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A Catalytic Version of a Nickel Promoted Intramolecular Tandem Cyclization-Cyanation Process

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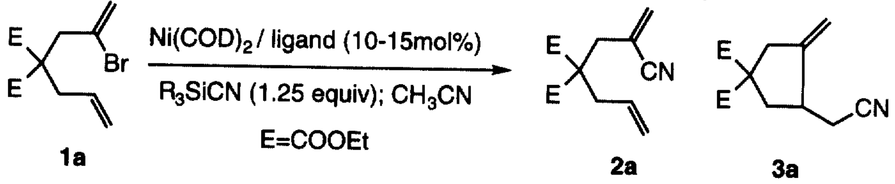
Abstract: A catalytic version of the intramolecular Ni-promoted tandem cyclization-cyanation process is described. Generally, the reaction leads to mixtures of cyclic and open chain adducts in moderate to good yields. The presence of external bidendate nitrogen ligands, although not essential for the reaction outcome, provides stability to the catalytic system.

As a result from our previous studies on stoichiometric intramolecular nickel promoted tandem cyclization-quenching of tethered vinyl bromides and alkenes,[1] we found trimethylsilylcyanide (TMSCN) to be an efficient quencher for the synthesis of carbo- and heterocyclic cyanomethyl derivatives. Due to the versatility and synthetic potential of this transformation, we focused our interest on the development of a catalytic version of the above process (Scheme 1). We describe herein our preliminary results along this line.



Scheme 1

For exploratory purposes, bromodiene **1a** was selected as a model substrate in order to optimize the reaction parameters (see Figure 1). Thus, treatment of **1a** with 10-15% Ni(COD)$_2$, 1 mol/equiv of a ligand and 1.2 equiv of trimethylsilyl cyanide (TMSCN) or triethylsilyl cyanide (TESCN)[2] in dry CH$_3$CN at room temperature,[3] cleanly afforded a mixture of the desired cycloadduct **3a**[4] and the open chain nitrile **2a**[5] in good to excellent overall yield as the only isolable products.[6] Interestingly, neither cyclic 1,4-dienes arising from β-hydride elimination from the presumed cycloalkylmethylnickel intermediate (see Scheme 2) nor isocyanide insertion adducts[7,8] were observed in our catalytic system. As a general trend, nitrogen ligands gave rise to higher conversion rates (between 70-100% after 0.5-3 h), whereas phosphorus ligands afforded better ratios of

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cyclic vs. linear adducts, albeit in low conversion even after prolonged reaction times.[9] Interestingly, the reaction took place even in the absence of external ligands, since total conversion of **1a** into a 1:1 mixture of **2a** and **3a** was observed after 30 min.

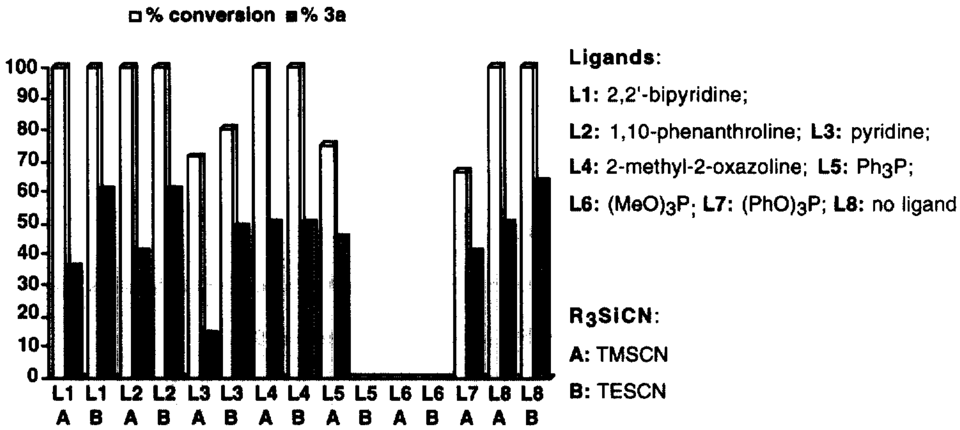
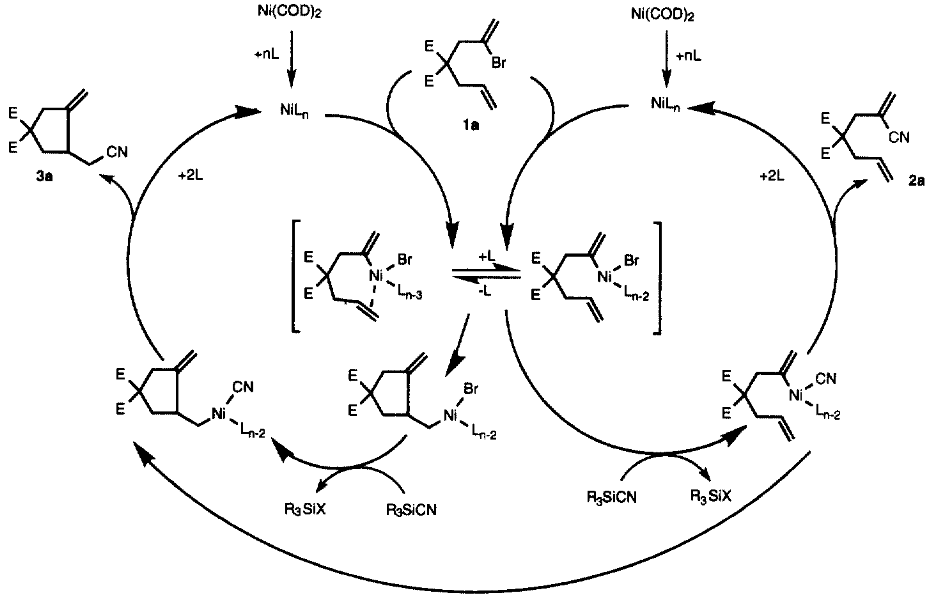


FIGURE 1

From a mechanistic standpoint, the overall process can be interpreted as the replacement of bromide by cyanide with or without olefin insertion, as depicted in Scheme 2. Oxidative addition of a nickel complex into the vinyl-Br bond would give a vinyl nickel intermediate that can cyclize either prior or after exchange of the bromo ligand by cyanide. Reductive elimination of alkenyl- or cycloalkylmethyl cyanonickel intermediates[10] would lead to open chain or cyclic nitriles respectively. This mechanistic proposal would reflect a competition between the rates of cyclization, bromo-cyano exchange, and reductive elimination.

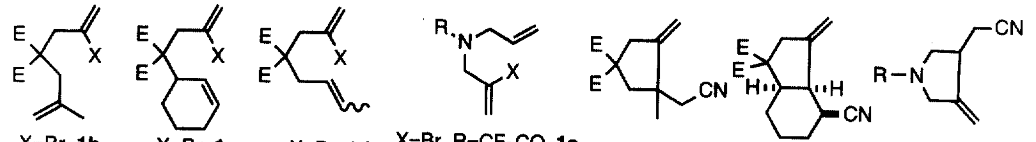


Scheme 2

Since the rate of exchange of bromide by cyanide can be controlled, in part, by the nature of the alkyl groups on the silyl cyanide, different trialkylsilylcyanides were evaluated starting from bromodiene **1a** in the presence of 2,2'-bipyridine as a ligand. As a general trend, bulky cyanides (Pr_3SiCN, *i*$PrMe_2SiCN$ and *t*$BuMe_2SiCN$)[2] gave rise to sluggish or uncomplete reactions where the open chain adduct **2a** was predominant. Among the cyanides tested, TMSCN and TESCN were chosen for further studies due to their efficiency in terms of reaction rates, overall substrate conversion, and product distribution. As above, the presence of an external ligand did not improve the overall efficiency of the catalytic process.[7] However, since the stability of the catalytic system was consistently higher in the presence of external ligands, we chose $Ni(COD)_2$/bipy (1:1, 15% mol) and TESCN (1.25 equiv) as standard catalytic system for further development.[11]

Several substrates were subjected to our standard catalytic tandem cyclization-cyanation system, as indicated in Table 1.

TABLE 1



X=Br, **1b**
X=CN, **2b**

X=Br, **1c**
X=CN, **2c**

X=Br, **1d**
X=CN, **2d**

X=Br, R=CF_3CO, **1e**
X=Br, R=Bn, **1f**
X=CN, R=CF_3CO, **2e**
X=CN, R=Bn, **2f**

3b

3c

E=COOEt

R=CF_3CO, **3e**
R=$PhCH_2$, **3f**

Entry	Substrate	Products(1)		Ratio 2 / 3	yield (%)[2]
1	**1a**	**2a**	**3a**	40: 60(3)	98
2	**1b**	**2b**	**3b**	30: 70	77
3	**1c**	**2c**	**3c**	55: 45	100
4	**1d**	**2d**	---	100: 0	47 (4)
5	**1e**	**2e**	**3e**	25: 75	75
6	**1f**	---	**3f**	0: 100	38 (5)

(1) For a general reaction procedure, see ref. 11
(2) overall isolated yield
(3) Experiments with $Ni(COD)_2$/2,2'-bipyridine (50%mol and 100% mol), improved the ratio **2a/3a** to 20:80 and 15:85, respectively
(4) 50 % recovered starting material
(5) Together with a mixture of unidentified products

The olefin insertion step was shown to be dependent upon the substitution patterns on the starting olefinic moiety, as indicated by **1d** (entry 4), where only the open chain adduct **2d** was observed. However, it is worth noting that bromodiene **1c** (entry 3) afforded cyclised adduct **3c** with total diastereoselectivity.[12] Surprisingly, amino-tethered bromodiene **1f** showed sluggish reactivity in comparison with that of the corresponding malonate analogue **1a** (compare entry 6 with 1). As indirect evidence of the low tolerance of this catalytic system towards amines as substrates, trifluoroacetamide **1e** (entry 5) afforded a reaction mixture comparable to that of **1a**, although in somewhat lower overall yield.

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References and Notes

1. a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133-12134. b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895-5904. c) Cancho, Y.; Martín, J.M.; Martínez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221-1232.

2. Prepared by transcyanation of the corresponding chlorotrialkylsilane with TMSCN according to: Becu, C.; Anteunis, M.J.O. *Bull. Soc. Chim. Belg.* **1987**, *96*, 115-117.

3. Although reactions at 0°C led to major formation of cyclic vs. linear adducts, low product conversions were always found. On the other hand, by heating to 40°C, no improvement of the cyclic vs. linear ratio was observed in comparison with room temperature experiments.

4. For related Pd(0) carbocyanation of unsaturated bonds incapable of hydrogen beta-elimination see: a) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1988**, *23*, 3499-3502. b) Grigg, R.; Santhakumar, S.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 3163-3164.

5. For a Ni(0) catalyzed cyanation of vinyl halides see: Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3137-3143.

6. Taking into account the stoichiometry of the reaction, trialkylsilyl bromides are presumably formed. Although we have not been able to isolate any of them due to the aqueous work-up, the corresponding trialkylsilanols have been isolated from crude reaction mixtures, and identified from their ^{1}H and ^{13}CNMR spectra.

7. Participation of a trialkylisonitrile, arising from a cyanide-isonitrile tautomerism, as a ligand in the catalytic process cannot be ruled out. For a Ni(0) catalyzed trialkylisonitrile insertion process see: Zhang, M.; Buchwald, S. L. *J. Org. Chem.*, **1996**, *61*, 4498-4499.

8. For metal-catalyzed silyl-cyanation of triple bonds see: Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635-8638. Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.*, **1988**, *53*, 3539-3548.

9. In some instances, prolonged reaction times led to decomposition of the catalytic system, as evidenced by precipitation of insoluble material from the reaction mixture.

10. Reductive elimination on alkylcyanonickel compounds to give nitriles has been extensively studied in relation to the mechanism of nickel catalyzed hydrocyanation of olefins. See: a) Casalnuovo, A.L.; RajanBabu, T.V.; Ayers, T.A.; Warren, T.H. *J. Am. Chem. Soc.* **1994**, *116*, 9869-9882. b) Tolman, C.A.; McKinney, R.J.; Seidel, W.C.; Druliner, J.D.; Stevens, W.R. *Adv. Catal.*, **1985**, *33*, 1-46 and references therein.

11. Typical experimental: A solution of 2,2'-bipyridine (0.15 equiv), in deoxygenated and freshly distilled CH_3CN (1 mL) is added dropwise under Ar to a solution of $Ni(COD)_2$ (0.15 equiv) in CH_3CN (20 mL) at room temperature. Immediately after, a solution of the starting vinyl halide **1** (1 mmol, see Table 1) and TESCN (1.25 equiv) in CH_3CN (20 mL) is added dropwise. The reaction is stirred at room temperature until no starting material is observed (tlc monitoring, typically 0.5-3 h) and evaporated to dryness. The residue is treated with 1*N* HCl (5 mL) and saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O. Drying (Na_2SO_4) and evaporation afforded a crude which was purified by flash chromatography. Optimization of reaction parameters was similarly carried out from **1a** as the starting halide (1 mmol), the appropriate ligands L_1-L_6 (0.15 equiv) and silyl cyanides (1.25 equiv) (see Figure 1). In general, reactions in the presence of TESCN were faster than those with TMSCN under otherwise identical conditions.

12. In our previous stoichiometric one-pot tandem cyclization-quenching process, **3c** was obtained as a complex diastereomeric mixture (see ref. 1).