

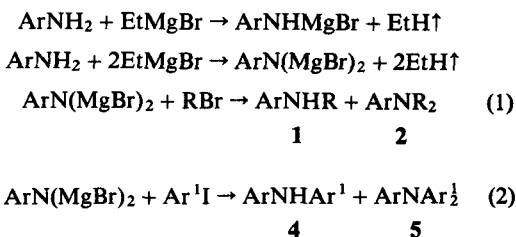
# N-ALKYLATION AND N-ARYLATION OF ANILINES STARTING FROM A MILD N–Mg REAGENT: ITS ACTIVATION CAUSING THE ‘N–C’ COUPLING TO EXTEND THE UNIFIED STRUCTURE–REACTIVITY RELATIONSHIP\*

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New *N*-alkylation and *N*-arylation procedures starting from anilinomagnesium (ArNHMgBr) are reported. For *N*-alkylation with alkyl bromides, addition of hexamethylphosphoramide to an ArNHMgBr solution in tetrahydrofuran (THF) is effective. After heating at 55 °C, *N*-monoalkylation product was obtained in 60–90% yield, slight dialkylation taking place. The combined use of aryliminodimagnesium [ArN(MgBr)<sub>2</sub>] with α,ω-dibromoalkanes led to *N*-arylazacycloalkanes. For *N*-arylation with iodobenzene, replacement of THF with pyridine and additional use of copper(I) iodide are effective. After heating at 115 °C with iodobenzene, mono- and diarylation products were obtained, the former being predominant. The combined use of ArNHMgBr and *N,N,N',N'*-tetramethylethylenediamine as the ligand of copper species is effective for elimination of diarylation and other undesired products, and leads to diarylamines in excellent yield. The method is of advantage over the conventional Ullmann and Chapman methods. The polar solvents and copper salt are effective additives for inducing ‘inert combinations’ of ArNHMgBr or ArN(MgBr)<sub>2</sub> with alkyl and aryl halides into *N*–C coupling, to extend the unified view proposed for the reactivity of magnesium reagents. The difference in the roles of *N*–Mg and *N*–Cu species is discussed.

## INTRODUCTION

This paper deals with *N*-alkylation and *N*-arylation of anilines starting from *N*–Mg reagents [ArN(MgBr)<sub>2</sub> (IDMg); ArNHMgBr (AnMg)] by use of bromoalkanes and iodobenzenes, respectively [see equations (1) and (2)]. The present procedure provides ‘*N*–C cross-coupling’ in addition to reported condensation, addition and replacement modes of *N*–Mg reagents in tetrahydrofuran (THF):<sup>1–4</sup>



Studies of the reactions of IDMg with carbonyl,<sup>1,4</sup> nitro<sup>2</sup> and cyano<sup>3</sup> substrates in our laboratory led to the proposal of a unified structure–reactivity relationship based on the relative efficiency of single electron transfer (SET).<sup>5</sup> The efficiency is evaluated by the difference between oxidation and reduction potentials of the reactants ( $\Delta E = E_{\text{ox}} - E_{\text{red}}$ ).<sup>6</sup> In view of the classification of reactions based on  $\Delta E$ , the present combinations of reactants have large values causing no SET: the halides are weak electron acceptors and the reagent is a weaker electron donor than RMgBr, both being unchanged. The *N*-alkylation in equation (1) is facilitated by the addition of strongly coordinating hexamethylphosphoramide (HMPA) in a calculated small molar amount based on the magnesium metal used, and the *N*-arylation in equation (2) is facilitated by the additional use of a copper salt. The selectivities in monoalkylation and -arylation are described and the activation of the mild reagent is discussed from the unified view of magnesium reagents.

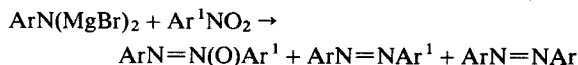
\* Aryliminodimagnesium Reagents, Part XXIV. For Part XXIII, see Ref. 3b.

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## RESULTS AND DISCUSSION

*N*-Alkylation [equation (1)]

A clue to the *N*-alkylation in equation (1) was discovered during a study of IDMg condensation with nitrobenzene ( $\text{Ar}^1\text{NO}_2$ ) giving azoxybenzene:<sup>2</sup>



Considering that the Mg atom in RMgBr is coordinated by two molecules of  $\text{Et}_2\text{O}$ ,<sup>7</sup> a two molar amount of HMPA based on the amount of Mg used was added. As a result, the yield of the azoxy product is improved, and *N*-ethylaniline is concurrently formed in 15–20% yield (not formed in the absence of HMPA).<sup>2c</sup> The latter yield resembles the excess amount of ethyl bromide (EtBr) used for complete conversion of magnesium into  $\text{EtMgBr}$ . The *N*-ethylation is interpreted in terms of activation of IDMg, due to elevation of its HOMO level by coordination of HMPA (donor number  $DN = 38.8$ ),<sup>8</sup> allowing SET to EtBr (weak acceptor). This interpretation is analogous to the result of MO calculations<sup>9</sup> indicating that the HOMO level of a (free) Grignard reagent is greatly elevated by coordination of two ether molecules. The concurrent formation of symmetrical azobenzene (by oxidative coupling via SET from IDMg) is also reduced by addition of HMPA, and an additional possibility that HMPA provides the reagent with 3d orbitals feasible for SET and/or migration of intermediate radicals is suggested.<sup>3b</sup>

From this understanding, the excess amount of EtBr is distilled off under nitrogen after IDMg preparation in THF ( $DN = 20.0$ ), and then a two molar amount of HMPA (based on the amount of Mg used) is added to the IDMg solution. After evolution of heat has ceased, alkyl bromide is added. The anilnomagnesium (AnMg) is similarly prepared and activated, and allowed to react with alkyl bromides.

The yields of *N*-monoalkyl- and *N,N*-dialkylanilines (1 and 2) obtained by use of IDMg and AnMg are given in Tables 1 and 2, respectively. Heating at 55 °C is needed for *N*-alkylation similarly for the reactions with other substrates. Monoalkylation predominates even with the use of IDMg, and is slightly favoured by the use of AnMg.

The yield of 1 is improved by the use of excess reagent and/or by a longer time of heating the mixture, although some attempts at further improving the yield were unsuccessful. *N*-Alkylation is accelerated slightly by addition of 2,4,6-trimethylnitrobenzene (Mes- $\text{NO}_2$  having a small  $E_{\text{red}}$ ) (8.0 mol%) to the 1:1 reaction mixture (see Figure 1), although the final yield is unimproved. Similarly to acceleration observed in Claisen-like self-condensation of *N,N*-dimethylacetamide (DMA) by IDMg,<sup>3b</sup> Mes $\text{NO}_2$  has access to the ligand

Table 1. Yields of 1 and 2 in reaction (1) using IDMg<sup>a</sup>

Run No.	RBr: R =	Molar ratio	Reaction time (h)	Yield (%)	
				1	2
1 <sup>a</sup>	<i>n</i> -Pr	1.0	3	0	0
2	<i>n</i> -Pr	1.0	3	75	16
3	<i>i</i> -Pr	1.0	3	58	0
4	<i>n</i> -Hex	1.0	3	79	5
5	<i>n</i> -Pr	1.0	24	76	4
6	<i>n</i> -Pr	5.0	3	78	0
7	<i>n</i> -Pr	0.5	3	52	8

<sup>a</sup> IDMg: HMPA = 1:4; reaction temperature = 55 °C.

<sup>b</sup> Without addition of HMPA.

Table 2. Yields of 1 and 2 in reaction (1) using AnMg<sup>a</sup>

Run No.	RBr: R =	Molar ratio	Reaction time (h)	Yield (%)	
				1	2
1	<i>n</i> -Pr	1.0	3	60	0
2 <sup>b</sup>	<i>n</i> -Pr	1.0	3	38	0
3 <sup>c</sup>	<i>n</i> -Pr	1.0	3	69	3
4	<i>n</i> -Pr	1.0	24	76	3
5	<i>n</i> -Pr	5.0	3	93	0
6	<i>n</i> -Hex	1.0	3	64	0
7	<i>n</i> -Hex	1.0	24	68	4
8	<i>n</i> -Hex	5.0	3	89	0

<sup>a</sup> IDMg: HMPA = 1:2; reaction temperature = 55 °C.

<sup>b</sup> AnMg: HMPA = 1:1.

<sup>c</sup> HMPA was used as solvent.

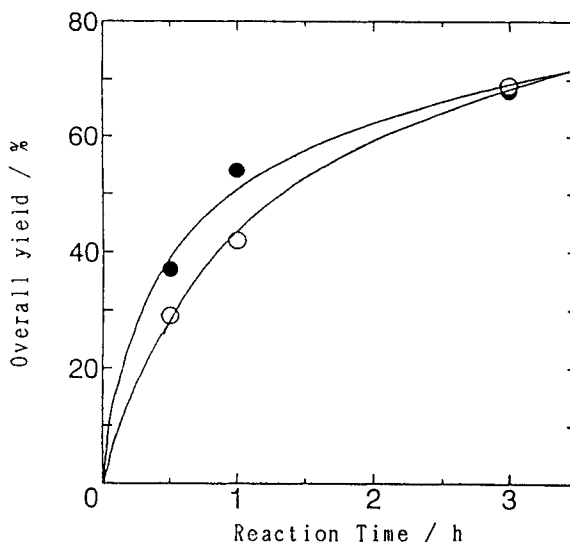


Figure 1. Time dependence of overall yield (1 and 2) in reaction (1) of AnMg with hexyl bromide (20 °C) in the (○) absence and (●) presence of Mes $\text{NO}_2$

Table 3. Yields of 3 in reaction (1')<sup>a</sup>

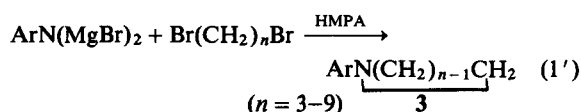
Run No.	Br(CH <sub>2</sub> ) <sub>n</sub> Br : n =	Reaction time (h)	Yield of 3 (%)
1	2	3	>0
2	3	3	44
3 <sup>b</sup>	3	24	60
4	4	3	55
5 <sup>b</sup>	4	24	85
6	5	3	81
7	6	3	39
8 <sup>b</sup>	6	24	89
9 <sup>b</sup>	9	48	69

<sup>a</sup>IDMg : HMPA : dibromide = 1 : 4 : 1. Reaction temperature = 55 °C.

<sup>b</sup>Twice the amount of THF was used.

sphere of the  $\sigma$ -complex formed from the reagent and bromide (RBr...Mg—N<) and mediates implicit SET inside the complex. Products due to radical dimerization and/or hydrogen abstraction are absent in accord with features of large  $\Delta E$  reactions of mild N—Mg reagents.<sup>3</sup>

Some  $\alpha,\omega$ -dibromoalkanes react with IDMg to give *N*-arylazacycloalkanes (3) in 50–90% yields [equation (1') and Table 3].



Except for three-membered aziridine, larger than four-membered compounds 3 are prepared in satisfactory yields by this procedure using twice the volume of THF and a longer time of heating. By comparison of the results in Table 3 with those in Tables 1 and 2 and from the absence of an *N*-( $\omega$ -bromo)alkylated aniline, its precursor containing MgBr, if it is formed as intermediate, is assumed to be rapidly cyclized.

In this study, *S*<sub>N</sub>1-inactive alkyl bromides were used and *S*<sub>N</sub>1-active allyl and benzyl bromides (capable of directly alkylating anilines) were excluded. The yield of 1 is not completely satisfactory, but *N*-monoalkylation according to equation (1) is of advantage over conventional methods requiring some controlled conditions. Efficient cyclization according to equation (1') without extreme dilution is not as effective as expected but is usable in practice.

#### Physical aspects

In all the reactions of C—Mg and N—Mg reagents including that of 1, the  $\Delta E$  value is simply related to the final distribution of products. A 'closed environment' for the later stages of reaction was proposed from the need for an aggregate excess of reagent (composing an assembly with radical intermediates) for product for-

mation irrespective of small and large  $\Delta E$  values,<sup>3</sup> providing a clue to the validity of the simple relationship (see above).

The unified view in terms of  $\Delta E$  implies an essential role of HOMO—LUMO interactions of the reactants, and 'activation of the reagent' implies elevation of reagent's HOMO level. By the novel use of HMPA in a calculated small amount, the reaction between components with fairly large  $\Delta E$  values is modified. The *N*-alkylation in equation (1) could be recognized as promotion of an 'inert class D combination' into 'class C' involving  $\sigma$ -complexation and inner-sphere SET.<sup>5b</sup> The effect of the addition of HMPA and/or pyridine (Py) on the product yields in IDMg reactions with Ar<sup>1</sup>NO<sub>2</sub> (class B) and Ar<sup>1</sup>CN (class C) reflects the relative values of  $\Delta E$ , *DN* and also the temperature (0 and 55 °C).<sup>3b</sup> Hence the lack of alkylation caused by addition of Py is reasonable because its smaller *DN* (33·1), implying weaker coordinating ability, is insufficient to allow SET to RBr having a larger *E*<sub>red</sub> than that of Ar<sup>1</sup>CN.<sup>3b</sup>

#### *N*-Arylation [equation (2)]

For the *N*-arylation according to equation (2), addition of HMPA is insufficient and the combined use of HMPA or Py with a copper salt is needed. The reaction in equation (2) is really that of N—Cu (see below), but is recognized as a further extension of N—Mg reactions. The difference between the roles of the two metallic reagents for the initiation of reactions must be as follows. In contrast with N—Mg species usually undergoing SET to substrates (incapable towards Ar<sup>1</sup>I) to generate a pair of cation and anion radicals, the N—Cu(I) species undergoes 'oxidative addition' to Ar<sup>1</sup>I (recognized as 'masked' SET). The possible mechanism is given later.

The present method for the preparation of diarylamines (4) is advantageous over the conventional methods owing to the better yields obtained by the one-pot method at lower temperatures (110–120 °C). The Ullmann procedures,<sup>10</sup> using *N*-acyl and/or *o*-carboxyl groups on the reaction components, require heating above 200 °C with a catalytic amount of metallic copper followed by removal of the extraneous groups. The Chapman procedures,<sup>11</sup> using aryl *N*-arylbenzimidate, require heating above 250–300 °C and removal of the resulting benzoyl group.

First, the possibility of *N*-arylation was explored by use of HMPA and copper(I) chloride. Toluene was added to IDMg and/or AnMg solution, THF was completely distilled off, HMPA, CuCl and Ar<sup>1</sup>I were successively added and the mixture was refluxed. The amounts of reactant and additives used, reaction time and types and yields of products are summarized in Table 4. By use of AnMg and/or excess aniline, formation of 4 predominates over 5. However, the latter is formed in a considerable amount and undesired oxidative and reductive coupling due to the SET

Table 4. Effects of various conditions on product distribution in reaction (2) of AnMg and IDMg with Ar<sup>1</sup>I

Run No.	R <sup>a</sup>	R <sup>1a</sup>	Additive	Solvent <sup>b</sup>	Molar ratio <sup>c</sup>	Reflux time (h)	Yield (%)				Recovery (%) <sup>d</sup>
							4	5	6	7	
1	MeO	MeO	CuCl, HMPA	Tol	A	5	63	24	15	0	7
2	MeO	Me	CuCl, HMPA	Tol	A	5	73	12	15	>0	<0
3	MeO	Me	CuCl, HMPA	Tol	B	5	93	5	11	0	0
4	MeO	Cl	CuCl, HMPA	Tol	A	5	70	18	12	6	0
5	MeO	Me	CuI	Py	C	5	67	26	12	0	3
6	MeO	MeO	CuI	Py	D	5	64	13	10	0	10
7	MeO	Me	CuI	Py	D	5	62	17	38	0	1
8	MeO	Cl	CuI	Py	D	5	57	38	20	0	0
9	Me	MeO	CuI	Py	D	5	79	8	10	0	7
10	Me	Me	CuI	Py	D	5	68	17	13	0	6
11	Me	Cl	CuI	Py	D	5	63	37	7	0	0
12	Cl	MeO	CuI	Py	D	5	55	18	9	0	7
13	Cl	Me	CuI	Py	D	5	66	25	5	0	6
14	Cl	Cl	CuI	Py	D	5	55	36	6	0	0
15	1-Np	1-Np	CuI	Py	E	3	69	0	>0	0	8
16	MeO	MeO	CuCl, HMPA	Tol	F	5	26	37	6	0	28
17	MeO	Me	CuCl, HMPA	Tol	F	5	28	30	8	0	22
18	MeO	Cl	CuCl, HMPA	Tol	F	5	23	53	8	5	4
19	Me	H	CuI, bipy	Py	G	24	73	14	4	0	>0
20	Me	H	CuCl <sub>2</sub> -bipy complex	Py	G	24	69	13	7	0	>0

<sup>a</sup>Np = naphthyl.<sup>b</sup>Tol = toluene (b.p. 110 °C); Py = pyridine (b.p. 115.5 °C)<sup>c</sup>(A) AnMg:CuCl:HMPA:Ar<sup>1</sup>I = 5:2.5:15:1; (B) AnMg:CuCl:HMPA:Ar<sup>1</sup>I = 5:2.5:15:1, EtMgBr:ArNH<sub>2</sub> = 1:2;(C) AnMg:CuI:Ar<sup>1</sup>I = 5:2.5:1; (D) AnMg:CuI:Ar<sup>1</sup>I = 5:2.5:1, EtMgBr:ArNH<sub>2</sub> = 1:2; (E) AnMg:CuI:Ar<sup>1</sup>I = 5:1:1;(F) IDMg:CuCl:HMPA:Ar<sup>1</sup>I = 1:1:6:1; (G) AnMg:additive:Ar<sup>1</sup>I = 5:0.05:1.<sup>d</sup>Amount of recovered Ar<sup>1</sup>I fluctuates owing to variations in its volatility.

involved, leading to symmetrical azoarene [ArN=NAr (6) from IDMg] and biaryl [Ar<sub>2</sub> (7) from Ar<sup>1</sup>I], are also notable. The need for the preparation of N-Mg, implying metal exchange (N-Mg → N-Cu), is noted.

Second, the effects of CuCl and CuI and those of HMPA and Py on the combined yields of 4 and 5 were compared. The reaction was carried out in HMPA at

110 °C or in refluxing Py (115 °C); the results are given in Table 5. Although the formation of 5 is not excluded, the condition of run 8 [successive addition of CuI (catalytic amount), 2,2'-bipyridine (Bipy) and Ar<sup>1</sup>I] seems best for monoarylation because adequate results arise from the combined use of less expensive Py and a small amount of copper salt. The formation of 7

Table 5. Effects of CuCl and CuI and solvents on reaction (2) of *p*-RAnMg with *p*-R<sup>1</sup>C<sub>6</sub>H<sub>4</sub>I

Run No.	R	R <sup>1</sup>	Additive	Solvent	AnMg:additive:Ar <sup>1</sup> I	Reaction temperature (°C)	Reaction time (h)	Yield (%)				Recovery (%) <sup>a</sup>
								4	5	6	7	
1	MeO	Me	CuCl	HMPA	5:2.5:1	110	5	77	7	7	10	0
2	MeO	Me	CuI	Py	5:2.5:1	Reflux	5	67	26	0	12	3
3	MeO	Me	CuI	Py	3:1.5:1 <sup>b</sup>	Reflux	5	18	4	0	7	49
4	MeO	Me	CuCl	Py	5:2.5:1 <sup>b</sup>	Reflux	5	62	17	0	38	1
5	MeO	Me	CuI	HMPA	5:2.5:1	110	5	71	20	6	13	2
6	MeO	Me	CuI	Py	5:0.25:1	Reflux	24	47	27	0	21	7
7	MeO	Me	CuI	HMPA	5:0.25:1	110	24	61	18	>0	14	>0
8	Me	H	CuI, Bipy	Py	5:0.05:1	Reflux	24	73	14	0	4	>0

<sup>a</sup>Amount of recovered Ar<sup>1</sup>I fluctuates owing to variations in its volatility.<sup>b</sup>EtMgBr:ArNH<sub>2</sub> = 1:2.

is eliminated by the use of a catalytic amount of  $\text{CuCl}_2$ -Bipy complex (run 17), although a longer time of reaction is needed. This, implying reduction of  $\text{Cu(II)}$  to  $\text{Cu(I)}$  by  $\text{AnMg}$ , is expected from the known oxidation of  $\text{IDMg}$  with  $\text{CuCl}_2$  and/or  $\text{CuBr}_2$ ,<sup>12</sup> and the slight formation of **6** is therefore reasonable.

A condition for the selective preparation of *para*-substituted **4** was revealed. By considering the role of Py in facilitating the 'oxidative addition and reductive elimination' processes of transition metal-mediated reactions (see below), Py and Bipy were replaced with *N,N,N',N'*-tetramethylethylenediamine (TMEDA). By refluxing in toluene as a co-solvent, the formation of **5** and **6** is almost completely suppressed (Table 6). The results of the reaction of  $\text{AnMg}$  with the catalytic and stoichiometric use of  $\text{CuI}$  are shown in Tables 7 and 8, respectively; the amount of  $\text{CuI}$  could be reduced to 5% of the  $\text{Ar}^1\text{I}$  used by prolonging the time of reaction (Table 7). Reactions using *p*-Cl- $\text{AnMg}$ , giving a low yield of **4** (Table 7, runs 7-9; Table 8, runs 9-11), are promoted by addition of Py, but the formation of **5** becomes notable (Table 8, runs 15-20). For preparative purposes, inverse combinations using *p*-Cl $\text{C}_6\text{H}_4\text{I}$  are recommended. The more precise role of Py is discussed later.

Effects of steric hindrance appear in experiments with the formation of 1,1'-dinaphthylamine and 2-methyl- and 2,4,6-trimethyl-diphenylamines, as shown by comparison of the results in Tables 4, 6 and 8: poor yield in

Table 6. Effects of  $\text{CuI}$ -Bipy complex on reaction (2) of  $\text{AnMg}$  with  $\text{Ar}^1\text{I}$  in Py<sup>a</sup>

Run No.	Ar = $\text{RC}_6\text{H}_4$ or $\text{R}_3\text{C}_6\text{H}_2$	$\text{Ar}^1 = \text{R}^1\text{C}_6\text{H}_4$ or $\text{R}^1\text{C}_6\text{H}_2$	Yield (%)			Recovery (%) <sup>b</sup>
			4	5	6	
1	4-MeO	4-MeO	46	23	8	5
2	4-MeO	4-Me	69	14	5	7
3	4-MeO	4-Cl	59	27	10	3
4	4-Me	4-MeO	72	14	10	9
5	4-Me	4-Me	70	19	11	>0
6	4-Me	H	69	13	7	>0
7	4-Me	4-Cl	55	42	8	2
8	4-Me	4-OH	0	0	6	43
9	4-Me	2-Me	71	0	10	14
10	4-Me	2,4,6-Me <sub>3</sub>	37	0	9	54
11 <sup>c</sup>	4-Me	2,4,6-Me <sub>3</sub>	53	0	13	34
12	4-Cl	4-MeO	59	27	5	8
13	4-Cl	4-Me	50	25	5	19
14	4-Cl	4-Cl	52	40	7	2
15	2-Me	4-Me	66	9	3	17
16	2,4,6-Me <sub>3</sub>	4-Me	56	10	3	19

<sup>a</sup> $\text{Ar}^1\text{I}$  was added at once at room temperature and the mixture in pyridine was refluxed for 24 h.

<sup>b</sup>Amount of recovered  $\text{Ar}^1\text{I}$  fluctuates owing to variations in its volatility.

<sup>c</sup>Refluxed for 48 h.

Table 7. Effects of  $\text{Cu(I)}$  (catalytic)-TMEDA on reaction (2) of  $\text{AnMg}$  with  $\text{Ar}^1\text{I}$  in toluene<sup>a</sup>

Run No.	Ar = $\text{RC}_6\text{H}_4$	$\text{Ar}^1 = \text{R}^1\text{C}_6\text{H}_4$	Yield (%)			Recovery (%) <sup>b</sup>
			4	5	6	
1	4-MeO	4-MeO	81	>0	3	17
2	4-MeO	4-Me	90	>0	16	9
3	4-MeO	4-Cl	94	>0	8	5
4	4-Me	4-MeO	85	>0	7	15
5	4-Me	4-Me	76	3	5	14
6	4-Me	4-Cl	86	6	26	8
7	4-Cl	4-MeO	35	>0	4	50
8	4-Cl	4-Me	58	3	6	35
9	4-Cl	4-Cl	58	>0	5	40
10	2-Me	4-Me	55	0	>0	30

<sup>a</sup>Reagent:  $\text{Ar}^1\text{I}:\text{CuI}:\text{TMEDA} = 5:1:0.05:5$ .  $\text{Ar}^1\text{I}$  was added at once at room temperature and the mixture in toluene was refluxed for 24 h.

<sup>b</sup>Amount of recovered  $\text{Ar}^1\text{I}$  fluctuates owing to variations in its volatility.

Table 8. Effects of  $\text{CuI}$  (stoichiometric)-TMEDA on reaction (2) of  $\text{AnMg}$  with  $\text{Ar}^1\text{I}$  in toluene<sup>a</sup>

Run No.	Ar = $\text{RC}_6\text{H}_4$ or $\text{R}_3\text{C}_6\text{H}_2$	$\text{Ar}^1 = \text{R}^1\text{C}_6\text{H}_4$ or $\text{R}^1\text{C}_6\text{H}_2$	Yield (%)			Recovery (%) <sup>b</sup>
			4	5	6	
1	4-MeO	4-MeO	60	>0	>0	9
2	4-MeO	4-Me	98	>0	>0	0
3	4-MeO	4-Cl	84	>0	>0	0
4	4-Me	4-MeO	83	>0	>0	11
5	4-Me	4-Me	76	>0	>0	11
6	4-Me	4-Cl	86	>0	>0	19
7	4-Me	2-Me	48	0	4	40
8	4-Me	2,4,6-Me <sub>3</sub>	17	0	>0	79
9	4-Cl	4-MeO	34	>0	>0	66
10	4-Cl	4-Me	44	>0	>0	19
11	4-Cl	4-Cl	26	>0	>0	29
12	2-Me	4-Me	12	0	>0	23
13	2-Me	2-Me	9	0	>0	72
14	1-Np <sup>c</sup>	1-Np <sup>c</sup>	9	0	>0	78
15 <sup>d</sup>	4-Cl	4-MeO	52	9	5	32
16 <sup>d</sup>	4-Cl	4-Me	66	27	7	2
17 <sup>d</sup>	4-Cl	4-Cl	65	26	5	6
18 <sup>c</sup>	4-Cl	4-MeO	45	30	3	9
19 <sup>c</sup>	4-Cl	4-Me	66	30	5	>0
20 <sup>c</sup>	4-Cl	4-Cl	66	30	4	>0
21 <sup>d</sup>	2-Me	4-Me	86	8	>0	5
22 <sup>d</sup>	2-Me	2-Me	62	5	>0	19
23 <sup>d</sup>	2,4,6-Me <sub>3</sub>	4-Me	93	6	>0	0

<sup>a</sup>Reagent:  $\text{Ar}^1\text{I}:\text{CuI}:\text{TMEDA} = 5:1:1:6$ .  $\text{Ar}^1\text{I}$  was added at once at room temperature and the mixture in toluene was refluxed for 3 h.

<sup>b</sup>Amount of recovered  $\text{Ar}^1\text{I}$  fluctuates owing to variations in its volatility.

<sup>c</sup>Np = naphthyl.

<sup>d</sup>Py (5 ml) was added.

<sup>e</sup>Py (10 ml) was added.

run 14 (Table 8) with a fair yield in run 15 (Table 4); poor yields in runs 12 and 13 with good yields in runs 21 and 22 (Table 8) and also in runs 9 and 15 (Table 6); poor yield in run 8 with an excellent yield in run 23 (Table 8) and with fair yields in runs 10, 11 and 16 (Table 6).

The 8-hydrogen on 1-naphthyl and 2-methyl on the phenyl groups of the reactants hinder diarylation but are advantageous for monoarylation, especially when Py is added to combined CuI–TMEDA. The yield of **4** is seriously decreased with combined CuI–TMEDA–toluene, and slightly so with CuI–Py and/or CuCl<sub>2</sub>–Bipy in Py.

Although the use of CuI–TMEDA–toluene is recommended for unhindered monoarylation, the catalysis caused by CuI–Bipy–Py is of interest from the general mechanistic viewpoint of transition metal-mediated reactions.<sup>13</sup> Possible sequences of steps for mono- and diarylation are depicted in Figure 2.

The sequence is initiated from N–Cu(I) species generated by metal exchange (and reduction). As cycle A indicates, the resultant Cu(III) species, probably stabilized by coordination of Py and Ar<sup>1</sup>I, 'reductively eliminates' a molecule of **4** to regenerate the N–Cu(I) species. Cycle B for diarylation may be initiated by migration of an Ar<sup>1</sup> group from Cu(III) to the N atom, generating new N–Cu(I) species; further oxidative addition and reductive elimination lead to **5**. Concerning the formation of **5** via catalysis (CuCl<sub>2</sub>–Bipy) in the reaction of *p*-Me-AnMg with *p*-ClC<sub>6</sub>H<sub>4</sub>I, the possibility of exchange of an H atom of **4** (eliminated from

cycle A) with MgBr of AnMg is excluded since added *p*-Me-*p*'-MeO(C<sub>6</sub>H<sub>4</sub>)<sub>2</sub>NH (20 mol%) was completely recovered without incorporation into products.

The effect of Py (5 or 10 ml; footnotes b and d in Table 8) in improving the overall yields of **4** and **5**, especially the latter, was studied using pyridines having 4-Me, 2-Me, 2,4-Me<sub>2</sub> and 2,6-Me<sub>2</sub> substituents. In the reaction starting from *p*-Cl-AnMg and *p*-MeOC<sub>6</sub>H<sub>4</sub>I using CuI–TMEDA–toluene, 4-Me-Py gave yields resembling those obtained with the use of Py, while 2-Me-Py reduced especially the yield of **5**. The roles of Py must be (i) stabilization of the first Cu(III) species (cycle A) and/or (ii) acceleration of Ar<sup>1</sup> migration (transfer into cycle B). Role (i) seems dominant over (ii), and competition of Py and TMEDA as the ligand is suggested.

Organocopper reagents are used for regio- and stereoselective syntheses,<sup>14</sup> and inorganic copper salts in combination with Py have been widely used for aromatic syntheses.<sup>15</sup> The use of N–Mg and CuI overcomes the S<sub>N</sub>-inactive nature of iodoarenes. It should be noted that extraneous organic moieties needed for the Chapman and even for revised Ullmann procedures<sup>15c</sup> are made useless for the first time by the procedures according to equation (2).

## REMARKS

Reaction (2) was first examined by use of toluene and a calculated amount of HMPA instead of THF for the purpose of carrying out the reaction at temperatures above 100 °C. The use of Py instead of toluene plus HMPA is of advantage in view of the easy purification and safe handling. It should be noted that incomplete removal of THF causes a serious decrease in yield, and that hydroxy-substituted Ar<sup>1</sup>I is not utilized (Table 6, run 8), probably owing to decomposition of N–Mg and/or N–Cu species. In preliminary experiments, NiCl<sub>2</sub> gave a much lower yield of **4** even if higher temperatures were applied, and PdCl<sub>2</sub> led to no reaction.

With the use of CuI(stoichiometric)–Py, competition experiments starting from two *para*-substituted IDMgs were carried out, the relative yields of **4** and **5** being depicted in Figure 3. The results show (i) no clear effect of substituents of IDMg and two clear effects of those of Ar<sup>1</sup>I, (ii) a lower overall yield from a *p*-MeO group than from *p*-Me and *p*-Cl groups and (iii) similar patterns in product distribution from *p*-MeO and *p*-Cl groups distinct from that of a *p*-Me group. Consistent with the above discussion, feature (i) may arise from reaction (2) starting after an ArNCu species is formed, feature (ii) implies a weaker accepting ability (larger *E*<sub>red</sub>) due to a *p*-MeO group common to all types of substrates<sup>6</sup> and feature (iii) suggests that the lone pair electrons of MeO and CO participate in complexation with copper species.

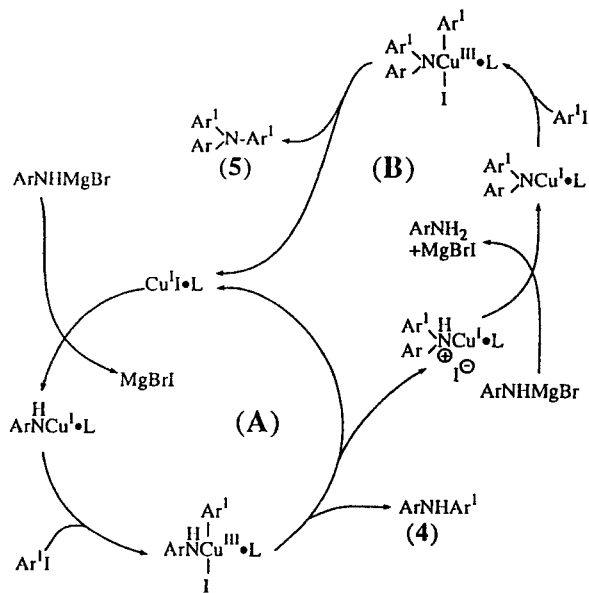


Figure 2. Possible pathway of reaction (2)



Table 9. Melting points and  $^1\text{H}$  NMR data for diphenylamines,  $\text{ArNHAr}^1$  ( $\text{Ar} = \text{RC}_6\text{H}_4$  or 1-naphthyl;  $\text{Ar}^1 = \text{R}^1\text{C}_6\text{H}_4$ ,  $\text{R}^1\text{C}_6\text{H}_2$  or 1-naphthyl)

R	R <sup>1</sup>	M.p. (°C)	$^1\text{H}$ NMR: $\delta$ in $\text{CDCl}_3$ (ppm)
<i>p</i> -MeO	<i>p</i> -MeO	96.1–96.3	6.93 and 6.84 (8H, Abq, $J = 8.8$ Hz), 5.27 (1H, s), 3.78 (3H, s)
<i>p</i> -MeO	<i>p</i> -Me	79.0–80.3	7.04–6.83 (8H, m), 5.38 (1H, s), 3.79 (3H, s), 2.28 (3H, s)
<i>p</i> -MeO	<i>p</i> -Cl	78.0–78.6	7.12 and 6.81 (4H, ABq, $J = 8.8$ Hz), 7.03 and 6.87 (4H, ABq, $J = 8.8$ Hz), 5.45 (1H, s), 3.79 (3H, s)
<i>p</i> -Me	<i>p</i> -Me	75.8–76.2	7.04 and 6.95 (8H, ABq, $J = 8.6$ Hz), 5.52 (1H, s), 2.29 (3H, s)
<i>p</i> -Me	H	86.0–86.5	7.28–6.85 (9H, m), 6.00 (1H, s), 2.33 (3H, s)
<i>p</i> -Me	<i>p</i> -Cl	78.3–78.8	7.15 and 6.98 (4H, ABq, $J = 8.8$ Hz), 7.07 and 6.93 (4H, ABq, $J = 8.8$ Hz), 5.58 (1H, s), 2.71 (3H, s)
<i>p</i> -Me	<i>o</i> -Me	Oil	7.18–6.88 (8H, m), 5.28 (1H, s), 2.30 (3H, s)
<i>p</i> -Me	2,4,6-Me <sub>3</sub>	Oil	6.96 and 6.43 (4H, ABq, $J = 8.8$ Hz), 6.29 (2H, s), 5.50 (1H, s), 2.30 (3H, s), 2.23 (3H, s), 2.17 (3H, s)
<i>p</i> -Cl	<i>p</i> -Cl	72.8–73.0	7.20 and 6.86 (8H, ABq, $J = 8.8$ Hz), 5.68 (1H, s)
<i>o</i> -Me	<i>o</i> -Me	Oil	7.20–6.86 (8H, m), 5.08 (1H, s), 2.26 (6H, s)
1-Np <sup>a</sup>	1-Np <sup>a</sup>	110.0–110.5	8.08 (2H, t), 7.88 (2H, t), 7.56–7.30 (8H, m), 7.03 (2H, d)

<sup>a</sup>Np = naphthyl.

### CONCLUSION

Because a more reactive reagent is less selective, manifestation of factors governing the reactions of highly reactive C–Mg (Grignard) reagents has been difficult for many years.<sup>16</sup> The moderate reactivity of N–Mg reagent and the  $\Delta E$  value as an estimate of relative SET efficiency are advantageous for revealing the so-far hidden factors for classifying and characterizing the reactions of magnesium reagents from the unified viewpoint of structure–reactivity relationships, which is further extended by the present methods (using HMPA and/or a copper salt) significant for ‘modifying the reactivity of the N–Mg reagents to bring the inert (no SET) combinations into reaction.’ The present work should contribute to a generalization of the understanding of metal-mediated reactions.

### EXPERIMENTAL

**Preparation of N–Mg reagents.** In a nitrogen-purged flask, a calculated amount of metallic Mg is placed and converted completely into EtMgBr with the use of EtBr in excess amount (15–20%) in THF. Anilines (*p*-MeO-, *p*-Me-, *p*-Cl-), weighed in a 5% excess molar amount based on that of Mg, are added and the mixture is stirred at room temperature for 30 min and at 55 °C for 30 min to complete evolution of EtH. The excess EtBr in the IDMg solution is distilled off with THF under nitrogen.

**Reaction and product separation.** The procedure according to equation (1) was described earlier. A typical procedure according to equation (2) using CuI–Py is as follows. After removal of excess EtBr, dry Py is added and all the amount of THF is distilled off.

Copper(I) iodide is added in a 0.5 molar and/or catalytic amount, and the resulting reddish brown solution is stirred for 20–30 min at room temperature. Iodobenzenes (*p*-MeO-, *p*-Me-, *p*-Cl-), in a 0.2 molar amount based on that of Mg, are added and the mixture is stirred at 115–120 °C for 5 or 24 h depending on the amount of CuI. The mixture is quenched with saturated  $\text{NH}_4\text{Cl}$  solution. To the resulting slurry, concentrated aqueous ammonia (10 ml) and *n*-hexane are added and the mixture is vigorously stirred to transfer copper species into the aqueous phase. After the hexane layer has been decanted, the residue is treated with hexane five times. The combined hexane solution is repeatedly washed with <0.5 M HCl to remove pyridine and unreacted aniline. The hexane solution is dried over  $\text{MgSO}_4$  and roto-evaporated, and the product mixture is chromatographed on silica gel (Wako Gel FC-40). All the products **4** are identified by  $^1\text{H}$  NMR and melting point determinations (see Table 9).

### REFERENCES

- (a) M. Okubo and S. Ueda, *Bull. Chem. Soc. Jpn.* **53**, 281 (1980); (b) M. Okubo, S. Hayashi, M. Matsunaga and Y. Uematsu, *Bull. Chem. Soc. Jpn.* **54**, 2337 (1981); (c) M. Okubo, *Bull. Chem. Soc. Jpn.* **58**, 3108 (1985).
- (a) M. Okubo, T. Takahashi and K. Koga, *Bull. Chem. Soc. Jpn.* **56**, 199 (1983); (b) M. Okubo and K. Koga, *Bull. Chem. Soc. Jpn.* **56**, 203 (1983); (c) M. Okubo, M. Tanaka, H. Shiku, A. Yamauchi and K. Matsuo, *J. Phys. Org. Chem.* **4**, 693 (1991).
- (a) M. Okubo, M. Tanaka, Y. Murata, N. Tsurusaki, Y. Omote, Y. Ikubo and K. Matsuo, *Chem. Lett.* 1965 (1991); (b) M. Okubo, K. Matsuo, N. Tsurusaki, K. Niwaki and M. Tanaka, *J. Phys. Org. Chem.* **6**, 509–519 (1993).



4. (a) M. Okubo and Y. Uematsu, *Bull. Chem. Soc. Jpn.* **55**, 1121 (1982); (b) M. Okubo, Y. Nakagawa, M. Yoshida and H. Yanase, *Bull. Chem. Soc. Jpn.* **58**, 2707 (1985).
5. (a) M. Okubo and K. Matsuo, *Yukigosei Kagaku Kyokaishi* **50**, 682 (1992); (b) M. Okubo and K. Matsuo, *Rev. Heteroatom Chem.* **9**, in press (1993).
6. (a) M. Okubo, T. Tsutsumi, A. Ichimura and T. Kitagawa, *Bull. Chem. Soc. Jpn.* **57**, 2679 (1984); (b) M. Okubo, T. Tsutsumi and K. Matsuo, *Bull. Chem. Soc. Jpn.* **60**, 2085 (1987).
7. (a) G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.* **85**, 1002 (1963); (b) L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.* **90**, 5375 (1968).
8. V. Gutmann, *The Donor-Acceptor Approach to Molecular Interactions*, Chapt. 2, Plenum Press, New York (1978).
9. S. Nagase and Y. Uchibori, *Tetrahedron Lett.* **23**, 2585 (1982).
10. (a) F. Ullmann, *Chem. Ber.* **36**, 2382 (1903); *Justus Liebigs Ann. Chem.* **355**, 312 (1907); (b) I. Goldberg, *Chem. Ber.* **39**, 1691 (1906); **40**, 4541 (1907).
11. (a) A. W. Chapman, *J. Chem. Soc.* **127**, 1992 (1925); 1743 (1927); (b) J. W. Schulenberg and S. Archer, *Org. React.* **14**, 1 (1965).
12. M. Okubo and H. Shiku, *Bull. Chem. Soc. Jpn.* **64**, 196 (1991).
13. J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.* **10**, 434 (1977).
14. (a) G. H. Posner, *Org. React.* **19**, 1 (1972); **22**, 253 (1975); (b) J. F. Normant, *J. Organomet. Chem. Libr.* **1**, 219 (1976).
15. (a) R. G. R. Bacon and H. A. O. Hill, *Chem. Soc. Rev.* **19**, 95 (1965); (b) P. E. Fanta, *Synthesis* **9** (1974); (c) J. Lindley, *Tetrahedron* **40**, 1433 (1984).
16. (a) K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.* **108**, 6263 (1986); (b) K. Maruyama, J. Hayami and T. Katagiri, *Chem. Lett.* 601 (1986); (c) K. Maruyama and T. Katagiri, *Chem. Lett.* 735 (1987); (d) K. Maruyama and T. Katagiri, *J. Phys. Org. Chem.* **1**, 21 (1989); **4**, 381 (1991).