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Graphical Abstract

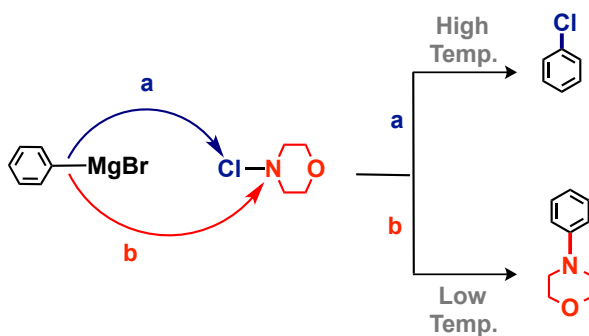
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Transition-metal free umpolung carbon-nitrogen vs. carbon-chlorine bond formation

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The formation of carbon-nitrogen (C–N) bonds via an umpolung substitution reaction has been achieved at -78 °C without the need for catalysts, ligands, or additives. The scope is limited to aryl Grignard reagents with N-chloroamines. The findings in this manuscript serve as a reference point for all C–N bond formation involving N-chloroamines and organometallic reagents. Knowing the yields of uncatalyzed reactions will be useful when determining the success of future catalytic methods.



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ABSTRACT

The formation of carbon-nitrogen (C–N) bonds via an umpolung substitution reaction has been achieved at $-78\text{ }^{\circ}\text{C}$ without the need for catalysts, ligands, or additives. The scope is limited to aryl Grignard reagents with N-chloroamines. The findings in this manuscript serve as a reference point for all C–N bond formation involving N-chloroamines and organometallic reagents. Knowing the yields of uncatalyzed reactions will be useful when determining the success of future catalytic methods.

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The formation of C–N bonds is essential for the synthesis of highly desirable pharmaceutical and biologically active targets. Current methods rely on transition metals such as palladium¹ and rhodium.² More recently the focus has shifted towards reagents that are more environmentally friendly and affordable catalysts like cobalt,³ copper,^{4,5,6} and nickel.^{7,8,9} Recent advances have discovered transition metal free methods that also result in C–N bond formation.¹⁰ We report herein a fast and easy method for the formation of C–N bonds resulting in arylated tertiary amines.

Considering our recent work involving iron catalysts and Grignard reagents to directly form carbon-carbon (C–C) bonds via directed C–H functionalization on aromatic heterocycles,¹¹ and the success of other earth-abundant transition metals accomplishing reactions of this type for the formation of both C–C and C–N bonds, we envisioned that iron-catalyzed reactions could play a role in amination reactions as well. When we began this investigation Bolm and Correa had already demonstrated that iron could efficiently catalyze the formation of C_{sp²}–N bonds from aryl iodides and nucleophilic nitrogen sources.¹² Our initial optimization focused on the coupling of N-chloroamines with phenylmagnesium bromide in an effort to form similar C_{sp²}–N bonds in an umpolung fashion (Scheme 1). The variables investigated included the screening of iron catalysts, nitrogen and phosphine ligands, several additives, and a range of temperatures.

Our initial efforts to use iron catalysts appeared successful. Several iron salts were shown to produce the expected product (**3a**) in reasonable yields (entries 1–8).

Inorganic salts had been shown to promote the presumed transmetalation step.¹³ In our studies, LiCl was detrimental to the yield (entry 9), and MgBr₂ completely shut down the reaction

(entry 10). Contrary to other's reports,¹⁰ chlorobenzene was the dominant byproduct that could be detected by GCMS along with small amounts of biphenyl, presumably arising from homocoupling of the Grignard reagent. In an attempt to minimize these side reactions, we lowered the temperature and varied the equivalents of Grignard reagent used (entries 11–13). We found that with 1.5 equivalents of Grignard reagent at $-78\text{ }^{\circ}\text{C}$ the reaction afforded a 75% isolated yield (entry 13). With these optimized conditions, we attempted to investigate and expand the substrate scope. Unfortunately the Fe(acac)₂ catalyzed reactions performed on other substrates showed a significant decrease in yield (Figure 1: 3b–3g), and other metals, CoBr₂ and Cu(OTf)₂, were detrimental (3b and 3c).

Not satisfied with these results, we screened several ligands hoping to increase our yield further. Our hypothesis was that the ligands could coordinate the Mg cation, thus increasing the nucleophilicity of the Grignard reagents;¹⁰ however, we observed that dinitrogen ligands had a small beneficial effect on the reaction (entries 15–19). Removing the iron as a control afforded the product in near-equal yields (entry 20). This was discouraging; but we quickly realized that the ligand itself was also not necessary for the reaction to occur (entry 21). This has been demonstrated previously by Knochel¹⁴ at $-45\text{ }^{\circ}\text{C}$, however only benzylic N-chloroamines were studied.

Transition-metal free reactions were performed at several temperatures (Table 2). The decrease in temperature showed a steady increase in product formation, as well as a decrease in overall byproducts.

The results of our extensive optimization showed that N-chloroamines and aryl Grignard reagents readily couple between

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-40 and -78 °C with no need for additives or catalysts. The coupling does occur at room temperature, but the biphenyl, the consequence of the homocoupling of the Grignard reagent, as well as chlorobenzene were present in high amounts. Prolonged reaction times had no immediate affect and eventually resulted in product decomposition.

2-methyl tetrahydrofuran (2-Me-THF) was used as the primary solvent. The yields achieved from these reactions are comparable to those performed in THF. We chose 2-Me-THF as it originates from a renewable source, consequently it is considered to be a more green solvent. Unfortunately, further attempts to expand the reaction to other amines beyond morpholine, and a variety of substituted Grignard reagents, still resulted in low yields (Scheme 3).

Only the original N-phenylmorpholine product (**3a**) showed high yields. Increasing the electron density using 4-methylphenyl (**3b**) and 4-methoxyphenyl (**3c**) Grignard reagents decreased the yield dramatically. The mesitylmorpholine (**3d**) and o-methylmorpholine (**3e**) reactions showed only trace amounts of products detected by NMR spectroscopy. This is presumably due to the steric hindrance that surrounds the carbon to be functionalized. The yield of the diarylated product (**3f**) was respectable since the reaction must have occurred twice on the dichloroamine substrate.

The metal-free umpolung amination can result in two different major products depending on the temperature of the reaction (Scheme 2). At relatively high temperatures (pathway a) the chloramine acts as an electrophilic source of chlorine; while at lower temperatures (pathway b) the same reagent acts as an electrophilic source of nitrogen. This can be explained by a Curtin-Hammett relationship, in which both reaction rates are temperature dependent, but one mechanism (pathway a) apparently slows significantly more than the competing mechanism as a function of temperature (pathway b). Alternatively, the higher temperature could enable a radical-mediated mechanism, as opposed to the polar mechanism (pathway a) shown in Scheme 2.

Despite poor yields observed for several substrates, we hypothesize that a systematic optimization of each metal-free reaction could yield synthetically useful yields. The reactions run smoothly and are complete upon the drop-wise addition of the Grignard reagent (<5 minutes). We hope that this work serves as a cautionary example to be considered when testing for presumed catalytic activity in future systems. Future efforts to use other organometallic reagents, such as organolithium or organozinc species, will be performed as well as the expansion of this reaction to include alkyl Grignards and amines.

Acknowledgments

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Supplementary Material

Experimental procedures and characterization of reported compounds is provided.

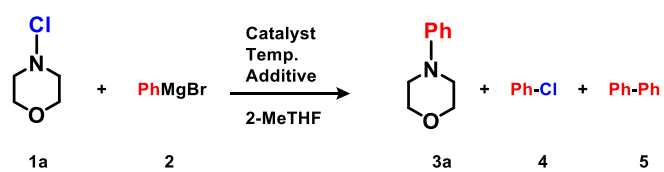
Scheme 1. Initial Optimization Outline

Table 1. Optimization of Reaction Conditions^a

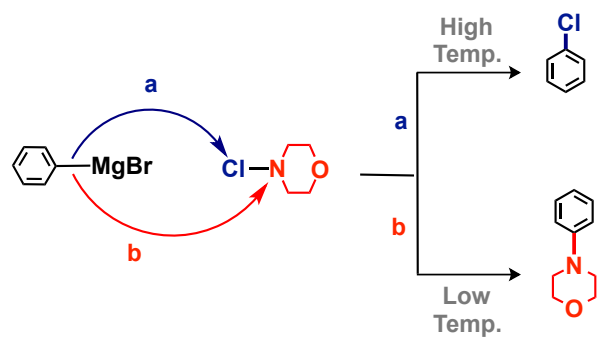
Entry	Catalyst (10 mol %)	Temp. (°C)	Additive	Isolated Yields ^b
1	FeCl ₂	0	None	36 ^b
2	Fe(SO ₄) ₃ •H ₂ O	0	None	62 ^b
3	Fe(C ₂ O ₄) ₂ •2H ₂ O	0	None	40 ^b
4	FeF ₃ •3H ₂ O	0	None	46 ^b
5	Fe(NO ₃) ₃ •9H ₂ O	0	None	19 ^b
6	Fe(acac) ₃	0	None	46 ^b
7	None	0	None	49 ^b
8	Fe(acac) ₂	0	None	88 ^b
9	Fe(acac) ₂	0	LiCl	58
10	Fe(acac) ₂	0	MgBr ₂	0
11	Fe(acac) ₂	-40	None	79
12	Fe(acac) ₂	-78	None	49 ^c
13	Fe(acac) ₂	-78	None	75
14	Fe(acac) ₂	-78	None	74 ^d
15	Fe(acac) ₂	-78	dtbpy	77
16	Fe(acac) ₂	-78	bpy	75
17	Fe(acac) ₂	-78	phen	84
18	Fe(acac) ₂	-78	binap	81
19	Fe(acac) ₂	-78	dppbz	74
20	None	-78	phen	80
21	None	-78	None	99

a.) All reactions performed on a 1.00 mmol scale with 1.5 eq. of Grignard reagent. b.) Yields determined by GC using dodecane as an internal standard c.) 1.0 eq Grignard reagent, d.) 2.0 eq. Grignard reagent. dtbpy = ditert-butylbipyridine, bpy = bipyridine, phen = 1,10-phenanthroline, dppbz = 1,2-Bis(diphenylphosphino)benzene.

Table 2. Effect of Temperature on C-N Bond Formation^a

Temperature (°C)	Yield ^b 3a	Yield ^b 4	3a : 4
22	48	55	0.9
0	59	30	2.0
-21	77	35	2.2
-41	86	36	2.4
-78	87	29	3.0

a.) All reactions performed on a 1.00 mmol scale, in acid-washed oven dried flasks. b.) yield determined by GC-MS using dodecane as an internal standard.

Scheme 2. Proposed temperature mediated pathways

Scheme 3. Reaction Scope

