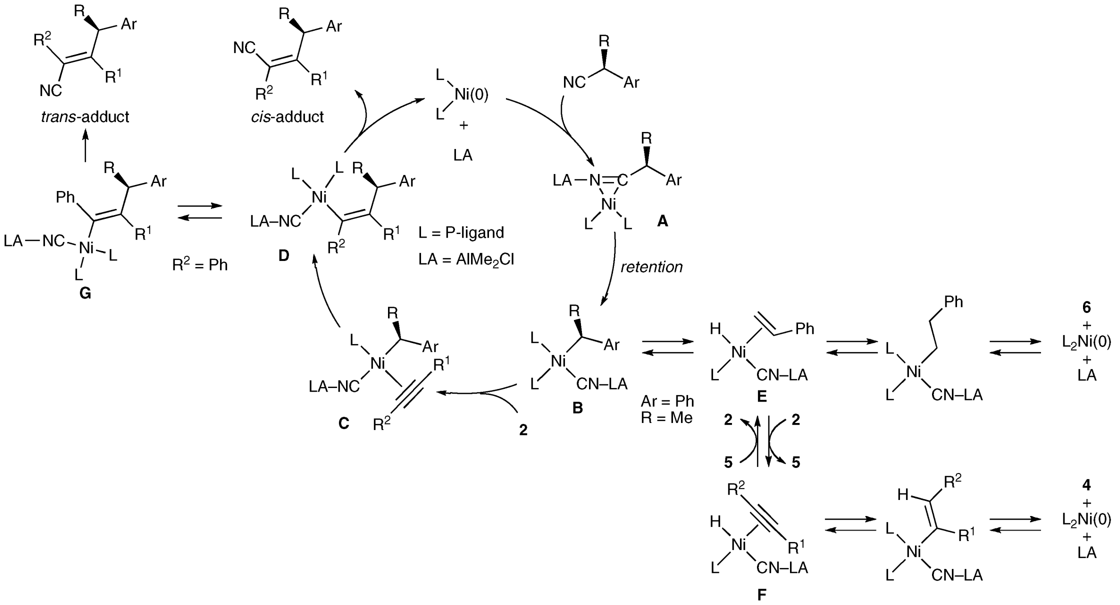
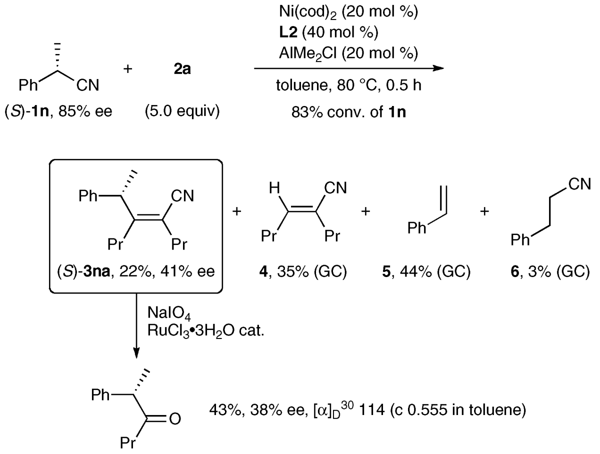


Fig. 1 ORTEP drawing for (*Z*)-**3ac**.

contrasts with non-stereospecific oxidative addition of benzyl halides to nickel(0).[11] Coordination of alkynes and then migratory insertion into ArCH$_2$–Ni bonds in **B**, giving **D** *via* **C**, followed by reductive elimination from **D**, would give the carbocyanation products and regenerate nickel(0) species, with the absolute configuration being retained during these elemental steps.[12] The partial loss of ee during the addition reaction may be ascribed to β-hydride elimination, and subsequent equilibrium between **E** and **F** followed by re-insertion. Particularly, the formation of **4**, styrene and hydrocinnamonitrile is in accord with these side reactions. In the case of phenyl substituted alkynes, **D** would isomerize to **G**, possibly through the conjugate addition of phosphorus ligands[13] followed by reductive elimination to give the *trans*-adduct. A LA catalyst is likely to accelerate the primary oxidative addition step,[2d,4f,4g,14] though other elemental steps may also be facilitated by the coordination of a cyano group to a LA catalyst.[9,15]



Scheme 1 Plausible mechanism.



(2)

In summary, we have demonstrated a nickel/Lewis acid-catalyzed stereo- and regioselective carbocyanation of alkynes using arylacetonitriles. Using (*S*)-α-phenylpropionitrile, the mechanism of the carbocyanation reaction including the oxidative addition of C–CN bonds with retention of its absolute configuration has been elucidated. Current efforts are directed to the development of a catalyst system for the carbocyanation reaction of alkynes using alkyl cyanides with a β-hydrogen, as well as other unsaturated bonds.

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