

Template Aggregative Activation: Metal Salt-reinforced Complex Bases in Arynic Synthesis†

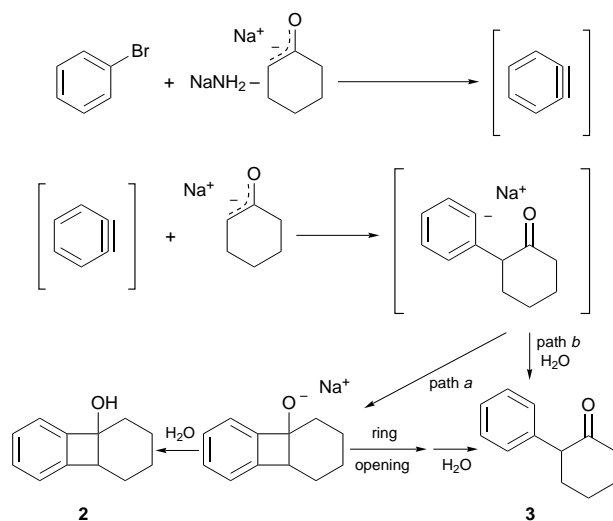
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A substantial effect on the reactivity of a common complex base is observed by the addition of metal salts MX_n ($M = Mg, Zn, Cu, Zr$); a template effect of the new aggregates is proposed.

We have previously showed that the complex bases $NaNH_2$ – $RONa$ ($RONa$ was a sodium alkoxide or ketone enolate) are useful reagents in organic synthesis.¹ The behaviour of such unimetal super bases² stems from the formation of aggregates³ whose properties are governed by the principles of aggregative activation.⁴ According to these principles it was



Scheme 1

expected that any addition of a metal salt to a given complex base should lead to aggregates with modified properties. In this way the insertion of a salt with cation-favouring template effects ought to favour intermolecular reactions initiated on the aggregates of the usual complex base. To verify this hypothesis we studied the condensation of $NaNH_2$ –cyclohexanone sodium enolate with bromobenzene. We have previously showed⁵ that this complex base generates benzyne which condenses with the enolate according to Scheme 1.

The expected consequence of a template effect was an increase in the reaction rate and the overall yield as well as an increase in the **2:3** ratio. The main results obtained with optimised amounts of added salts are reported in Table 1. According to our hypothesis, it appeared that under appropriate conditions the reaction rates were increased while the **2:3** ratio curiously decreased. In the presence of a too large excess of added salt (1.5 or 1 equiv. depending on the nature of the salt) no reaction was observed and the starting bromobenzene was recovered. As far as overall yields and the **2:3** ratio were concerned, the best results were obtained with $MgBr_2$, $CuCl$ and $ZrCl_4$. The condensation observed with $CuCl_2$ was rather surprising since cupric salts induce the oxidation and coupling of carbanions.⁶ No such reaction was presently observed. The nature of the counteranion of the salt seems to play a part as exemplified by the difference in reactivity observed between $ZnCl_2$ and $ZnBr_2$. On the other hand, steric effects could be partially responsible for the

Table 1 Condensation of benzyne and cyclohexanone sodium enolate in the presence of metal salt-reinforced complex bases (MCB)^a

Run	MX_n	Equiv.	t/h^b	Yield (%) ^c			Total yield (%) ^c
				2	3	2:3	
1	None	—	7	40	37	1.08	77
2	$MgBr_2$	0.1	0.5	48	30	1.6	78
3	$MgBr_2$	0.2	1.5	64	27	2.37	91
4	$ZnCl_2$	0.1	1.5	53	28	1.9	81
5	$ZnCl_2$	0.2	3	53	38	1.4	91
6	$ZnBr_2$	0.1	7.5	40	36	1.11	76
7	$ZnBr_2$	0.2	7	42	41	1.02	83
8	$CuCl$	0.1	2.25	42.5	34	1.25	76.5
9	$CuCl$	0.2	3	60	27	2.22	87
10	$CuCl$	0.5	4	64	30	2.13	94
11	$CuCl_2$	0.2	6	54	30	1.8	84
12	$CeCl_3$	0.1	3	53	33	1.6	86
13	$CeCl_3$	0.2	4	33	28	1.17	61
14	$ZrCl_4$	0.1	1.5	64	28	2.3	92
15	$ZrCl_4$	0.2	2	67	28	2.4	95
16	$(C_5H_5)_2ZrCl_2$	0.2	3	19	12	1.58	31
17	$(C_5H_5)_2ZrCl_2$	0.5	2	22	24.5	0.9	56.5

^aMCB = $NaNH_2$ (4 equiv.)–cyclohexanone enolate (2 equiv.)– MX_n (0.1–0.5 equiv.) prepared in DME at 40 °C. All reactions were performed on a 25 mmol scale of bromobenzene at room temperature. ^bReaction time after which no evolution was observed. ^cIsolated yields.

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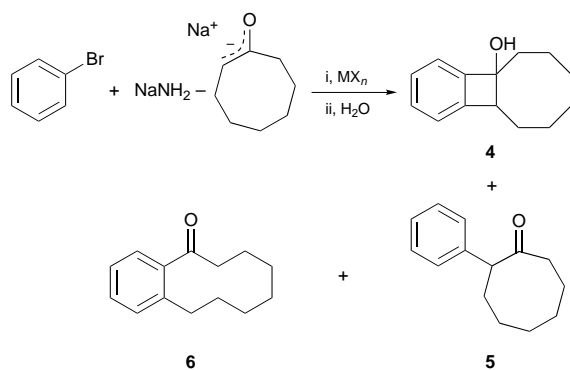
lower reactivity observed with $(C_5H_5)_2ZrCl_2$ compared with $ZrCl_4$. Moreover, we also observed the formation of coupling products of the benzyne and cyclopentadienyl ligand which accounts for the low yield of the arynic condensation.

Table 2 Condensation of benzyne and cyclooctanone sodium enolate in the presence of metal salt-reinforced complex bases (MCB)^a

Run	MX _n	Equiv.	t/h ^b	Yield (%)			4/(5+6)	Total yield (%) ^c
				4 ^c	5 ^d	6 ^d		
1	None	—	1.5	37	21	42	37:63	54
2	MgBr ₂	0.2	2	67	11	22	67:33	55
3	ZrCl ₄	0.2	1.5	72	9	19	72:28	57

^aMCB = NaNH₂ (4 equiv.)–cyclooctanone enolate (2 equiv.)–MX_n (0.2 equiv.) prepared in THF at 40 °C. All reactions were performed on a 25 mmol scale of bromobenzene at room temperature.

^bReaction time after which no evolution was observed. ^cIsolated yields. ^dYields determined by GC analysis using internal standard method. The (5+6) ratios were confirmed by ¹H NMR.

**Scheme 2**

We next examined the condensation of benzyne and cyclooctanone sodium enolate which was previously found to be not very efficient for the synthesis of benzocyclobutenol (4).⁵ Indeed, the major products obtained with a classical complex base prepared in THF were the phenylcyclooctanone 5 and the benzocyclodecanone 6 (Scheme 2 and Table 2, run 1).⁷ We found that the addition of a catalytic amount of ZrCl₄ or MgBr₂ (0.2 equiv.) led to a complete inversion of selectivity.

In conclusion, these results confirm that the insertion of a coordinating cation into the complex base aggregates may improve the reactivity and selectivity of these reagents.

Experimental

Merck sodamide powder was used. THF freshly distilled from benzophenone–sodium couple and 1,2-dimethoxyethane (DME) distilled over sodium and stored over sodium were used. Commercially available (Aldrich) cyclohexanone, cyclooctanone and bromobenzene were used after standard distillation. Metal salts [ZnCl₂, CuCl, CuCl₂, CeCl₃, ZrCl₄ and (C₅H₅)₂ZrCl₂] were purchased from Aldrich and used after drying under vacuum (20 mmHg) at 100 °C for 16 h. Anhydrous MgBr₂ was prepared accord-

ing to a previously reported procedure.⁸ All products were purified by flash chromatography and characterized by analytical and spectral data (¹H NMR, ¹³C NMR, IR, MS). These data were consistent with those of authentic samples.⁵ GC analyses were carried out with a Shimadzu GC-8A instrument equipped with a 15 m HP1 column.

General Procedure.—Cyclohexanone (20 mmol) in DME (10 ml) was added dropwise to a stirred suspension of NaNH₂ (60 mmol) in DME (10 ml) under nitrogen and the mixture was heated at 40 °C for 2 h. Dry metal salt (2–10 mmol) was then added at once and the heating was continued for 0.5 h. The obtained metal salt-reinforced complex base (MCB) was allowed to warm to room temperature and bromobenzene (25 mmol) in DME (10 ml) was dropwise added. The reaction was monitored by GC analysis of small aliquots using the tetradecane as internal standard. After completion, the reaction medium was poured on ice (100 ml) and the products were obtained after classical work-up and separation by flash chromatography.

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References and notes

- See for example: M. A. Zouaoui, A. Mouaddib, B. Jamart-Grégoire, S. Ianelli, M. Nardelli and P. Caubère, *J. Org. Chem.*, 1991, **56**, 4078 and references cited therein.
- P. Caubère, *Chem. Rev.*, 1993, **93**, 2317.
- P. Palmas, P. Tekely, B. Jamart-Grégoire, P. Caubère and D. Canet, *J. Am. Chem. Soc.*, 1994, **116**, 11 604.
- P. Caubère, *Rev. Heteroatom. Chem.*, 1991, **4**, 78.
- P. Caubère, N. Derozier and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 1971, 302.
- See for example: Y. Ito, T. Konaike and T. Saegusa, *J. Am. Chem. Soc.*, 1975, **97**, 2912.
- P. Caubère, G. Guillaumet and M. S. Mourad, *Tetrahedron*, 1973, **29**, 1857. In the present work, yields of compounds 5 and 6 were determined by GC analyses and the 5:6 ratio was confirmed by ¹H NMR analyses.
- J. J. Brunet, L. Mordenti and P. Caubère, *J. Org. Chem.*, 1978, **43**, 4804.