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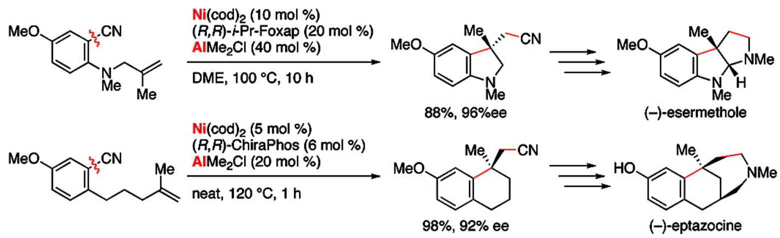

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Intramolecular Arylcyanation of Alkenes Catalyzed by Nickel/$AlMe_2Cl$

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We report herein the intramolecular arylcyanation reaction of alkenes catalyzed cooperatively by nickel and $AlMe_2Cl$. The reaction allows us to simultaneously construct both benzylic quaternary carbons and C−CN bonds in a single operation with high atom economy. The scope and mechanism are investigated as well as preliminary results on the enantioselective version of the reaction to provide novel access to asymmetric quaternary stereocenters.[1]

We recently disclosed that the arylcyanation reaction of alkynes[2] is significantly accelerated by Lewis acid catalysts.[3,4] The synergistic catalysis has been found to be very powerful for the activation of C−CN bonds of a range of nitriles, allowing the participation of even acetonitrile in the carbocyanation reaction. We then became interested in application of the binary catalysis to alkenes as substrates, because the transformation would afford nitriles with up to two newly formed sp^3-carbon stereocenters.[5] First, we synthesized **1a**[6] to examine the feasibility of the intramolecular arylcyanation reaction across double bonds (entry 1, Table 1).[7] Treatment of **1a** with $Ni(cod)_2$ (5 mol %), PMe_3 (10 mol %), and $AlMe_2Cl$ (20 mol %) in toluene at 100 °C for 7 h gave **2a** in 93% yield, which was derived from the insertion of the olefinic moiety into the Ar−CN bond in a 5-*exo*-trig fashion. Only a trace amount of the adduct was observed in the absence of $AlMe_2Cl$. Silyl and amino tethers as well as methoxy and chloro groups on the aromatic ring were all tolerated under these conditions to afford corresponding nitriles **2b**−**2g** in good yields (entries 2−8). Disubstituted double bonds conjugated with a carbonyl and those having a phenyl or silyl substituent also participated in the addition reaction (entries 9−12). A high degree of stereospecificity was observed with **1k** and **1l**, giving the respective diastereomers **2k** and **2l** (entries 13−15).[8] Thus, the alkene-arylcyanation proceeds through syn stereochemistry. Larger ring systems including six- and seven-membered compounds were successfully constructed (entries 16−20), whereas no four-membered ring formation was observed from 2-allylbenzonitrile. Reactions of benzonitriles bearing a monosubstituted double bond such as 2-(but-3-en-1-yl)benzonitrile resulted in olefin isomerization and the formation of 1-methylindene derived probably from carbonickelation followed by β-hydride elimination and isomerization (vide infra).

By studying the stoichiometric reaction of substrate **1a** with a nickel(0) species, probable reaction intermediates were observed and characterized by NMR spectroscopy and/or X-ray crystal structure determination (Scheme 1). The reaction of $Ni(cod)_2$, $P(n\text{-}Bu)_3$, $AlMe_2Cl$, and **1a** gave the $AlMe_2Cl$ adduct of η^2-nitrile complex **3** immediately.[9−11] $AlMe_2Cl$ seems to promote the coordination of the cyano group to nickel(0), because no η^2-nitrile complex was observed in its absence. The oxidative addition of the Ar−CN bond of **3** proceeded at room temp within 6 h to give **4**.[4,12] The molecular structures of **3** and **4** were unambiguously identified by X-ray crystallography (Figure 1). Upon heating at 60 °C for 46 h, **4** was further converted to **6**[13] presumably via **5**, the insertion step through a tetra- or penta-coordinate intermediate or the preceding ligand exchange step appearing to be rate-determining. Treatment of **6** with a stoichiometric amount of **1a** resulted in regeneration of **3**, suggesting

Table 1. Nickel/$AlMe_2Cl$-Catalyzed Intramolecular Arylcyanation of Alkenes[a]

entry	substrate	ligand	time (h)	product	yield (%)[b]
1	**1a**	PMe_3	7	**2a**	93
2	**1b**	PMe_3	20	**2b**	18[c]
3	**1b**	$PCyPh_2$	20	**2b**	92
4[d]	R = H (**1c**)	PMe_3	4	**2c**	86
5	R = MeO (**1d**)	PMe_3	3	**2d**	76
6	R = H (**1e**)	PMe_3	7	**2e**	79
7	R = Cl (**1f**)	PMe_3	7	**2f**	82
8	R = MeO (**1g**)	PMe_3	7	**2g**	85
9	**1h**	PMe_3	3	**2h**	71[c]
10	**1h**	PPh_3	3	**2h**	74
11	R = Ph (**1i**)	PMe_3	6	**2i**	89
12	R = $SiMe_2Ph$ (**1j**)	PMe_3	6	**2j**	84
13	**1k**	PMe_3	0.5	**2k**	48[c,e]
14	**1k**	PMe_2Ph	0.5	**2k**	88[e]
15	**1l**	PMe_2Ph	1	**2l**	76[f]
16	**1m**	PMe_3	3	**2m**	16[c]
17	**1m**	DMPE[g]	3	**2m**	91
18	**1n**	PMe_3	3	**2n**	96
19	**1o**	PMe_3	5	**2o**	9[c]
20	**1o**	DMPE[g]	5	**2o**	58

[a] The reactions were carried out using a substrate (1.0 mmol), $Ni(cod)_2$ (5 mol %), a ligand (10 mol %), and $AlMe_2Cl$ (20 mol %) in toluene at 100 °C. [b] Isolated yields. [c] Yields estimated by GC with a 0.036−0.100 mmol scale. [d] Reaction run on a 3.0 mmol scale. [e] dr = 98:2 (>99:1 after isolation). [f] dr = 97:3 (>99:1 after isolation). [g] $Me_2P(CH_2)_2PMe_2$ (5 mol %).

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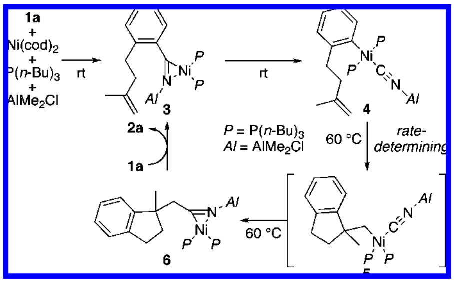
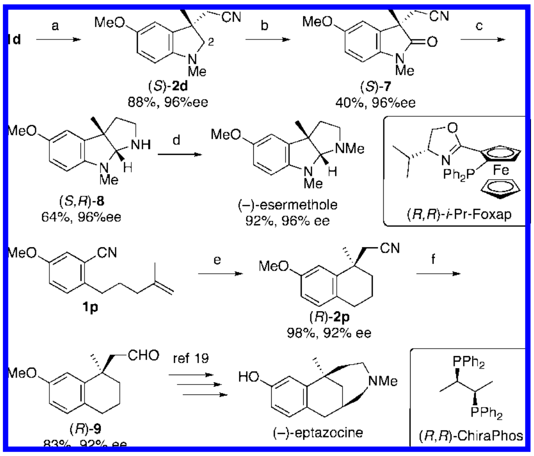
Scheme 1. Plausible Mechanism of the Reaction



Scheme 2. Enantioselective Intramolecular Arylcyanation and Its Application to Natural Product Syntheses[a]



[a] Reagents and Conditions: (a) Ni(cod)$_2$ (10 mol %), (*R*,*R*)-*i*-Pr-Foxap (20 mol %), AlMe$_2$Cl (40 mol %), DME, 100 °C, 10 h; (b) PhIO (6.0 equiv), CH$_2$Cl$_2$, room temp, 2.5 h; (c) LiAlH$_4$ (4.0 equiv), THF, room temp, 1 h, then reflux, 0.5 h; (d) HCHO aq (5.0 equiv), NaBH(OAc)$_3$ (5.0 equiv), MeOH, 0 °C to room temp, 1.5 h; (e) neat, Ni(cod)$_2$ (5 mol %), (*R*,*R*)-ChiraPhos (6 mol %), AlMe$_2$Cl (20 mol %), 120 °C, 1 h; (f) DIBAL-H (2.0 equiv), toluene, −78 °C, 2 h, then 1 M HCl (aq), THF, 0 °C to room temp, 2 h.

that the formation of the η^2-nitrile complex is more favorable for conjugated nitriles than alkyl cyanides because of the lower energy levels of the π^* orbitals of the conjugated cyano groups to better stabilize back-bonding interactions with nickel(0).[14]

With a broad substrate scope and mechanistic insights, we focused on the asymmetric version of the reaction.[15] After a brief survey of chiral ligands for the reaction of **1d**, phosphino-oxazoline ligand (*R*,*R*)-*i*-Pr-Foxap[16] was found effective to give (*S*)-**2d** in 96% ee and 88% yield (Scheme 2). Oxidation of the C-2 position of the indoline framework gave (*S*)-**7**,[17] which was converted to (−)-esermethole through (*S*,*R*)-**8**,[7,18] a synthetic precursor of potent acetylcholinesterase inhibitors such as (−)-physostigmine[19] and (−)-phenserine.[20] Yet, the enantioselective formation of a six-membered ring was achieved with **1p** using (*R*,*R*)-ChiraPhos as a ligand to give (*R*)-**2p** in 92% ee and 98% yield. The cyano group of (*R*)-**2p** was reduced to give aldehyde (*R*)-**9**, which is a synthetic precursor of (−)-eptazocine, an analgesic substance available commercially.[21]

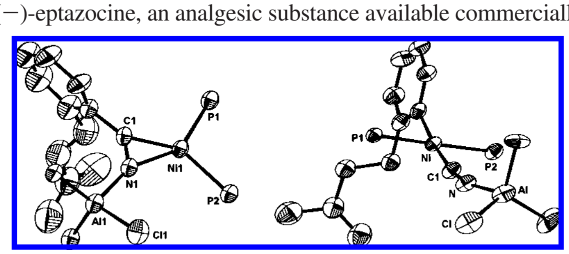


Figure 1. Molecular structures of **3** and **4**. Butyl groups are omitted.

In summary, the intramolecular arylcyanation of alkenes is demonstrated to be a versatile protocol to synthesize a range of synthetically interesting nitriles having a benzylic quaternary carbon. Characterization of important intermediates in the catalytic cycle and synthetic applications including enantioselective versions of the reaction has also been achieved. Efforts are currently directed toward development of similar transformations of nitriles of other types as well as the intermolecular arylcyanation of olefins.

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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.

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(8) The relative stereochemistry of **2k** was determined by X-ray crystallography.
(9) Selected spectral data for **3**. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ −0.26 (s, 6H, −Al(C***H***$_3$)$_2$Cl), 4.84 (s, 1H, −CH$_2$CH$_2$C(CH$_3$)=C***H***$_2$), 4.93 (s, 1H, −CH$_2$CH$_2$C(CH$_3$)=C***H***$_2$). ^{13}C NMR (100 MHz, C$_6$D$_6$): δ −5.8 (s, −Al(***C***H$_3$)$_2$Cl), 110.4 (s, −CH$_2$CH$_2$C(CH$_3$)=***C***H$_2$), 145.5 (s, −CH$_2$CH$_2$***C***(CH$_3$)=CH$_2$), 183.9 (dd, J_{CP} = 10.6, 35.7 Hz, −***C***N). ^{31}P NMR (109 MHz, C$_6$D$_6$): δ 7.4 (d, J_{PP} = 24.0 Hz), 18.1 (d, J_{PP} = 24.0 Hz).
(10) A triethylborane adduct of a η^2-acetonitrile nickel complex has been reported by Jones, see: Atesin, T. A.; Li, T.; Lachaize, S.; Brennessel, W. W.; Garcia, J. J.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7562.
(11) The catalytic reaction of **1a** employing PBu$_3$ as a ligand also gave **2a** in a good yield.
(12) Selected spectral data for **4**. ^{1}H NMR (400 MHz, C$_6$D$_6$): δ −0.06 (s, 6H, −Al(C***H***$_3$)$_2$Cl), 4.91 (s, 1H, −CH$_2$CH$_2$C(CH$_3$)=C***H***$_2$), 4.96 (s, 1H, −CH$_2$CH$_2$C(CH$_3$)=C***H***$_2$). ^{13}C NMR (100 MHz, C$_6$D$_6$): δ −6.8 (brs, −Al(***C***H$_3$)$_2$Cl), 110.3 (s, −CH$_2$CH$_2$C(CH$_3$)=***C***H$_2$), 145.7 (s, −CH$_2$CH$_2$***C***(CH$_3$)=CH$_2$), 154.8 (t, J_{CP} = 23.1 Hz, −***C***N). ^{31}P NMR (109 MHz, C$_6$D$_6$): δ 13.5 (s).
(13) Selected spectral data for **6**. ^{1}H NMR (270 MHz, C$_6$D$_6$): δ 0.03 (s, 3H,−Al(C***H***$_3$)$_2$Cl), 0.04 (s, 3H,−Al(C***H***$_3$)$_2$Cl). ^{31}P NMR (109 MHz, C$_6$D$_6$): δ 5.4 (d, J_{PP} = 27.3 Hz), 18.7 (d, J_{PP} = 27.3 Hz).
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