Enhanced Cram Selectivity in Carbonyl Alkylation *via* 'Naked' Anions and anti-Cram Selectivity *via* 'Naked' Cuprates

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Enhanced Cram selectivity is observed *via* the reaction of aldehydes (**1**) with 'naked' anions (**2**) prepared *in situ* from RM and Bu_4NBr, while anti-Cram selectivity results from the reaction of (**1**) with 'naked' cuprates (**4**) prepared *in situ* from R_2CuLi and Bu_4NBr.

We reported recently that the Cram selectivity in carbonyl alkylation reactions is enhanced with RLi (or RMgX)–crown reagents, while the anti-Cram isomer is produced preferentially with cuprate–crown reagents.[1] We expected that the complexation of M^+ by crown-type compounds would produce the observed stereoselectivity. If that were the case, a 'naked' anion would enhance Cram selectivity and a 'naked' cuprate would produce anti-Cram selectivity. We report that enhanced Cram selectivity is realized *via* the reaction of aldehydes (**1**) with (**2**) ('naked' anion) prepared *in situ* from RM and Bu_4NBr and that anti-Cram selectivity is produced through the reaction of (**1**) with (**4**) ('naked' cuprate) prepared *in situ* from R_2CuLi and Bu_4NBr. The results are summarized in Table 1.

Cram selectivity in the reaction of (**1**; R^1 = Ph) with R^2M (M = Li, MgX, · · ·) is normally in the range 5 : 1—1 : 1.[1,2] Accordingly, use of (**2**) evidently enhances the Cram selectivity (entries 1—5, Table 1), though the extent of the enhancement is not so high as with the RM–crown reagents. Further, use of BF_3 enhances the Cram selectivity (entry 2 *vs.* 1, Table 1), presumably owing to change of the directionality of $^-Bu\ ^+NBu_4$ attack towards the RCHO–BF_3 complex. With other aldehydes (**1**; $R^1 = C_6H_{11}$), the extent of the enhancement is small (entry 8); the ratio in the reaction with BuLi itself was 2.9 : 1. In the case of 2-benzylpropanal, no enhancement is observed (entry 10); the ratio with BuLi was 1 : 1.

The anti-Cram isomer is produced preferentially by using (**4**) regardless of the structure of the aldehyde (entries 6, 9,

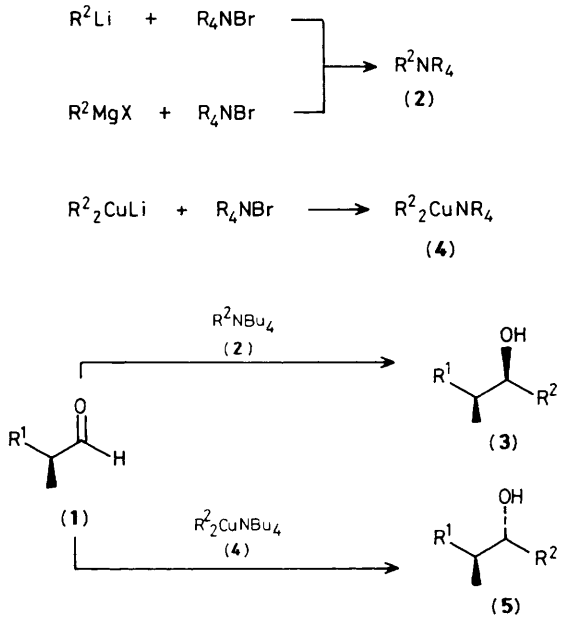
Table 1. Enhanced Cram selectivity *via* $RNBu_4$ and anti-Cram selectivity *via* R_2CuNBu_4.[a]

Entry	Aldehyde (1) R^1	(2) R^2	(4) R^2	Product ratio[b] (3) : (5)	Total yield,[b] %
1	Ph	Bu		6 : 1	100
2	Ph	Bu		8 : 1	93
3	Ph	Et[d]		8 : 1	100
4	Ph	Me		6 : 1	100
5	Ph	Me		5 : 1	83
6	Ph		Bu	1 : 1.9	72
7	Ph		Bu_2CuLi	3 : 1	99
8	C_6H_{11}	Bu		3.4 : 1	87
9	C_6H_{11}		Bu	1 : 1.5	14[f]
10	$PhCH_2$	Bu		1 : 1	100
11	$PhCH_2$		Bu	1 : 1.6	62

[a] All reactions were carried out on 1 mmole scale under argon. When the total yield was not 100%, the rest was recovered aldehyde and/or reduction product. [b] Determined by capillary g.l.p.c. [poly(ethylene glycol), 25 m]. [c] One equiv. of BF_3–OEt_2 was added at −78 °C. [d] EtMgBr or MeMgBr was used. Normally, alkyl-lithiums were used except where otherwise indicated. [e] The aldehyde was treated with Bu_2CuLi itself. [f] A major product was the reduced alcohol, 2-cyclohexylpropanol.

and 11; especially entry 6 *vs.* 7). This is synthetically very important, since only two methods have hitherto been available to obtain the anti-Cram isomer predominantly.[1,3] Normally, tetrabutylammonium bromide was used to produce (**2**) and (**4**). Tetrabutylammonium chloride and iodide worked similarly, but the anti-Cram selectivity was somewhat lower with these reagents.

The naked cuprate (**4**) was usually prepared at −78 °C by adding R_4NBr to a solution of lithium cuprate in tetrahydrofuran (THF). Interestingly, (**4**) could be also prepared by adding 2 equiv. of RLi to a THF suspension of CuI (1 equiv.) and Bu_4NBr (1 equiv.). The latter method is operationally more convenient. The naked anion (**2**) was prepared at −78 °C by adding RLi or RMgX to a THF suspension of Bu_4NBr.



The present development clearly indicates that the effect of crown-type compounds[1] is due to the inclusion of metal cations. Synthetically, the ammonium method is cheaper than the crown method. Mechanistically, the anti-Cram selectivity seems to be a reflection of a radical intermediate as suggested previously,[1] since the reduced product is frequently formed as a by-product.

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