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## Reaction of an electrogenerated 'iminium cation pool' with organometallic reagents. Direct oxidative α-alkylation and -arylation of amine derivatives

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Abstract—We have developed an efficient direct oxidative  $\alpha$ -alkylation and -arylation of carbamates based on the 'cation pool' method. Grignard reagents, organozinc compounds, and organoaluminum compounds are effective as carbon nucleophiles toward iminium cation pools generated by low temperature electrolysis of carbamates. © 2001 Elsevier Science Ltd. All rights reserved.

Recently we have developed the 'cation pool' method,<sup>1</sup> which involves the generation and the accumulation of a relatively unstable carbocation and the subsequent reaction with a nucleophile under non-oxidative conditions. For example, carbamates are electrochemically oxidized at low temperature to accumulate the acyliminium cation, which is characterized as a solution of a single cationic species by NMR spectroscopy. The addition of carbon nucleophiles to the 'iminium cation pool' affords the corresponding carbon-carbon bond formation products in high yields (Scheme 1). The 'cation pool' method provides not only a powerful tool for the mechanistic studies of the process involving carbocations but also a useful synthetic method that overcomes the conventional two-step transformation. There is no need for trapping of a carbocation by a heteroatom nucleophile such as alcohol, the isolation of the trapped carbocation, and the regeneration of the carbocation using a Lewis acid (Scheme 2).<sup>2-4</sup>

In our previous work, organosilicon compounds such as allylsilanes and silyl enol ethers were used as carbon nucleophiles.<sup>1</sup> In order to expand the scope of the 'cation pool' method, we examined the use of other organometallic compounds such as Grignard reagents as carbon nucleophiles. There was no information on the direct reaction of spectroscopically well-characterized acyliminium cations with such organometallics. Herein we report that alkyl, alkenyl, alkynyl, and aryl Grignard reagents, as well as alkylzinc and alkylaluminum compounds, serve as effective nucleophiles toward iminium cation pools. The present method provides a useful method for the introduction of a substituent at the  $\alpha$ -carbon of amine derivatives.<sup>5</sup>



Scheme 1. Cation pool method.

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Scheme 2. Conventional two-step method.

We initially examined the reactions of the electrogenerated iminium cation pools with Grignard reagents. A typical procedure is as follows. Methyl pyrrolidinecarboxylate was anodically oxidized in CH<sub>2</sub>Cl<sub>2</sub> at -72°C to generate the 'iminium cation pool'.<sup>6</sup> After completion of the electrolysis (2.5 F/mol was consumed), 2 equiv. of phenylmagnesium bromide in ether was added and the mixture was stirred at the same temperature for 10 min. The work up followed by chromatography gave methyl 2-phenylpyrrolidinecarboxylate in 79% yield (Eq. (1)). In marked contrast to the reaction with Grignard reagents, the reactions with alkyllithium were not practically useful. For example, the reaction with phenyllithium in hexane led to the formation of the desired compound only in very low yield (4%). Probably higher basicity of organolithium compounds caused the decomposition of the iminium cation via  $\beta$ -proton elimination.



The reactions with other Grignard reagents having a primary, secondary alkyl and ally groups also took place smoothly, as shown in Table 1. Alkenyl, alkynyl, and homoallyl magnesium halides can also be utilized although the yields are moderate. Aryl magnesium halides, such as phenylmagnesium bromide and o- or p-substituted phenylmagnesium bromides, are also added to the iminium cation smoothly to give the corresponding arylated compounds. It is worth noting that p-fluorophenylmagnesium bromide, having an electronegative group on the aromatic ring, could be utilized. The result overcomes our previous work in which only highly electron-rich aromatic compounds can be utilized as carbon nucleophiles.<sup>1</sup> Other cation pools generated from the carbamates of piperidine and

diethylamine were also found to be effective for the reaction with Grignard reagents.

The reaction of the 'iminium cation pool' and benzylmagnesium halide exhibited an interesting feature. Three isomeric products were formed as a mixture, as shown in Eq. (2). The formation of the coupling products at aromatic o- and p-carbons suggests that the mechanism involves the initial electron transfer from the Grignard reagent to the iminium cation to generate benzyl radical, although the detailed mechanism has not been clarified as yet.

Other organometallic compounds such as organozinc<sup>7</sup> and organoaluminum<sup>8</sup> reagents are also effective as carbon nucleophiles. For example, diethylzinc, ethylzinc iodide, triethylaluminum, and diethylaluminum chloride readily react with the iminium cation pool generated from methyl pyrrolidinecarboxylate to give the ethylated product in good to moderate yields (Table 2). Low basic character of organozinc and organoaluminum reagents, which might suppress the competing elimination process, seems to be responsible for the success of the reactions.<sup>4d</sup> This tendency is consistent with the known softness of iminium cations.<sup>9</sup>

In summary, we have developed an efficient direct oxidative carbon–carbon bond formation at the  $\alpha$ -position of carbamates based on the 'cation pool' method. The present findings open a rich variety of synthetic applications of the iminium cation pool method, especially in the field of synthesis of alkaloids. Further investigations using other organometallic reagents and mechanistic studies are in progress.

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Table 1. Reaction of Grignard reagents to electrogenerated 'iminium cation pool'a

substrate	nucleophile <sup>b</sup>	product	% yield <sup>c</sup>
N CO <sub>2</sub> Me	EtMgCI / Et <sub>2</sub> O	N CO <sub>2</sub> Me	65%
	<i>n-</i> BuMgCl / Et <sub>2</sub> O		67%
	MgCl / Et <sub>2</sub> O	N CO <sub>2</sub> Me	57%
	MgBr / THF	N CO <sub>2</sub> Me	45%
	MgBr/Et <sub>2</sub> O	N CO <sub>2</sub> Me	68%
	MgBr / Et <sub>2</sub> O	N CO <sub>2</sub> Me	54%
	PhMgBr / THF,Et <sub>2</sub> O <sup>d</sup>	∧ N CO₂Me	58%
	MgBr / Et <sub>2</sub> O		63%
	MgBr / Et <sub>2</sub> O		69%
	MeO – MgBr / Et <sub>2</sub> O	OMe	61%
	F	√ N CO₂Me	66%
∕_N CO₂Me	PhMgBr / Et <sub>2</sub> O	N CO <sub>2</sub> Me	72%
N COoMe	PhMgBr / Et <sub>2</sub> O	N CO <sub>2</sub> Me	57%
	MgBr / Et <sub>2</sub> O	N CO <sub>2</sub> Me	50%

<sup>a</sup> After the electrolysis (2.5 F/mol based on the carbamates), a carbon nucleophile (2 equiv.) was added to the 'cation pool' thus generated at  $-72^{\circ}$ C. <sup>b</sup> Et<sub>2</sub>O or THF solutions of Grignard reagents were used. Grignard reagents were purchased or prepared from corresponding organic halides. <sup>c</sup> Isolated yield. <sup>d</sup> Phenylacetylenylmagnesium chloride was prepared by treating phenylacetylene in THF with C<sub>2</sub>H<sub>5</sub>MgBr at room temperature for 4 h.

 Table 2. Reaction of organozinc and organoaluminum

 reagents to the 'iminium cation pool' generated from

 methyl pyrrolidinecarboxylate<sup>a</sup>

Nucleophile <sup>a</sup>	% Yield
Et <sub>2</sub> Zn/hexane	74
EtZnI/Et <sub>2</sub> O <sup>b</sup>	65
Et <sub>3</sub> Al/hexane	72
Et <sub>2</sub> AlCl/hexane	55

 $^{\mathrm{a}}$  Hexane or  $\mathrm{Et}_{2}\mathrm{O}$  solutions of the organometallic compounds were used.

<sup>b</sup> Ethylzinc iodide was prepared by addition of ethyl iodide to zinc/ copper couple.

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