Metal Ion Activation of Nitriles. Syntheses of 1,3-Bis(arylimino)isoindolines

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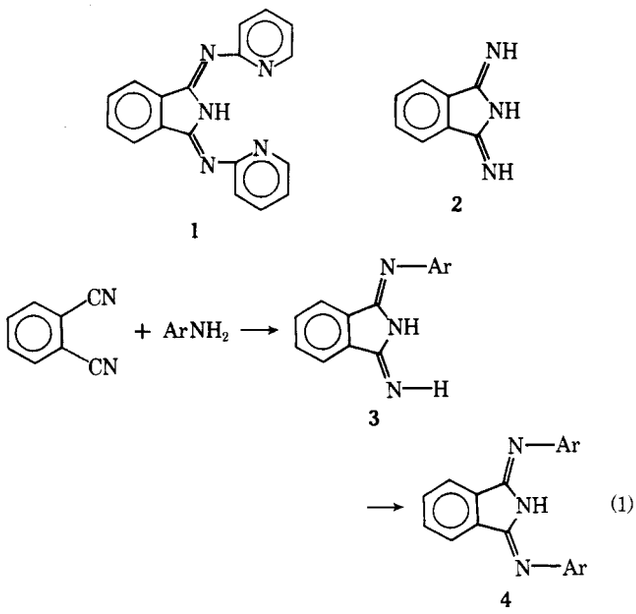
Two new syntheses utilizing metal ion facilitation for the preparation of 1,3-bis(arylimino)isoindolines (BAIIs) under mild conditions are described. Alkaline earth salts catalyze the nucleophilic addition of a large number of primary aromatic amines to phthalonitrile, to form both chelating and nonchelating BAIIs; the salts presumably function as Lewis acid type catalysts and may be applicable to a variety of nucleophilic additions to nitriles. Several divalent transition metal acetates and chlorides facilitate the addition to phthalonitrile of those primary aromatic amines which lead to formation of chelating BAIIs. In the latter case metal chelate complexes were isolated directly and experimental observations are consistent with the metal ion functioning, at least in part, as a template for the reactants. Treatment of the BAII metal chelate complexes with excess KCN liberates the free BAII ligand.

To avoid the formation of phthalocyanine and related pigment type by-products which frequently accompany the formation of 1,3-bis(arylimino)isoindolines (BAIIs) using previously reported syntheses, a method for catalyzing BAII formation under mild conditions was sought. Two new syntheses utilizing metal ion facilitation are reported here along with their application to the preparation of a series of new BAIIs.[1,2] One of the new methods of nitrile activation may be applicable to a variety of nucleophilic additions to the nitrile grouping.

The parent 1,3-bis(2-pyridylimino)isoindoline (1) was first prepared by Linstead et al. via the intermediate **2**, but was later prepared from phthalonitrile and 2-aminopyridine directly in a single step.[3,4] Variations of these methods have appeared but in general the initial nucleophilic addition of aromatic amine to phthalonitrile requires either severe reaction conditions, including high temperatures, or a catalyst.[5]

The addition of a primary amine to phthalonitrile results in an intramolecular cyclization to form a relatively stable 1-arylimino-3-iminoisoindoline **3**, which may undergo addition of a second amine with loss of ammonia and formation of the BAII **4** (eq 1).



When the amine is a 2-amino heterocycle, the monosubstituted diimine **3** is more reactive toward addition of a second amine, and accordingly is less easily isolated. An attempt to selectively prepare unsymmetrical BAIIs, by taking advantage of the stepwise nature of their formation, was unsuccessful.

Results and Discussion

Alkaline Earth Salt Catalysis. Several alkaline earth salts were found to facilitate the addition of primary aromatic amines to phthalonitrile under mild conditions. The *homogeneous* system obtained with $CaCl_2$, $Mg(ClO_4)_2$, or MgI_2 in alcoholic solvents was effective for the synthesis of a variety of BAIIs as indicated in Tables I and II, and in catalyzing some related amine–nitrile addition reactions. In general, product yields were dependent on the solvent, alkaline earth salt, and to a lesser extent on the amine.

Effect of Solvent. Alcohols appear to be the preferred solvents; satisfactory product yields and reaction times were observed with 10 mol % of catalyst in refluxing 1-butanol (Table II). Catalysis by calcium chloride was also observed in lower boiling alcohols but reaction rates were too slow for synthetic utility. In other polar solvents such as methyl ethyl ketone, acetonitrile, or dimethylformamide, the phthalonitrile could be recovered unreacted, although a reaction was observed in some aromatic solvents.

Magnesium perchlorate also facilitates the synthesis of BAIIs in aromatic solvents (benzene, toluene) but the activation of phthalonitrile under such *heterogeneous* conditions required stoichiometric quantities as indicated in Table III. Adding a small amount (10%) of ethanol to the benzene did not raise the yield; suggesting that the alcohol does not play an important part in the activation by alkaline earth salts. The reaction in aromatic solvents frequently afforded a small amount of insoluble orange crystals which analyzed for MgL_2 (where L = the conjugate base of **1**). The infrared spectrum (KBr) of the orange crystals was similar to that observed for free BAII **1** but with a reduction in intensity of the 1630 cm^{-1} band and the appearance of a new band at 1530 cm^{-1}; similar changes in spectra are observed on coordination of **1** to transition metal ions. Treatment of the orange crystals with ammonium chloride gave free BAII **1** and alternatively treatment with cupric acetate afforded the corresponding metal complex, CuLOAc. The limited solubility of the orange crystals precluded further characterization by solution spectroscopic methods but the data suggest that the crystals are probably a magnesium(II) adduct of BAII **1**.

Effect of Alkaline Earth Salt. Magnesium iodide was an active catalyst, although its deliquescent nature made it unsuited for general use. Anhydrous magnesium perchlorate (Anhydrone) has a superior shelf life and a higher catalytic activity but the explosion hazard associated with its use reduces its synthetic utility.[6] Calcium chloride (both dihydrated and anhydrous) was an active catalyst in alcoholic solvents and of the several active alkaline earth salts anhydrous calcium chloride was the catalyst of choice as shown in Table II.

Effect of Amine. Calcium chloride catalysis was applied

Table I. Yield Data, $CaCl_2$-Catalyzed Syntheses of 1,3-Bis(arylimino)isoindolines

Compd no.	Registry no.	Amine[a]	Registry no.	Yield,[b] %	Color	Mp, °C	Anal.[c]
1	14526-01-3	2-Aminopyridine	504-29-0	76	Yellow	181–183	
8	61702-00-9	2-Amino-3-methylpyridine	1603-40-3	82	Yellow	135–136	C, H, N
9	61702-01-0	2-Amino-4-methylpyridine	695-34-1	84	Yellow	165–166	C, H, N
10	61702-02-1	2-Amino-5-methylpyridine	1603-41-4	85	Yellow	215–216	C, H, N
11	61702-03-2	2-Amino-6-methylpryridine	1824-81-3	95	Yellow	136–137	C, H, N
12	61702-04-3	2-Amino-4,6-dimethylpyridine	5407-87-4	78	Yellow	137–138	C, H, N
13	61702-05-4	2-Amino-4-ethylpyridine	33252-32-3	66	Yellow	105–106	C, H, N
14	61702-06-5	2-Amino-4-propylpyridine	61702-15-6	47	Yellow	70–71	C, H, N
15	61702-07-6	2-Amino-4-*sec*-butylpyridine	61702-16-7	72	Yellow	105–106	C, H, N
16	61702-08-7	2-Amino-4-*tert*-butylpyridine	33252-26-5	48	Yellow	234–235	C, H, N
17	61702-09-8	2-Amino-4-amylpyridine	60781-86-4	71	Yellow	101–102	C, H, N
18	61702-10-1	2-Amino-5-chloropyridine	1072-98-6	46	Yellow	243–244.5	C, H, N
19	61702-11-2	2-Amino-5-bromopyridine	1072-97-5	27	Yellow	246–247.5	C, H, N
20	61702-12-3	2-Amino-5-nitropyridine	4214-76-0	67	Gold	308–310	C, H, N
21	16612-53-6	2-Aminothiazole	96-50-4	25	Gold	260–261	C, H, N
22	61702-13-4	2-Amino-4-methylthiazole	1603-91-4	36	Gold	241–244	C, H, N
23	61702-14-5	3-Aminopyridine	462-08-8	67	Yellow	182–183	
24	32313-77-2	Aniline	62-53-3	20	Yellow	128–129	

[a] See Experimental Section for general reaction conditions; amines were commercially available or their preparation is given in the Experimental Section. [b] Yield of recrystallized product. [c] New compounds analyzed for the elements indicated to within ±0.3% of calculated values.

Table II. Effect of Alkaline Earth Salt on Yield of BAII

Amine	Catalyst	Catalyst/ phthalonitrile	Solvent	Yield, %
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	EtOH	6.5
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	PrOH	26
2-Aminopyridine[a]	$CaCl_2 \cdot 2H_2O$	1.0	BuOH	60
2-Aminopyridine[b]			BuOH	2
2-Aminopyridine[b]	$CaCl_2 \cdot 2H_2O$	0.1	BuOH	48
2-Aminopyridine[b]	MgI_2	0.1	BuOH	34
2-Aminopyridine[b]	$Mg(ClO_4)_2$	0.1	BuOH	58
2-Aminopyridine[b]	$CaCl_2$	0.1	BuOH	76

[a] Experimental conditions: 2 mmol of phthalonitrile, 5 mmol of amine, and stated amount of catalyst were heated in 20 mL of solvent at reflux for 48 h. [b] Experimental conditions: 5 mmol of phthalonitrile, 10.5 mmol of amine, and stated amount of catalyst were heated in 10 mL of solvent at reflux for 48 h.

Table III. Alkaline Earth Salt Catalysis in Hydrocarbon Solvents[a]

Amine	Catalyst	Catalyst/ nitrile	Solvent	Reflux time, h	Yield, %
2-Aminopyridine	$Mg(ClO_4)_2$	0.1	C_6H_6[b]	48	9[c]
2-Amino-4-methylpyridine	$Mg(ClO_4)_2$	0.1	C_6H_6	48	10[c]
2-Aminopyridine	$Mg(ClO_4)_2$	0.1	(1:10) EtOH–C_6H_6	24	2.5
2-Aminopyridine	$Mg(ClO_4)_2$	0.5	C_6H_6	48	37[c]
2-Aminopyridine	$Mg(ClO_4)_2$	1.0	C_6H_6	48	50
2-Aminopyridine	$CaCl_2$	0.5	C_6H_6	48	<1

[a] Experimental conditions: 10 mmol of phthalonitrile, 21 mmol of amine, and stated amount of catalyst were refluxed in 20 mL of solvent. [b] Similar yield was obtained in toluene. [c] Average of two or more runs.

to the addition of a variety of primary aromatic amines to phthalonitrile resulting in the synthesis of a number of new chelating and nonchelating BAIIs as shown in Table I. The reactivity of amines toward calcium chloride catalysis paralleled that observed toward alkoxide catalysis with the exception of aniline, which was less reactive with calcium chloride. 2-Aminopyrimidine and 2-amino-6-methylpyrimidine were unreactive toward both alkoxide and calcium chloride catalysis, an observation ascribed to the presumably low nucleophilicity of the amino groups. The yield data in Table I suggest that 2-aminopyridines bearing electron-withdrawing substituents and amino heterocycles where the cycle contains more than one heteroatom are less reactive substrates than 2-aminopyridine itself and alkylated 2-aminopyridines. Thus the data suggest that the prime requisite of the amine is associated with its nucleophilicity.

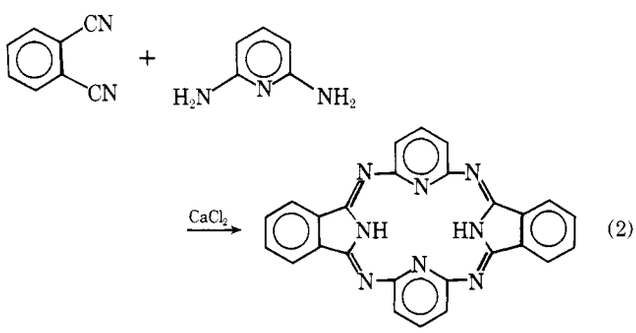
Mechanism. While the details of the mechanism of activation remain uncertain, it seems that at least in alcoholic solvents the alkaline earth salts function as Lewis acid type catalysts. Organonitrile complexes with a variety of metal ions including some of the alkaline earth cations (e.g., Be and Mg) are known.[7-9] The most common form of bonding between nitriles and metal ions is thought to be linear with the metal center coordinated to the nitrogen lone pair,[7] resulting in

polarization of the carbon–nitrogen bond; with some transition metal ions this leads to significant activation of the bond toward nucleophilic addition.[10] Spectroscopic studies have shown that alkaline earth cations perturb the C≡N stretching frequency in the same manner that Lewis acids do;[11] thus it seems likely that alkaline earth cations functioning as weak Lewis acids could activate the nitrile C≡N bond. Lewis acid catalysts have been employed to catalyze a number of amine to nitrile addition reactions in recent years.[12-14]

Earlier, Meyers et al. reported the use of *stoichiometric* amounts of magnesium perchlorate (in aromatic solvents) to facilitate the intramolecular cyclization of enamine nitriles.[6,15,16] The magnesium perchlorate facilitated addition of primary amines to phthalonitrile in aromatic solvents described above may be related to the observation by Meyers, but the reaction in alcoholic solvents is seemingly homogeneous and catalytic suggesting a different role for the metal cation.

There is no evidence to suggest that the alkaline earth cation facilitates addition of the second amine. The intermediate **3** was observed spectroscopically in solution and could be isolated; its conversion to the BAII **1** under the usual reaction conditions did *not* require the presence of a catalyst.

Application. The generality of alkaline earth salt activation of nitriles toward amine addition was evident from the effect of calcium chloride on some other nitrile–amine reactions. Calcium chloride successfully catalyzed the addition of 2,6-diaminopyridine to phthalonitrile to form macrocycle **5** in 70% yield (eq 2).[17]



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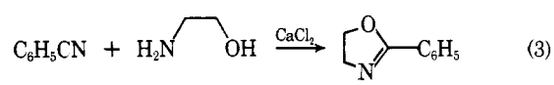
Calcium chloride also catalyzed the synthesis of 2-substituted 2-oxazolines and 4*H*-5,6-dihydrooxazines (eq 3 and 4). Treating benzonitrile and 2-aminoethanol with 10 mol % $CaCl_2$ at 110–120 °C afforded 2-phenyl-2-oxazoline in 92% yield (isolated). Similar treatment of 3-aminopropanol and benzonitrile with $CaCl_2$ gave a 67% yield of 2-phenyl-4*H*-5,6-dihydrooxazine. (These synthetic intermediates had previously been isolated in 85 and 72% yields, respectively, after nitrile activation by the Lewis acids $Cd(OAc)_2 \cdot 2H_2O$ and $ZnCl_2$[12].) Thus it appears that alkaline earth cations may be useful as mild catalysts toward a number of nucleophilic additions to organonitriles.



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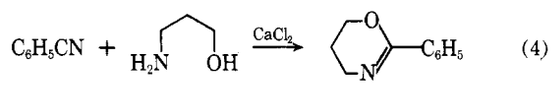

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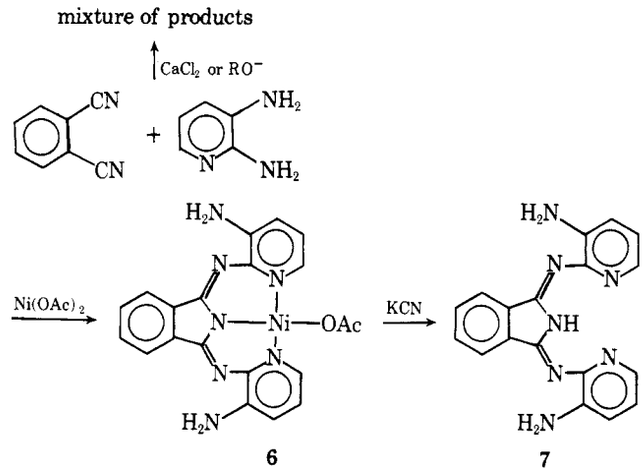
Transition Metal Ion Facilitated Synthesis of BAIIs. Several divalent first row transition metal salts facilitate the addition of primary aromatic amines to phthalonitrile to form *chelating* BAIIs which are isolated as the corresponding metal chelate complexes, ML(X).[1b] The experimental conditions are mild and yields may be quite favorable. Treatment of the BAII–metal complex with excess KCN liberates the free BAII ligand, thus affording a two-step sequence for the synthesis of chelating BAIIs.

An Example. The synthetic utility of this approach is best illustrated by the preparation of the BAII chelating ligand obtained from 2,3-diaminopyridine via the template formation of NiL′(OAc) (Scheme I). The products expected from

Scheme I



6 **7**

phthalonitrile and 2,3-diaminopyridine when using a catalyst which does not discriminate between the two amino groups include three BAIIs and the 2:2 macrocycle analogous to **5**. Using the template approach, adduct formation between phthalonitrile and 2,3-diaminopyridine was directed stereochemically to favor the chelated BAII **6**. The template product **6** was subsequently treated with potassium cyanide to afford **7**, the only BAII product isolated.

Effect of Solvent. Refluxing phthalonitrile with 2.1 equiv of amine and 1 equiv of transition metal salt in methanol or ethanol (the mildest conditions of any of the BAII preparations) afforded the BAII metal chelate complexes, ML(X), in yields as high as 75%. With the exception of the special cases discussed below, the use of higher boiling alcohols did not improve the yield. The use of other low-boiling organic solvents was limited by the poor solubility of transition metal salts but the reaction was successfully run in the donor solvent pyridine. Increasing the ratio of phthalonitrile or amine to metal ion did significantly increase the yield. The only side products isolated were small amounts of metallophthalocyanines.

Effect of Metal Ions and Counterions. The direct synthesis of BAII metal chelate complexes was observed with divalent Co, Ni, Cu, and Zn salts. The yields of metal complex obtained with Co, Ni, and Cu ions were significantly higher than with Zn (Table IV), an observation which may be associated with the strong preference of Zn(II) for tetrahedral coordination geometry. For 2-aminopyridine and most ring-alkylated 2-aminopyridines the yields of ML(OAc) were comparable for Co, Ni, and Cu, but with certain aromatic amines (e.g., 2-aminothiazole, 2,3-diaminopyridine, and 2-amino-6-methylpyridine) yields were more sensitive to the selection of the metal ion; in such cases $Ni(OAc)_2$ was usually the metal salt of choice. No determined effort was made to expand the list of metal ion facilitators although stable BAII complexes have also been formed with second and third row transition metal ions.[2,18]

Only metal salts with the counterions OAc^- and Cl^- were studied. The acetate complexes, ML(OAc), were very stable. With chloride as the counterion a mixture of complexes was obtained, probably ML(Cl), ML(OH), and ML(OR) resulting from partial anion exchange with the solvent alcohol. Treat-

Table IV. Representative Yield Data for Metal-Template Syntheses of BAII Complexes[a]

Amine	Metal salt	Product	Solvent	Reflux time, h	Yield,[b] %
2-Aminopyridine			EtOH	1200	0
2-Aminopyridine	$Co(OAc)_2 \cdot 4H_2O$	CoL(OAc)	EtOH	48	55
2-Aminopyridine	$Zn(OAc)_2 \cdot 2H_2O$	ZnL(OAc)	EtOH	72	7
2-Aminopyridine	$NiCl_2 \cdot 6H_2O$	"NiL(Cl)"	EtOH	48	50
2-Aminopyridine	$Ni(OAc)_2 \cdot 4H_2O$	NiL(OAc)	Pyridine	24	23
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$	CuL'(OAc)	EtOH	6	50
2-Amino-6-methylpyridine	$Ni(OAc)_2 \cdot 2H_2O$		EtOH	24	0
2-Amino-6-methylpyridine	$Ni(OAc)_2 \cdot 4H_2O$ (+$CaCl_2$)	NiL'(OAc)	EtOH	24	33
2-Amino-6-methylpyridine	$NiCl_2 \cdot 6H_2O$	"NiL'Cl"	PrOH	72	64
2-Aminothiazole	$Ni(OAc)_2 \cdot 4H_2O$	NiL'(OAc)	MeOH	24	42
2-Amino-4-methylthiazole	$Ni(OAc)_2 \cdot 4H_2O$		EtOH	24	0
3-Aminopyridine	$NiCl_2 \cdot 6H_2O$		EtOH	24	0

[a] Conditions: 2 mmol of phthalonitrile, 2 mmol of metal salt, 4.2 mmol of amine, and 10 mL of solvent. [b] For crude reaction product suitable for treatment with KCN.

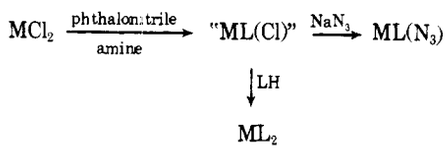
Table V. Yield Data for Two-Step Template–KCN Synthesis of Chelating BAIIs

Amine	Metal salt	Yield data, %		
		Template step[a]	KCN rxn[a]	Overall[b]
2-Aminopyridine	$Ni(OAc)_2 \cdot 4H_2O$		96	
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$		99	
2-Amino-4-methylpyridine	$Cu(OAc)_2 \cdot 2H_2O$	(69)[c]		48
2-Amino-6-methylpyridine	$NiCl_2 \cdot 6H_2O$	(60)[c]		44
2-Amino-5-bromopyridine	$Cu(OAc)_2 \cdot 2H_2O$	(55)[c]		27
2-Aminothiazole	$Cu(OAc)_2 \cdot 2H_2O$			42
2,3-Diaminopyridine	$Ni(OAc)_2 \cdot 4H_2O$			15

[a] For experimental conditions see the Experimental Section. [b] Based on phthalonitrile. [c] Yield of crude product.

ment of the mixture with a strongly nucleophilic anion (e.g., N_3^-) resulted in conversion to a homogeneous material, $ML(N_3)$. Similarly, treatment of the mixture "NiL(Cl)" with added BAII ligand afforded the known material,[3,18] ML_2, with ligand:metal ion stoichiometry of 2:1 (Scheme II).

Scheme II



Effect of Amine. The choice of aromatic amine appeared to be limited to amines which form tridentate chelating BAIIs. Amines which failed under the usual conditions for transition metal facilitated BAII synthesis were (a) those which lacked an annular nitrogen with an amino group in the α position (e.g., aniline, 3-aminopyridine); (b) those which satisfied (a) but lacked an amino group of sufficient nucleophilicity (e.g., 2-aminopyrazine, 2-aminopyrimidine); and (c) those which satisfied both (a) and (b) but contained a relatively bulky substituent in the other position α to the ring heteroatom (e.g., 2-amino-6-methylpyridine, 2-amino-4-methylthiazole). The limitation (c) was in some cases overcome by the use of increased reaction temperatures as shown in Table IV.

Treatment of the BAII Complex with Potassium Cyanide. Treatment of the template product, ML(X), with excess potassium cyanide in an appropriate solvent afforded the free BAII ligand in almost quantitative yield. No external source of proton was required; apparently the BAII anion is readily protonated by solvent or traces of moisture present. Ethanol was the solvent of choice with the more soluble complexes and dimethylformamide with the less soluble.

Yield data are reported in three columns of Table V. In the first, the values refer to crude BAII–metal complex as isolated from the template reaction. Values in the second column refer only to yields from treatment of purified BAII metal chelate complex with KCN, and values in the last column refer to the overall two-step sequence of BAII preparation without purification of the intermediate BAII metal chelate complex.

The BAII ligands obtained via the two-step sequence were identical with those prepared by other methods; in general, yields were lower than for the $CaCl_2$-catalyzed reaction except for special cases where the transition metal ion directed the course of the reaction to selectively favor one available amino group over another as illustrated in Scheme I.

The Role of the Metal Ion. Our conclusions are based primarily on the observation that, unlike the $CaCl_2$-catalyzed reaction, the transition metal catalyzed reaction imposed stereochemical restrictions on the amine.

It appears that the aromatic amine must be a nitrogen heterocycle with a relatively nucleophilic amino group α to the annular N atom but with no bulky substituent in the other position α to the annular nitrogen.

These stereochemical requirements coupled with the very mild reaction conditions contrast with the requirements for the $CaCl_2$-catalyzed reaction and suggest that a different type of metal ion activation is in operation.

Although it is difficult to unambiguously document the role of the transition metal ion as a template, the following sequence is both plausible and consistent with experimental data. Almost certainly the initial step on mixing involves formation of a metal 2-aminopyridine complex in which the pyridine is coordinated via the ring nitrogen.[19] If the free amino group is in the α position it is in a position stereochemically favored for interaction with a nitrile group coordinated in an adjacent coordination site; a free amino group

in the β or γ positions could not take advantage of this type of intramolecular interaction. (The activation of nitriles toward nucleophilic attack by coordination to transition metal ions is well known.[10]) A bulky substituent in the other α position of the heterocycle is likely to result in changes in the stereochemistry of the coordination sphere. In general, steric interactions associated with coordination of 2,6-disubstituted pyridines are relieved by a reduction in the number of ligands about the metal center or by coordination of the pyridine such that the plane of the ring is perpendicular to the plane of the metal and other donor atoms.[20,21] This modification of the coordination sphere could make interaction of the α-amino group with a coordinated nitrile less favorable. The different roles of the transition metal and alkaline earth ions appear to be related to the presence or absence of a metal ion–amine interaction during the formation of the BAII.

An ancillary experiment was run in which a catalytic amount (10 mol %) of anhydrous calcium chloride was added to the standard template reaction on a hindered amine (2-amino-6-methylpyridine); this resulted in the isolation of the BAII metal complex, NiL'(OAc), in 35% yield. In the absence of calcium chloride no complex formation was observed, presumably because the hindered aminopyridine could not achieve the favored coordination geometry for the template effect to occur. With calcium chloride present, the calcium chloride functioned as a Lewis acid type catalyst and activated the nitrile toward attack by the free amino group. The BAII chelating ligand was formed free in solution and was subsequently scavenged by the nickel acetate to form NiL'(OAc). This result further illustrates the difference in mechanism of action between alkaline earth ions and transition metal ions in the formation of BAIIs.

Conclusions

Two new methods employing metal ion facilitation have been reported for the synthesis of 1,3-bis(arylimino)isoindoline, BAII, chelating ligands. The first method involves facilitation by alkaline earth salts in alcoholic solvents and may operate by Lewis acid type activation of the C≡N bond. This method of activation was extended to the preparation of the 2-oxazoline and the 4*H*-5,6-dihydrooxazine derived from benzonitrile and the appropriate amino alcohol, indicating that the application of alkaline earth salt catalysis to nucleophilic addition of amines to nitriles may be of general utility. In the second method transition metal salts stoichiometrically facilitate the synthesis of chelating BAIIs which are isolated as the corresponding metal complexes. The transition metal ions facilitate the addition of certain aromatic 2-amino heterocycles to phthalonitrile under mild conditions seemingly by a transition metal template effect. The BAII ligand may be freed from the complex by treatment with potassium cyanide.

The chemical and physical characterization of BAII–transition metal chelate complexes will be discussed in a forthcoming publication.

Experimental Section

Phthalonitrile and the aromatic amines were obtained from commercial sources (and were used as obtained) unless noted otherwise. Infrared spectra were recorded for KBr pellets on a Perkin-Elmer Model 457 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard and were reported in parts per million downfield from Me_4Si; the spectrometer was a JEOL Model JNM-100. Visible spectra were recorded on a Cary Model 15 spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory.

Purification and Characterization of BAIIs. The BAIIs are yellow or gold, crystalline materials of seemingly indefinite shelf life. Although sensitive to acid they are stable at least to mild base and have considerable thermal stability especially when coordinated to transition metal ions. They are insoluble in water and soluble in organic solvents; the solubilities of BAIIs in organic solvents usually increase with the presence of alkyl substituents and decrease with the presence of electronegative substituents or two heteroatoms in the aryl groups.

Unreacted starting materials may usually be removed by washing of the dry reaction product with water followed by recrystallization of the residue from ethanol-water. The most persistent impurity is phthalocyanine, formed by self-condensation of phthalonitrile, which when solubility permits is conveniently removed by dissolving the impure BAII in chloroform and filtering through a fine glass frit or a short column of alumina.

In general the intensely colored BAIIs have an ϵ of 19 000–22 000 for λ_{max} in the visible region.[3] The infrared spectra of the aminopyridine derived BAIIs usually contain a very strong $\nu_{C=N}$ in the 1650–1600 cm^{-1} region and four moderate-strong bands in the 1600–1400 cm^{-1} region ascribed to pyridyl skeletal vibrations.[22] NMR spectra were recorded where solubility permitted and representative data are shown in Table VI. The NMR spectra support the BAII structure; in many cases signals for the aryl hydrogens are well separated and assignments can be made. On the benzene ring the α hydrogens appear at lower field than the β hydrogens, presumably owing to deshielding by the imino C=N π-electron cloud.[23] For BAII derived from ring-alkylated aminopyridines the pyridyl hydrogens are usually shifted downfield from Me_4Si in the following order: $H_5 < H_3 < H_4 < H_6$. Carbon, hydrogen, and nitrogen analyses consistent with the indicated stoichiometry were obtained for all new BAII as indicated in Table I.

2-Amino-4-alkylpyridine. These amines were prepared by the method of Case and Kasper[24] from 4-alkylpyridine and sodium amide (Fisher Scientific Co.): 4-ethyl, 55% yield, mp 66–70 °C (lit. 70–71 °C[24]); 4-propyl, 50% yield, as deliquescent white crystals stored in a desiccator over Drierite;[25] 4-*tert*-butyl, 12%, mp 82–83 °C; 4-amyl, 58% yield, colorless crystals, mp 55–56 °C (lit.[26] 58–58.5 °C).

4-*sec*-Butylpyridine. A method similar to that of Brown and Murphey was employed.[27] Approximately 500 mL of NH_3 was condensed in a 1-L flask; 1 mol of sodium amide (Fisher) followed by 1.0 mol of 4-ethylpyridine was added to the flask. After stirring under NH_3 reflux for 30 min, 1.1 mol of ethyl iodide was added via an addition funnel to the orange-red suspension over a 1.5-h period. Stirring was continued after the ethyl iodide addition was complete and the solvent was allowed to evaporate slowly. Water (50 mL) was added to the residue and the layers were separated. The aqueous layer was extracted with ether and the combined organic layers were dried over Na_2CO_3, concentrated, and distilled. A colorless oil, 117.2 g (87%), bp 120–125 °C (90 mm) [lit.[27] 128–130 °C (100 mm)], was collected. The oil exhibited an NMR signal typical for a *sec*-butyl group in addition to the usual pattern for 4-substituted pyridine.

2-Amino-4-*sec*-butylpyridine. This new 2-aminopyridine was prepared according to the general procedure of Case and Kasper[24] from 4-*sec*-butylpyridine (described above). The product was obtained as white crystals (49%): mp 64–65 °C; NMR ($CDCl_3$) δ 7.9 (d) 1 H, 6.44 (d) 1 H, 6.29 (s) 1 H, 4.66 (s, br) 2 H, 2.48 (m) 1 H, 1.54 (m) 2 H, 1.19 (d) 3 H, 0.94 (t) 3 H.

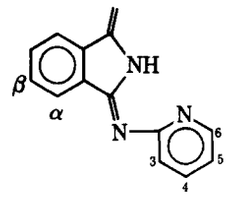
Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.97; H, 9.32; N, 18.70.

1-(2-Pyridylimino)-3-iminoisoindoline (3). Phthalonitrile (10 mmol), 10 mmol of 2-aminopyridine, and 60 mg of sodium methoxide in 100 mL of ethanol were heated at reflux for 48 h. The visible spectrum showed a ratio of λ_{max} 3360/λ_{max} 4060 at 3.6. Upon cooling the solution was concentrated in vacuo. The residue was taken up in EtOAc–CH_2Cl_2 and chromatographed over alumina. Elution with CH_2Cl_2 and with EtOAc removed unreacted phthalonitrile and the BAII but left **3** on the column. Elution with 3/1 CH_2Cl_2–EtOH eluted **3**. Concentration of the eluent afforded 617 mg (28% yield) of yellow powder, mp 138–140 °C, λ_{max} (EtOH) 3360 (ϵ 13 200).

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.04; H, 4.74; N, 25.25.

Reaction of 1-(2-Pyridylimino)-3-iminoisoindoline (3) with 2-Amino-4-methylpyridine. A 115-mg (0.505 mmol) sample of **3** and 1.0 mmol of 2-amino-4-methylpyridine were heated in refluxing *n*-BuOH for 12 h. TLC analysis (SiO_2, EtOAc) indicated only a single yellow spot (R_f 0.5–0.6). The solvent was allowed to evaporate at room temperature and the residue was washed with water, dried, and then dissolved in hot EtOH. On cooling 66 mg of fine yellow needles deposited, mp 169–170 °C. Recrystallization of the needles from benzene–hexane left the melting point unchanged. NMR analysis ($CDCl_3$) showed a ratio of alkyl (singlet) hydrogen to aromatic hydrogen of 1/18 in contrast to the 3/11 ratio expected for the simple addition product.

Table VI. Selected Chemical Shift Data for New Chelating BAII Ligands



Compd no.	Derived from (amine)	Solvent	Chemical shifts[a] H_α	H_β	H_3	H_4	H_5	H_6	Substituent
8	2-Amino-3-methylpyridine	$CDCl_3$	8.14 (m)	7.68 (m)[b]		7.67 (m)[b]	7.05 (q)	8.48 (d) $J = 5$	2.65 (s)
9	2-Amino-4-methylpyridine	$CDCl_3$	7.98 (m)	7.50 (m)	7.22 (s)		6.84 (d)	8.36 (d) $J = 4$	2.37 (s)
10	2-Amino-5-methylpyridine	$CDCl_3$	8.00 (m)	7.55 (m)[b]	7.31 (d)	7.56 (m)[b]		8.37 (s)	2.40 (s)
11	2-Amino-6-methylpyridine	$CDCl_3$	8.16 (m)	7.71 (m)	7.28 (d) $J = 7.5$	7.7 (m)	7.02 (d) $J = 8.0$		2.61 (s)
12	2-Amino-4,6-dimethylpyridine	$CDCl_3$	8.12 (m)	7.68 (m)	7.09 (s)		6.84 (s)		2.40 (s), 2.56 (s)
13	2-Amino-4-ethylpyridine	$CDCl_3$	8.18 (m)	7.70 (m)	7.43 (s)		7.05 (d)	8.57 (d) $J = 5$	α 2.78 (q) β 1.34 (t)
14	2-Amino-4-propylpyridine	$CDCl_3$	7.98 (m)	7.50 (m)	7.20 (s)		6.82 (d)	8.38 (d) $J = 5$	α 2.61
7[c]	2,3-Diaminopyridine[d]	C_5D_5N	8.25 (m)[b]	7.64 (m)		7.39 (d)	7.12 (q)	8.25[b]	H_2N 6.13 (s)
22	2-Amino-4-methylthiazole	$CDCl_3$	7.73 (q)	7.54 (q)	6.70 (s)				2.58 (s)

[a] Chemical shifts are reported in parts per million downfield from Me_4Si, the internal standard. [b] Overlapping signal. [c] Registry no., 61702-17-8. [d] Registry no., 452-58-4.

2-Phenyl-2-oxazoline. In a round-bottom flask, 0.1 mol of benzonitrile, 0.2 mol of 2-aminoethanol, and 0.01 mol of anhydrous calcium chloride were heated with stirring under argon for 8 h at 110–120 °C (much longer reaction times resulted in reduced yield with the formation of nonvolatile products). The reaction mixture was distilled under reduced pressure to afford a fraction of colorless oil [bp 75–84 °C (2–3 mm)] which analyzed for a single component by VPC. The IR and NMR spectra of the oil were consistent with the structure of 2-phenyl-2-oxazoline; the yield was 13.6 g (92%).

2-Phenyl-4*H*-5,6-dihydrooxazine. In a round-bottom flask, 0.1 mol of benzonitrile, 0.15 mol of 3-aminopropanol, and 0.01 mol of anhydrous calcium chloride were heated with stirring at 110–120 °C for 20 h. The viscous, yellow reaction product was distilled under reduced pressure and a fraction was collected of colorless oil [bp 95–115 °C (ca. 2 mm)], 10.8 g (67% yield), which analyzed for a single component by VPC and exhibited IR and NMR spectra consistent with the structure of 2-phenyl-4*H*-5,6-dihydrooxazine.

General Preparation for BAIIs Using Alkaline Earth Salts. In a round-bottom flask outfitted with a reflux condensor, 10 mmol of phthalonitrile, 21 mmol of primary aromatic amine, and 1 mmol of alkaline earth salt along with 20 mL of 1-butanol were heated at reflux for 48 h. On cooling the BAII product frequently crystallized from solution. The BAII was usually recrystallized from ethanol or ethanol–water; other recrystallization solvents employed include chloroform–hexane and pyridine–ethanol. If the BAII did not crystallize from 1-butanol the solvent was allowed to evaporate, and the residue was washed with water, dried, and recrystallized from ethanol–water.

Small amounts of phthalocyanine, which occasionally accompanied BAII formation, were removed by taking up the impure BAII in chloroform and filtering through a fine glass frit or through a short column of alumina.

Analysis for Low Yields of BAII. When the preparation afforded only a low yield of BAII, the yield was most easily quantified spectroscopically. The 1-butanol was allowed to evaporate and the residue was washed with water, dried, and then dissolved in ethanol. After appropriate dilution the absorption at 384 nm was recorded and the concentration was determined using ϵ 21 800 as determined for pure 1.

Isolation of a Mg–BAII Complex. Five millimoles of phthalonitrile, 10.5 mmol of 2-aminopyridine, and 5 mmol of magnesium perchlorate (Anhydrone) in 10 mL of benzene were heated at reflux for 48 h. After cooling the solvent was allowed to evaporate at room temperature and the residue was washed with water. After drying, the residue (1105 mg of yellow powder) was extracted with hot ethanol leaving behind 535 mg of orange, crystalline powder. The infrared spectrum of the orange powder was similar to that of NiL(OAc). The powder analyzed for MgL_2. Anal. Calcd for $C_{36}H_{24}N_{10}Mg$: C, 69.63; H, 3.90; N, 22.56. Found: C, 69.40; H, 4.18; N, 22.28.

The ethanol extract described above was analyzed spectrophotometrically and contained 0.87 mmol of BAII 1.

A small amount of orange powder was treated with excess ammonium chloride in ethanol–water (10/1) and heated for 2 h. The orange crystals gradually went into solution and on cooling yellow needles deposited, identified as BAII 1, mp 182–183 °C.

General Preparation for BAII Chelate Complexes Using Transition Metal Salts. In a round-bottom flask outfitted with a reflux condensor, 2 mmol of phthalonitrile, 4.2 mmol of primary aromatic amine, and 2 mmol of transition metal dichloride or diacetate along with 10 mL of ethanol (or methanol) were heated at reflux generally for not more than 24 h. After the reaction mixture was allowed to cool, it was filtered and the residue was washed with water, alcohol, and acetone or ether. After drying, the residue (which was often crystalline) was suitable for direct use in the KCN reaction. This residue was essentially identical spectroscopically (IR, visible) with material prepared from treatment of the metal salt with the appropriate chelating BAII. The purification and chemical characterization of transition metal–BAII complexes will be discussed in a forthcoming publication.

Treatment of BAII–Metal Complexes with KCN. A. In a beaker 0.9 mmol of recrystallized (toluene) CuL′(OAc) derived from BAII **9**, 4 mmol of potassium cyanide, and 10 mL of ethanol were stirred at room temperature. After 5 h an additional 2 mmol of KCN was added. The disappearance of CuL′(OAc) (R_f 0.1) and the appearance of free L′H (**9**) (R_f ca. 0.5) was followed by TLC (silica gel, ethyl acetate). After 9 h the solvent was allowed to evaporate at room temperature and the residue was thoroughly washed with water. The residue consisted of a quantitative yield of fine, yellow needles, mp 164–165 °C (for authentic **9**, mp 165–166 °C).

B. The tan-brown powder (753 mg) obtained from a 2 mmol scale template preparation of NiL′(OAc), where L′ is derived from BAII **21**, 20 mmol of potassium cyanide, and 10 mL of dimethylformamide were heated at reflux for 36 h. Upon cooling 40 mL of water was added; the mixture was filtered, washed with water, and dried. The residue was treated with hot chloroform and filtered through a fine glass frit to remove a small amount of phthalocyanine type material. From chloroform–ethanol yellow-gold needles of BAII **21** were obtained in an overall yield of 60% for the two-step sequence.

Preparation of BAII 7 Derived from 2,3-Diaminopyridine. In a round-bottom flask outfitted with a reflux condensor 6 mmol of phthalonitrile, 12.6 mmol of 2,3-diaminopyridine, 6 mmol of $Ni(OAc)_2 \cdot 4H_2O$, and 30 mL of methanol was stirred at room tem-

perature for 2 h and then heated at reflux for 48 h. After cooling to room temperature the mixture was filtered and washed with water to afford after drying 1790 mg of brown, crystalline powder.

A 400-mg sample of the brown powder and 650 mg of KCN in 10 mL of chloroform and 7 mL of methanol was stirred at room temperature for 48 h. TLC (silica gel, ethyl acetate) indicated at least three components. After the solvent was allowed to evaporate, the residue was washed thoroughly with water and dried to afford 306 mg of brown powder. The brown residue was extracted with hot benzene and the extract was chromatographed over silica gel. Elution with 10/1 benzene–CH_2Cl_2 and with 10/1 benzene–EtOAc eluted an orange band which upon concentration gave orange crystals of BAII **7**, mp 221.5–224 °C. The yield was 15% based on phthalonitrile. The infrared spectrum was consistent with the usual pattern for BAII and NMR data are included in Table VI. No other BAII products were observed, suggesting that either they were not formed or that if formed they had very unexpected solubility and chromatographic properties.

When phthalonitrile and 2,3-diaminopyridine were treated with $CaCl_2$ according to the procedure given earlier, a mixture of products was obtained. TLC analysis (SiO_2, ethyl acetate) of the mixture did not indicate the presence of **7**; however, we are unable to say with certainty if any other BAII products were present.

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Registry No.—**3**, 61702-18-9; phthalonitrile, 91-15-6; Mg BAII complex, 61846-66-0.

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Substituent Rearrangement and Elimination during Noncatalyzed Fischer Indole Synthesis

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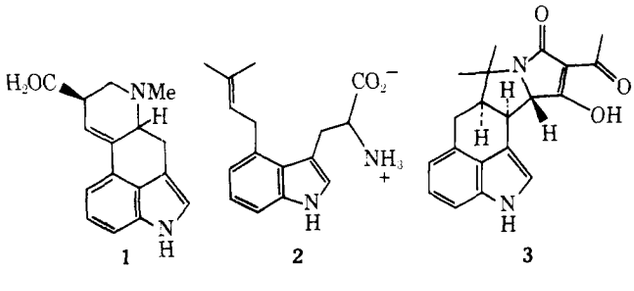
Treatment of 2,3,3-trimethyl-4-pentenal phenylhydrazone in refluxing ethylene glycol led to 1-(3-methylbut-2-en-1-yl)-3-methylindole, presumably through allylic rearrangement to the indolic nitrogen of the intermediate 3-(1,1-dimethylallyl)-3-methylindolenine; no rearrangement to a 4-allylindole derivative was observed. Treatment of 1,3-cyclohexanedione-2-chloro-6-(3-methylbut-2-en-1-yl) phenylhydrazone in refluxing *o*-dichlorobenzene led to 5-allyl-7-chloro indole derivatives, while in aqueous sulfuric acid a 4-alkyl-7-chloro indole derivative was obtained. These derivatives presumably arise via rearrangement of a C-3a isoprenylated intermediate. The formation of these products is discussed in relation to ergot alkaloid biosynthesis.

The biosynthesis of lysergic acid (**1**) proceeds from L-tryptophan[1] and mevalonic acid.[2] Recently, an enzyme, dimethylallyltryptophan synthetase,[3] has been isolated which directly forms **2** by coupling L-tryptophan with dimethylallyl pyrophosphate. A related alkaloid, cyclopiazonic acid (**3**), has been shown to derive from a C-4 isoprenylation of a tryptophan derivative.[4] Since such C-4 alkylations are without precedent in the chemistry of indoles, we undertook a study of some chemical model systems for this process.



1 **2** **3**

Two hypotheses seemed to offer reasonable chemical explanations for an overall C-4 alkylation during the enzymic reaction. These involved a preliminary conversion of tryptophan to the C-3 substituted derivative, as **4a**, which could undergo subsequent [3,3]-sigmatropic rearrangement to **2** (Scheme I). An alternative is a sequential indoline formation, as **12**, from tryptophan and its direct isoprenylation at C-3a (Scheme III) to **13** followed by a [1,2] shift, thereby establishing the requisite 4-isoprenylated substitution. It is of interest that in this latter scheme isoprenylation of the indoline